Pharmacological Management in HEADACHE

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Outline

- Headache diagnosis and classification
- Migraine
  - Pharmacology of anti-migraine drugs
  - Abortive medication
  - Preventive medication
  - Status migrainosus
  - Refractory migraine

The International Classification of Headache Disorders, 3rd edition (beta version)

Part one: the primary headaches

1. Migraine
2. Tension-type headache
3. Trigeminal autonomic cephalalgias
4. Other primary headache disorders

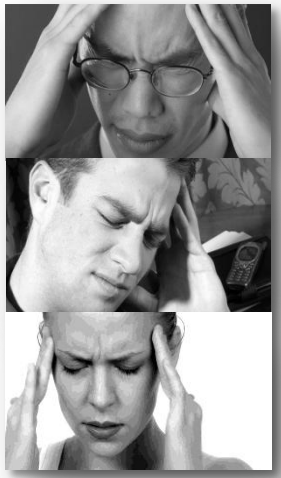
Part two: the secondary headaches

5. Headache attributed to trauma or injury to the head and/or neck
6. Headache attributed to cranial or cervical vascular disorder
7. Headache attributed to non-vascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homoeostasis
11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
12. Headache attributed to psychiatric disorder

Part three: painful cranial neuropathies, other facial pains and other headaches

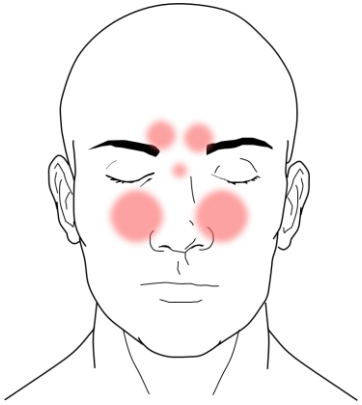
13. Painful cranial neuropathies and other facial pains
14. Other headache disorders

Approaching headache problem

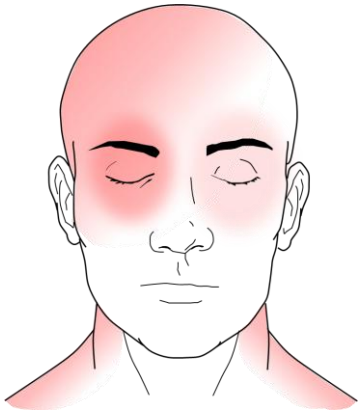


- What area of the head is affected?
- How long have the patient suffered from headache?
- How often does the headache recur?
- How long does the headache last?
- Is there any pattern to the recurrence of the headache?
- What is the quality of pain?
  (type, severity, associated symptoms, trigger factors)
- Previous medication and concurrent drug use?

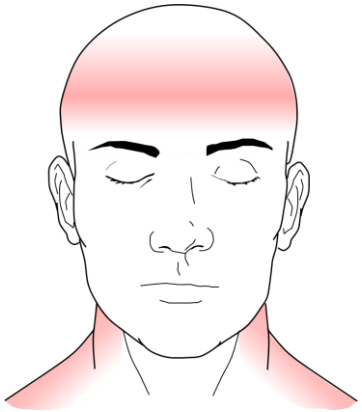
Headache sites and diagnoses



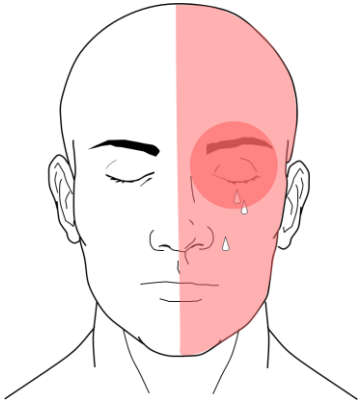
sinusitis



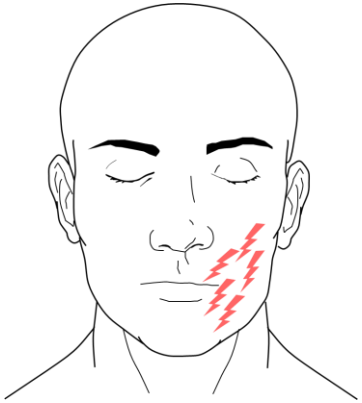
migraine



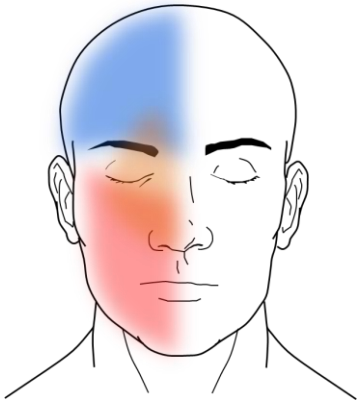
Tension-type



TAC



Trigeminal neuralgia



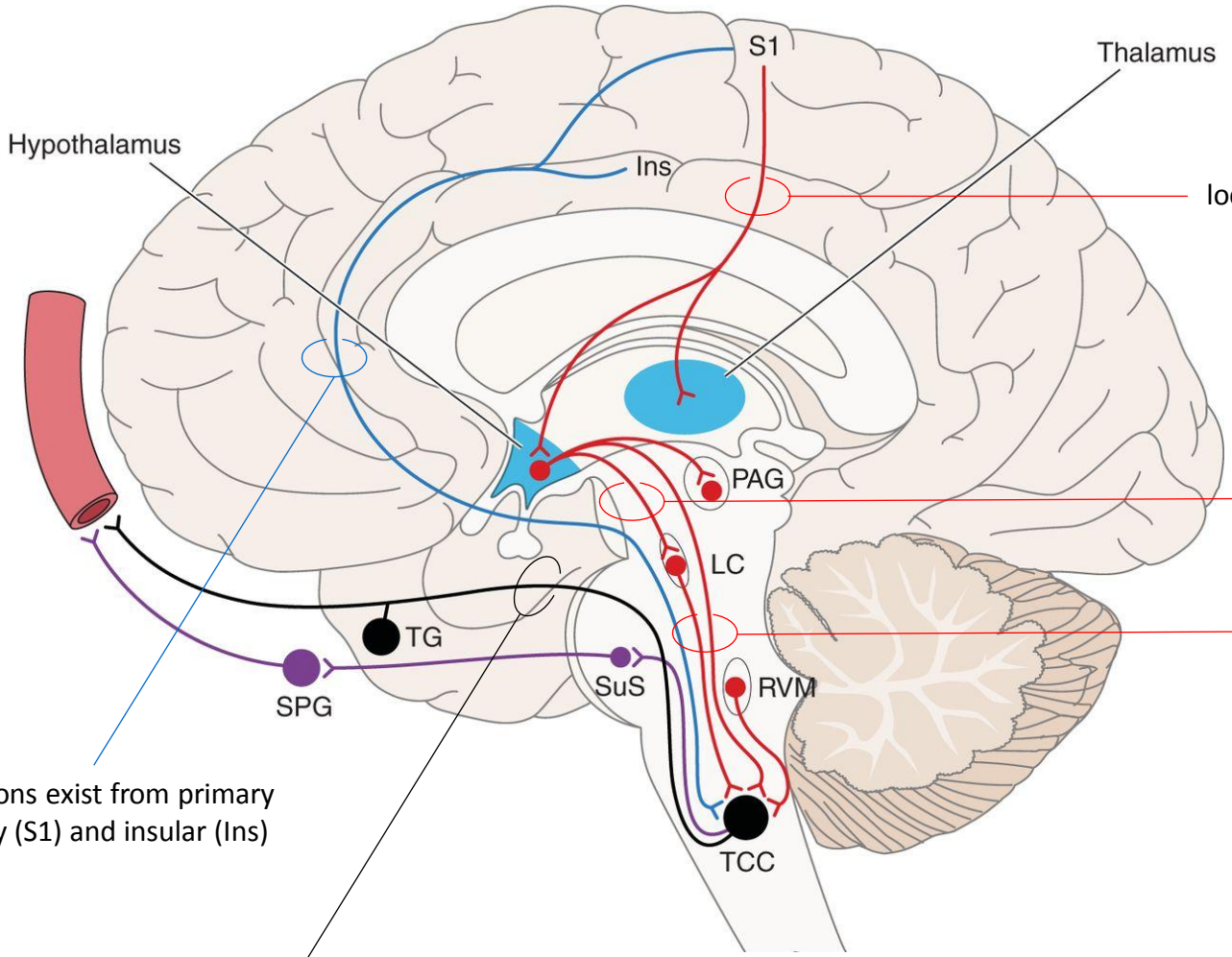
Cranial neuralgias

Key clinical features - common headache disorders

Headache	Tension-type headache	Migraine	Trigeminal autonomic cephalalgias				Trigeminal neuralgia
			Cluster headache	Paroxysmal hemicrania	Hemicrania continua	SUNCT/SUNA	
Sex (M:F)	4:5	3:1	5:1	1:1	1:2	3:2	2:3
Duration	30 min to 7 days (episodic)	4–72 h	15–180 min	2–30 min	Continuous headache	1–600 s	1–120 s
Frequency	Episodic or chronic (variable from rare to daily)	Episodic or chronic (variable from rare to daily)	1–8/day	>5 daily for more than half of the time	Continuous headache	>1 daily for more than half of the time	Very variable frequency
Pain type							
Location	Bilateral	Unilateral or bilateral	Unilateral	Unilateral	Unilateral	Unilateral; V1/V2>V3	Unilateral; V2/V3>V1
Quality	Pressing/tightening (non-throbbing)	Throbbing	Variable	Variable	Variable	Neuralgiform pain	Neuralgiform pain
Severity	Mild to moderate	Moderate to severe	Very severe	Very severe	Moderate to very severe	Very severe	Very severe
Migrainous symptoms	–	+++	+/–	–	+/–	–	–
Autonomic features	No	+/–	+++	+++	+++	+++	Sparse
Triggers			Alcohol (within 30 min)			Cutaneous	Cutaneous
Indomethacin response	+/– (as simple analgesic)	± (as simple analgesic)	–	+++	+++	–	–

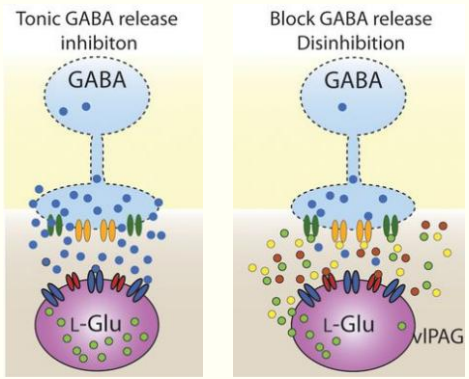
Sinclair et al. **Prac Neurol** 2015;15:411-423

Dysfunction of TCC modulatory pathway contributes to triggering migraine

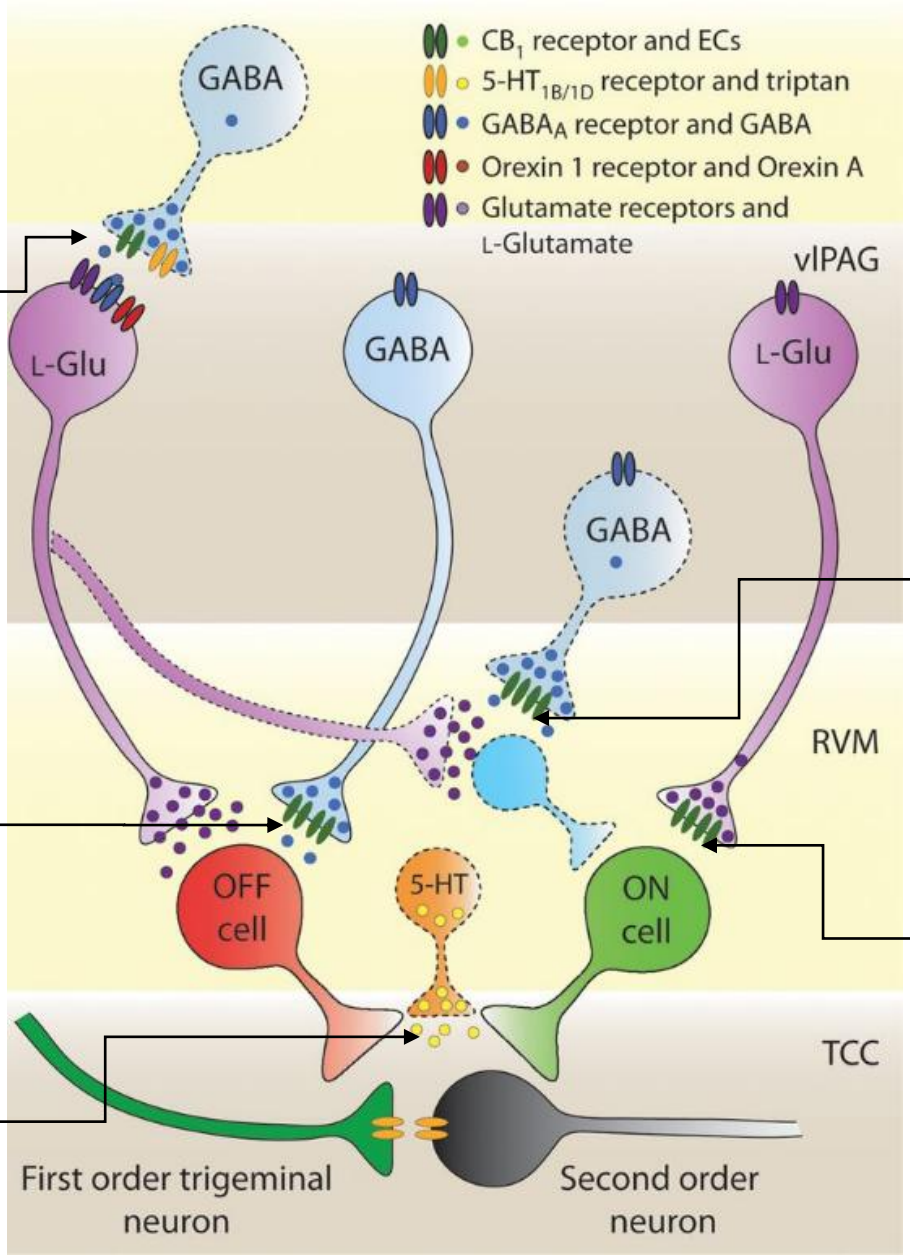


Goadsby et al. **Physiol Rev** 2017;97: 553–622

5-HT and endocannabinoids: modulation of trigeminovascular nociceptive transmission



ECs (green circles) and 5-HT agonists (yellow circles) activate presynaptic receptors inhibiting the release of GABA, increasing the likelihood of activation of "OFF" cells in the RVM.



CB1 receptors situated presynaptically on GABAergic projections to "OFF" cells, when activated by endogenous or exogenous ECs, inhibit the release of GABA, increasing "OFF" cell activity by disinhibition.

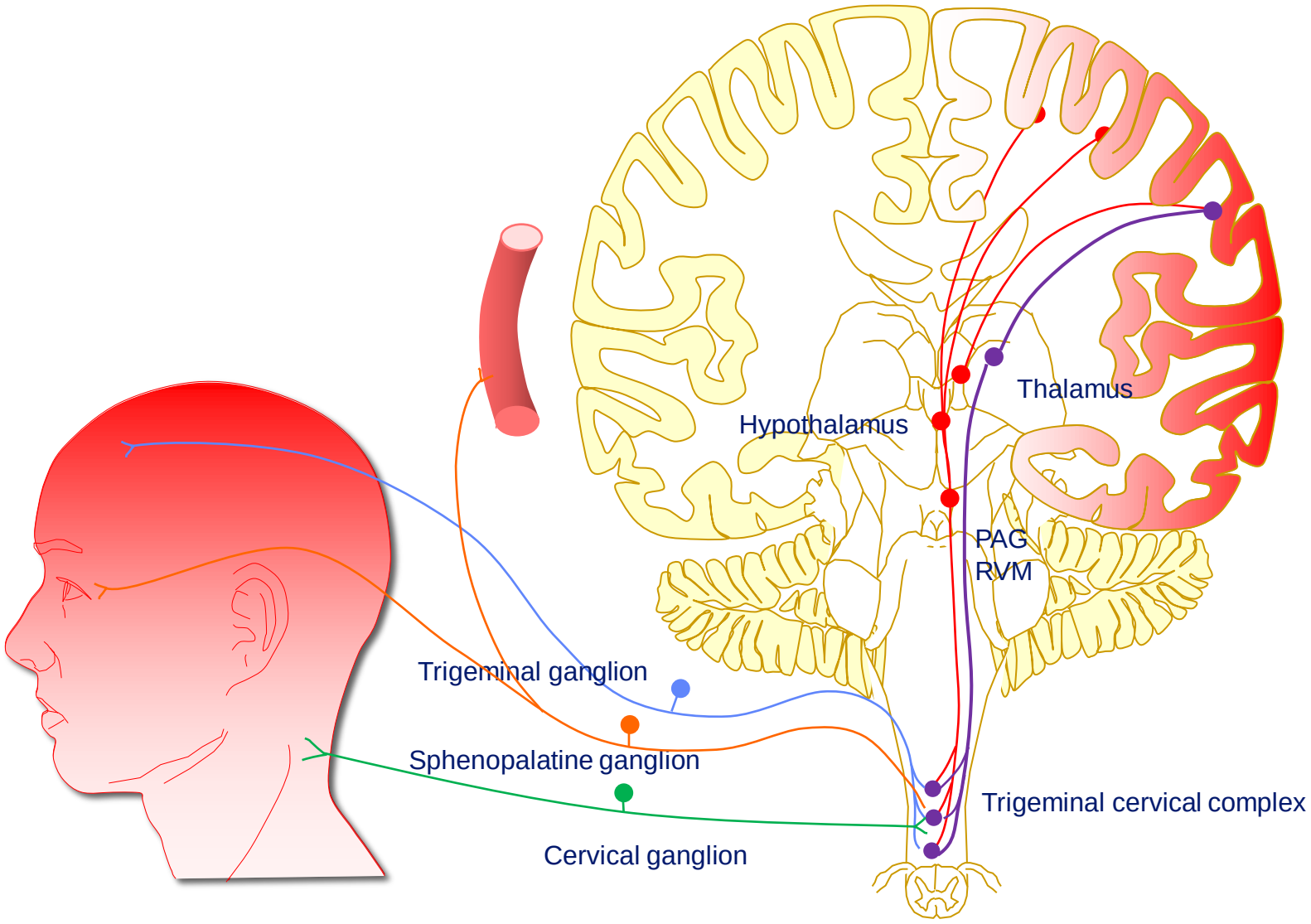
a state-dependent and bidirectional control of pain modulation through serotonergic projections from the RVM to the TCC

"ON" cell activity may also be inhibited by CB1 receptor-mediated inhibition of presynaptic release of GABA from neurons that synapse on inhibitory interneurons (light blue neuron-dashed lines).

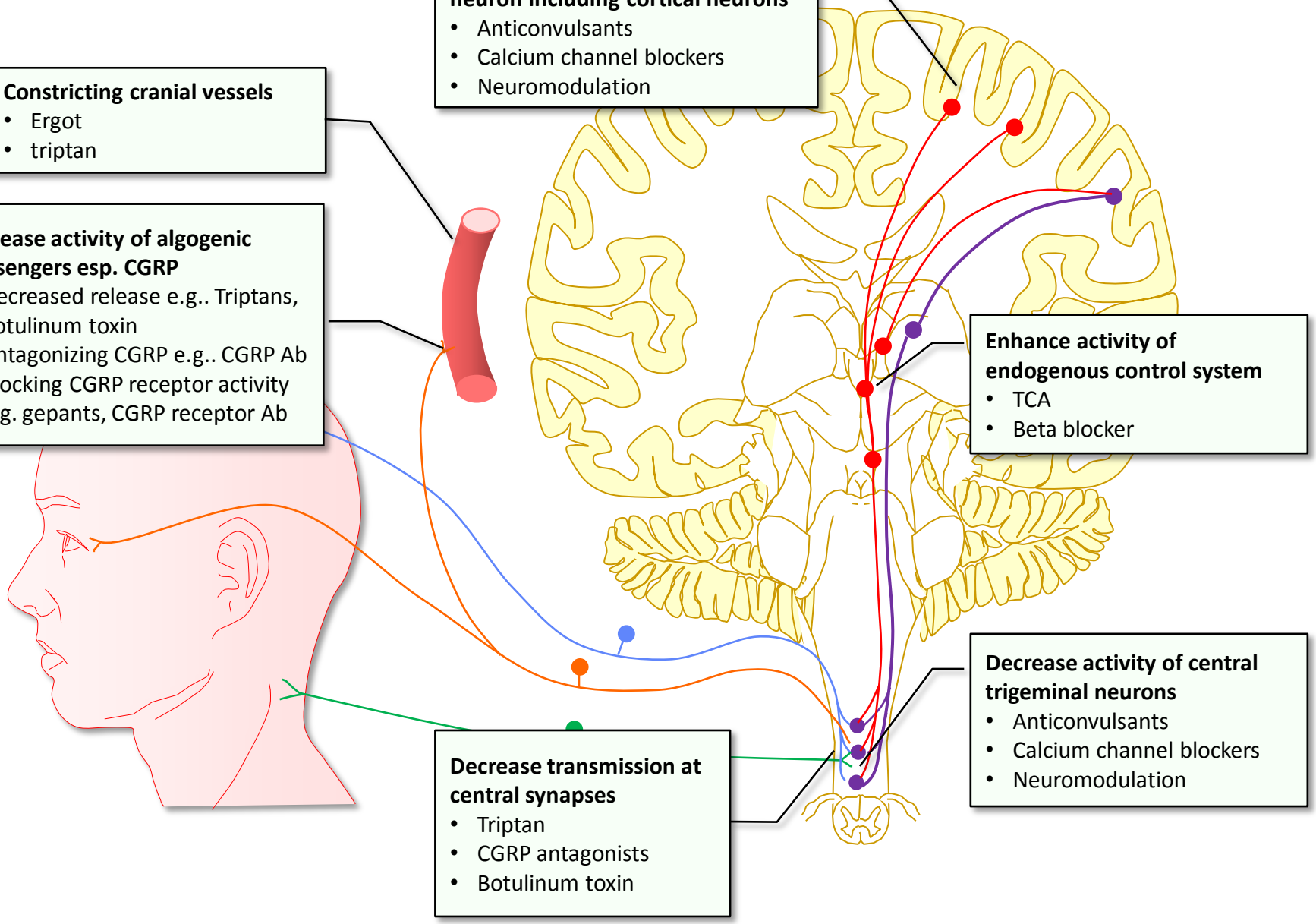
Presynaptic CB1 receptors on glutamatergic projections to "ON" cells inhibit the release of glutamate blocking "ON" cell activation

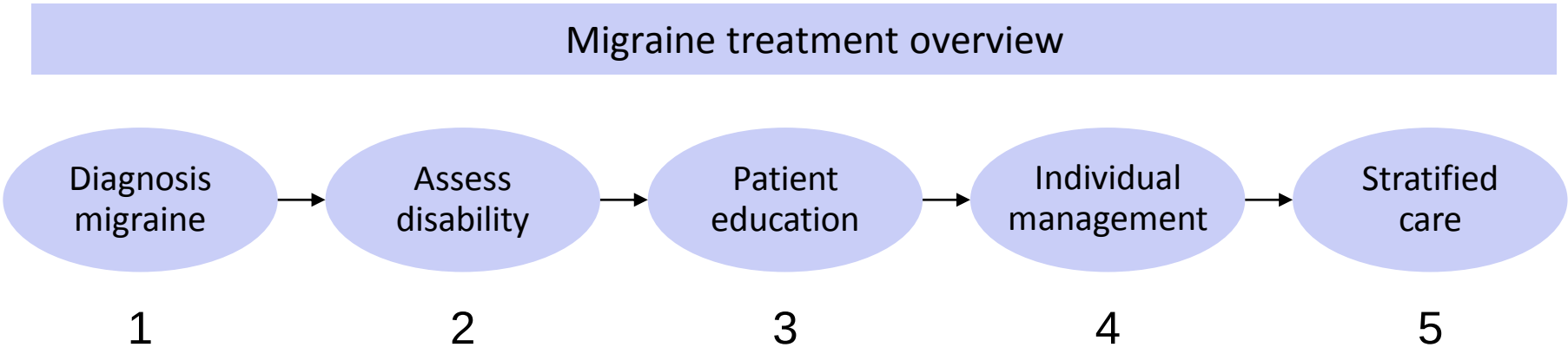
Goadsby et al. **Physiol Rev** 2017;97: 553–622

CSD and activation of trigeminal nociceptive system



Potential therapeutic target for anti-migraine therapy




Migraine treatment overview
Diagnosis migraine
Assess disability
Patient education
Individual management
Stratified care
1
2
3
4
5

Migraine – Abortive medication

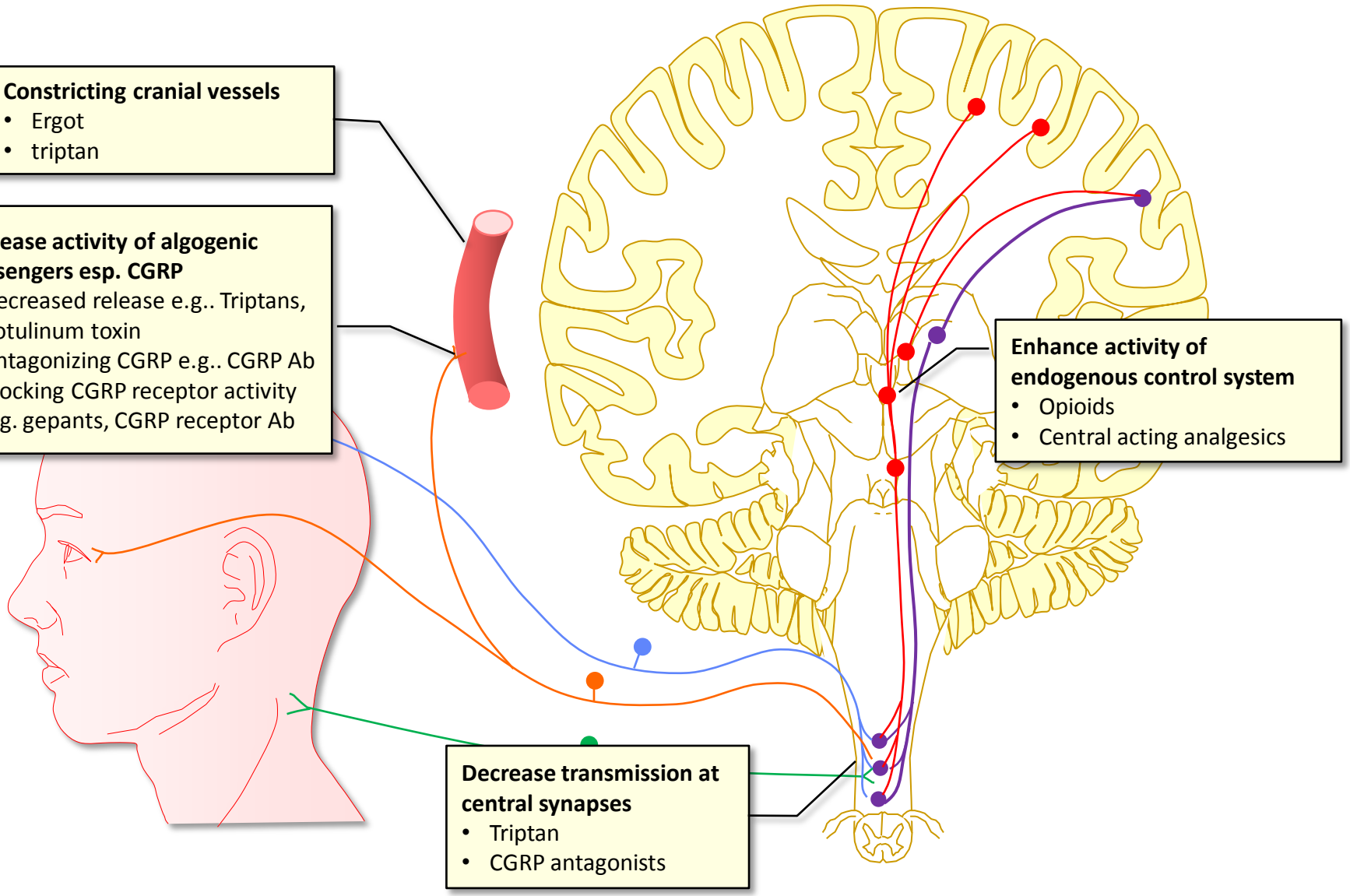
Abortive therapies – goal

- Treat attacks rapidly and consistently and prevent recurrence
- Restore the patient's ability to function
- Minimize the use of backup and rescue medications
- Optimize self-care and reduce subsequent use of resources
- Be cost-effective in overall management
- Have minimal or no adverse events

Potential therapeutic target for anti-migraine therapy – abortive medication

Constricting cranial vessels
- Ergot
- triptan

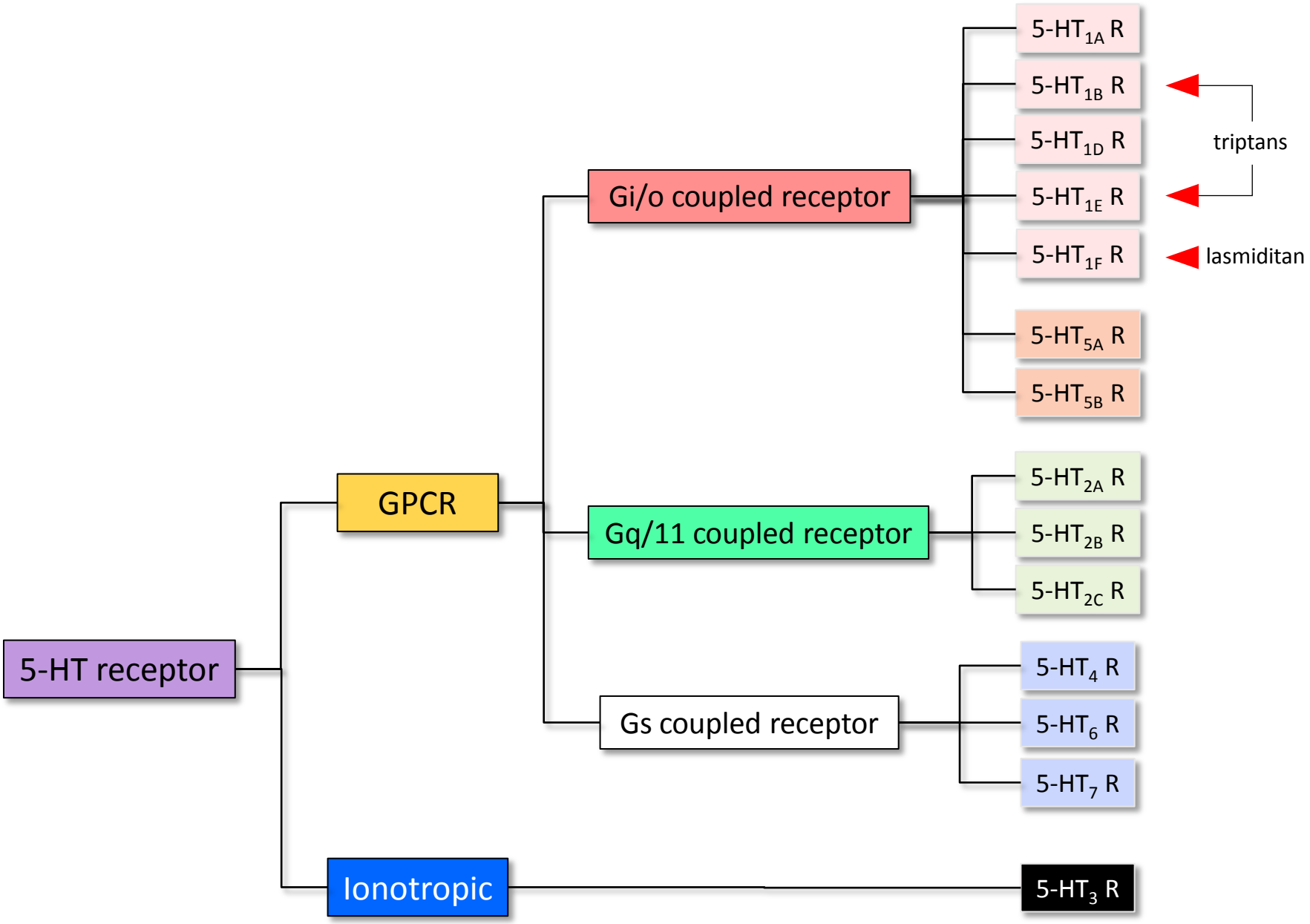
Decrease activity of algogenic messengers esp. CGRP
- Decreased release e.g.. Triptans, botulinum toxin
- Antagonizing CGRP e.g.. CGRP Ab
- Blocking CGRP receptor activity e.g. gepants, CGRP receptor Ab



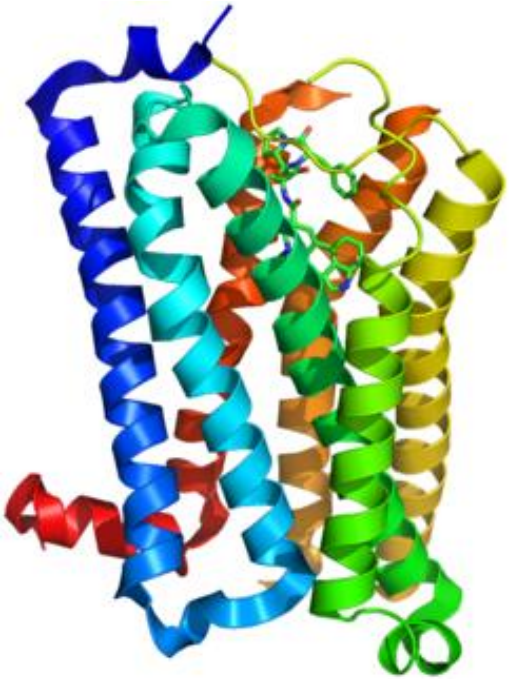
Enhance activity of endogenous control system
- Opioids
- Central acting analgesics

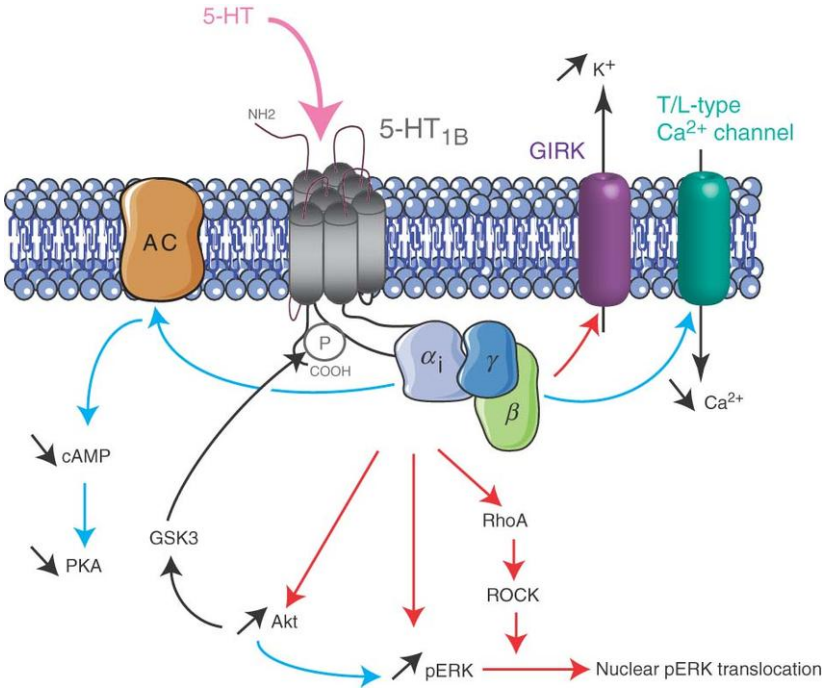
Decrease transmission at central synapses
- Triptan
- CGRP antagonists

5-HT receptor classification



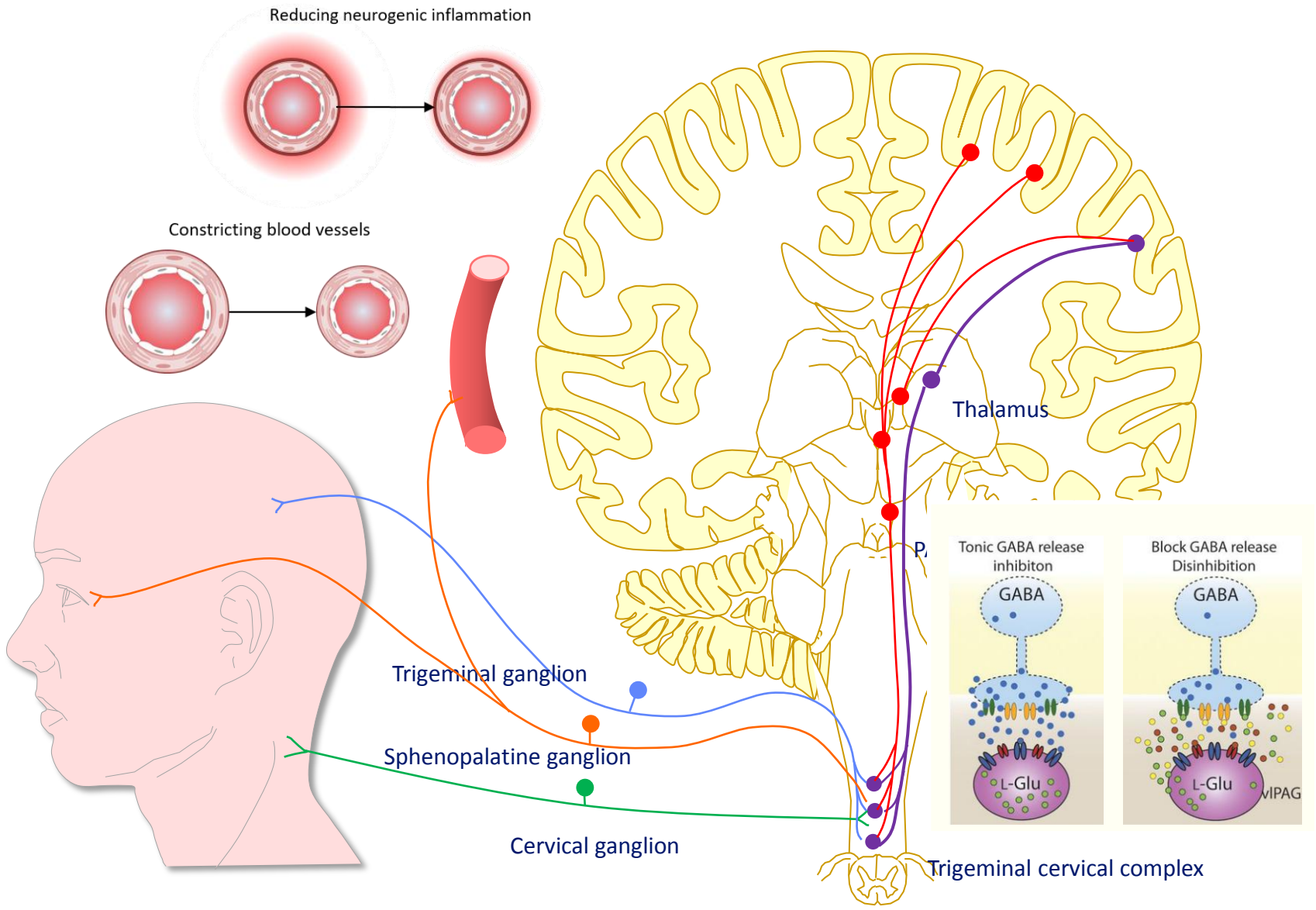
5-HT_{1B} receptor signalling pathways



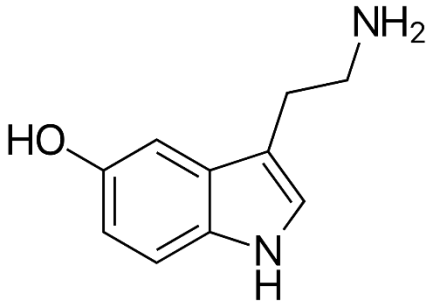


The 5-HT_{1B}R is negatively coupled to AC/PKA/cAMP signaling via $G_{\alpha i}$ protein. Its activation decreases neurotransmitter release in neurons through opposite changes in K^+ and Ca^{2+} conductances. Stimulation of nuclear ERK translocation (transcription activation) following 5-HT_{1B}R activation depends on kinases' cascade. Blue arrow, inhibition; red arrow, stimulation.

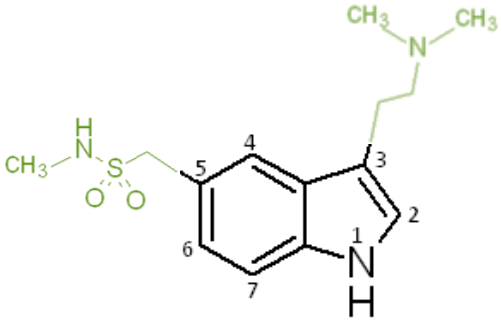
Potential targets for triptans



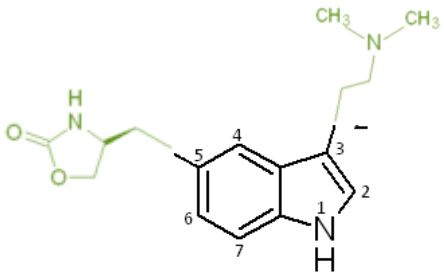
Sumatriptan and derivatives



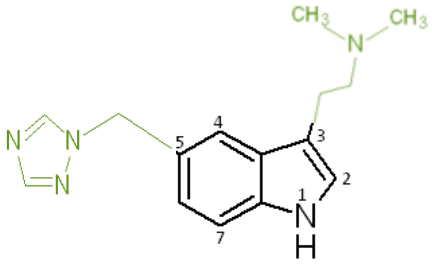
serotonin



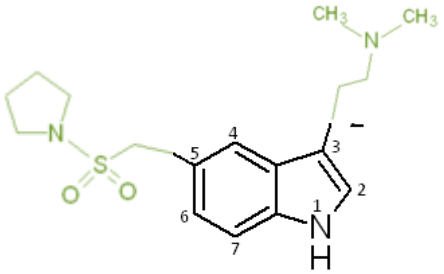
sumatriptan



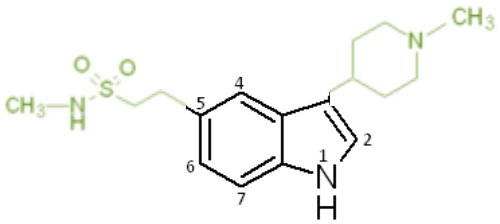
zolmitriptan



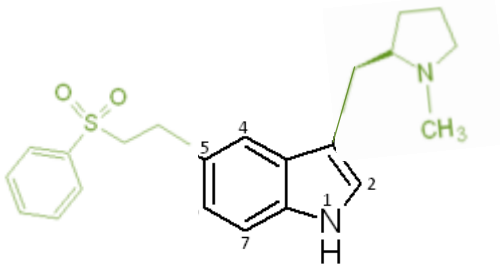
rizatriptan



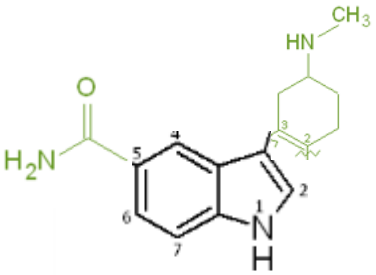
almotriptan



naratriptan

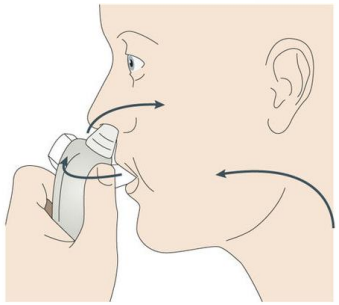


eletriptan



frovatriptan

Triptan – non-oral mode of administration



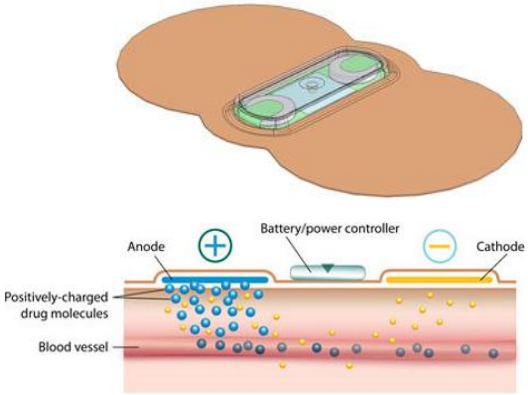
Inhaler

DHE

zolmitriptan

sumatriptan

Nasal spray



Patch

Subcutaneous injection

Comparing triptans

Triptan	Peak serum concentration	Half-life	Usual dose (maximum daily dose)	Cost (per tablet)
Almotriptan	1.5–2 h	3.5 h	12.5 mg (25 mg)	3.0 GBP (12.5 mg)
Eletriptan	1.5–2 h	4 h	40 mg (80 mg)	3.8 GBP (40 mg)
Frovatriptan	2–4 h	26 h	2.5 mg (5 mg)	2.8 GBP (2.5 mg)
Naratriptan	2–3 h	6 h	2.5 mg (5 mg)	3.8 GBP (2.5 mg)
Rizatriptan	1–1.5 h	2 h	10 mg (20 mg)	4.5 GBP (5 mg)
Sumatriptan	2–3 h	2 h	50–100 mg (300 mg)	0.3 GBP (50 mg)
Sumatriptan subcutaneous	12 min	1.9 h	6 mg (12 mg)	21.2 GBP (per injection)
Sumatriptan intranasal	1–1.5 h	2 h	10–20 mg (40 mg)	5.9 GBP (per dose)
Zolmitriptan	1–1.5 h	2.5 h	2.5–5 mg (10 mg)	3.8 GBP (2.5 mg)
Zolmitriptan intranasal	15 min	3 h	5 mg into one nostril, once (10 mg)	11.0 GBP (per spray)

Drugs listed alphabetically. All doses apply to the oral route, except where otherwise specified.

Sinclair et al. **Prac Neurol** 2015;15:411-423

Comparing abortive medication

Acute treatment	Dose/Format	Moderate-to-severe to NO pain	Moderate-to-severe to mild pain	Placebo effect to NO pain
Sumatriptan	Injection	59	79	15
Sumatriptan	100 mg oral	32	61	11
Zolmitriptan	2.5 mg oral	30	61	10
Sumatriptan	Nasal spray	24	50	10
Ibuprofen	200 or 400 mg oral	26	57	12
Aspirin	100 mg oral	24	52	11
Diclofenac	50 mg oral	22	55	-
Paracetamol	100 mg oral	19	56	10
Naproxen	500 or 825 mg oral	17	50	8

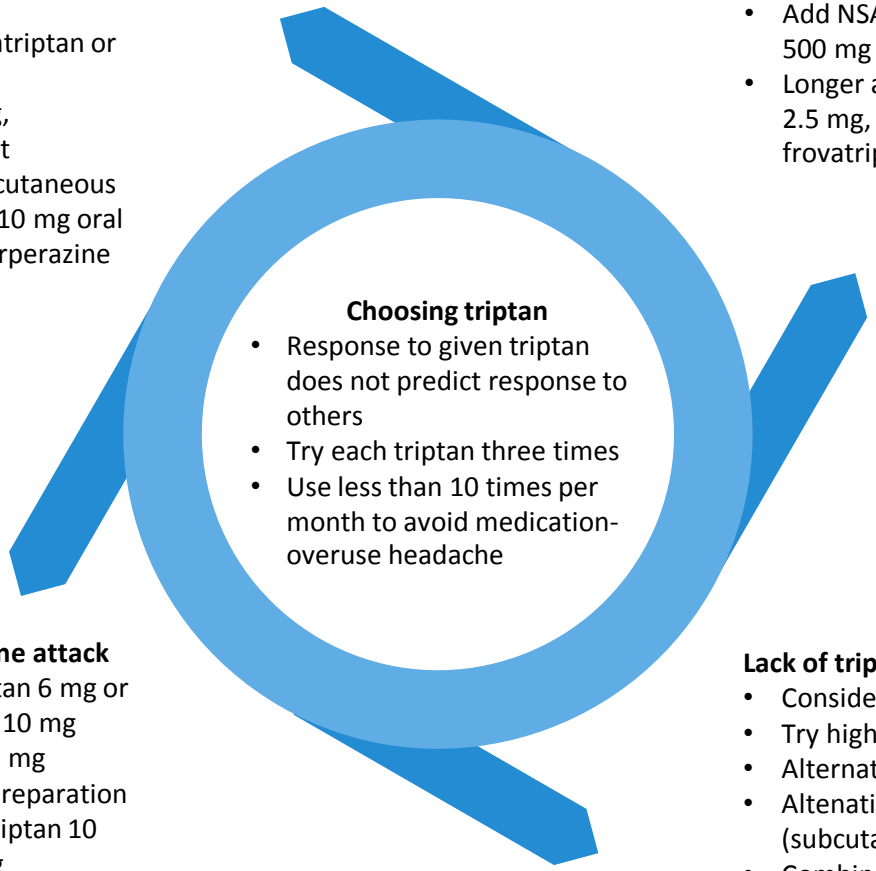
Triptan selection in acute migraine

Early nausea and vomiting

- Alter triptan formulation
  - Nasal spray 10 mg sumatriptan or 5 mg zolmitriptan
  - Rizatriptan wafer 10 mg, zolmitriptan 2.5 mg melt
    Sumatriptan 10 mg subcutaneous
- Antiemitics: domperidone 10 mg oral or 6. mg per rectal prochlorperazine 3. 6mg buccal

Recurrence of headache

- Add NSAID for example naproxen 500 mg or paracetamol
- Longer acting triptan; naratriptan 2.5 mg, almotriptan 12.5 mg or frovatriptan 2.5 mg



Rapidly progressing migraine attack

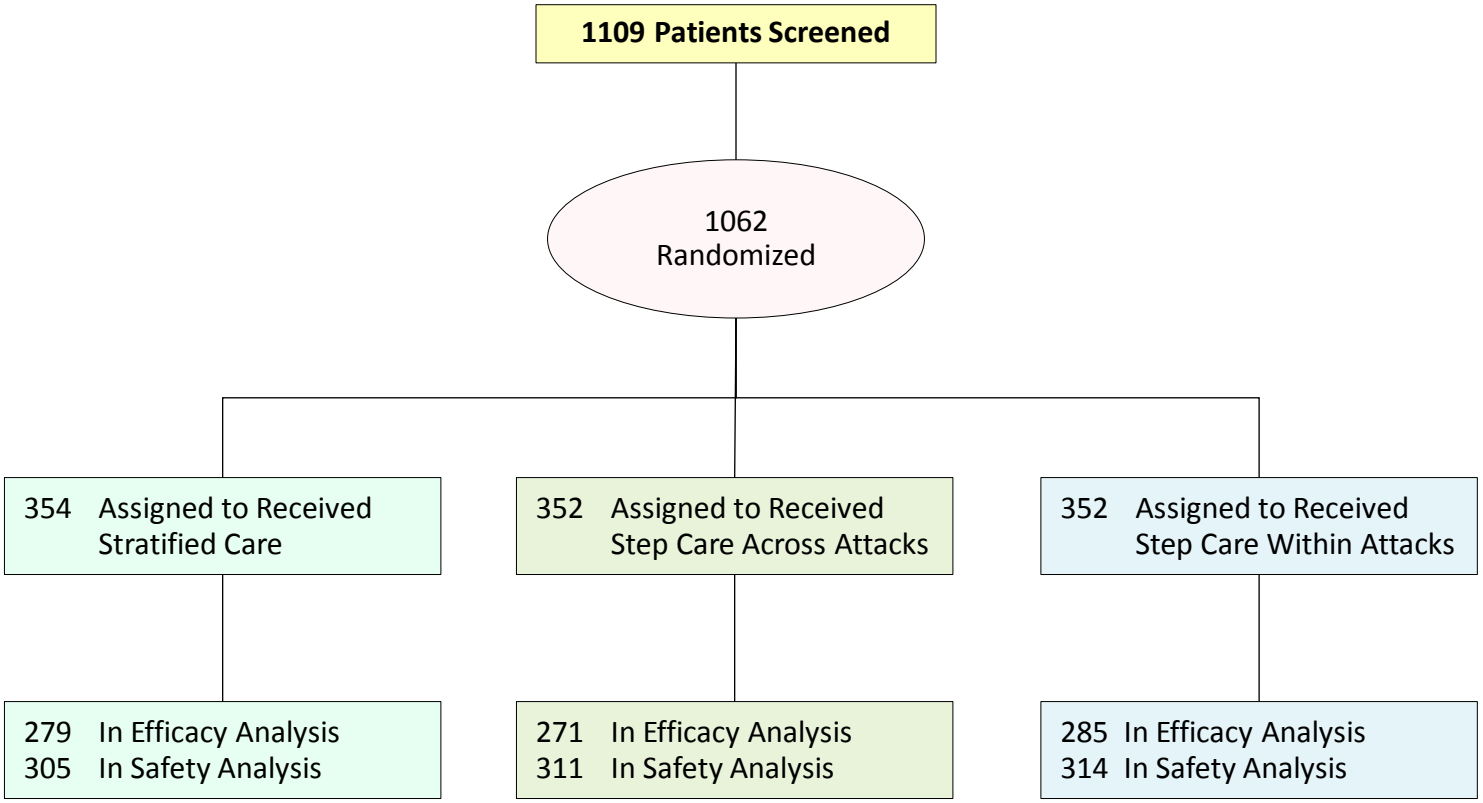
- Subcutaneous sumatriptan 6 mg or nasal spray sumatriptan 10 mg
- Intranasal zolmitriptan 5 mg
- Fast acting oral triptan preparation - eletriptan 40 mg, rizatriptan 10 mg, zolmitritptan 2.5 mg
- An additional pro-kinetic for example domperidone 10 mg

Lack of triptan response

- Consider preventive
- Try higher dose
- Alternative triptan
- Altenative formulation (subcutaneous, intranasal)
- Combination therapy with NSAID (ibuprofen 800 mg or naproxen 500 mg.

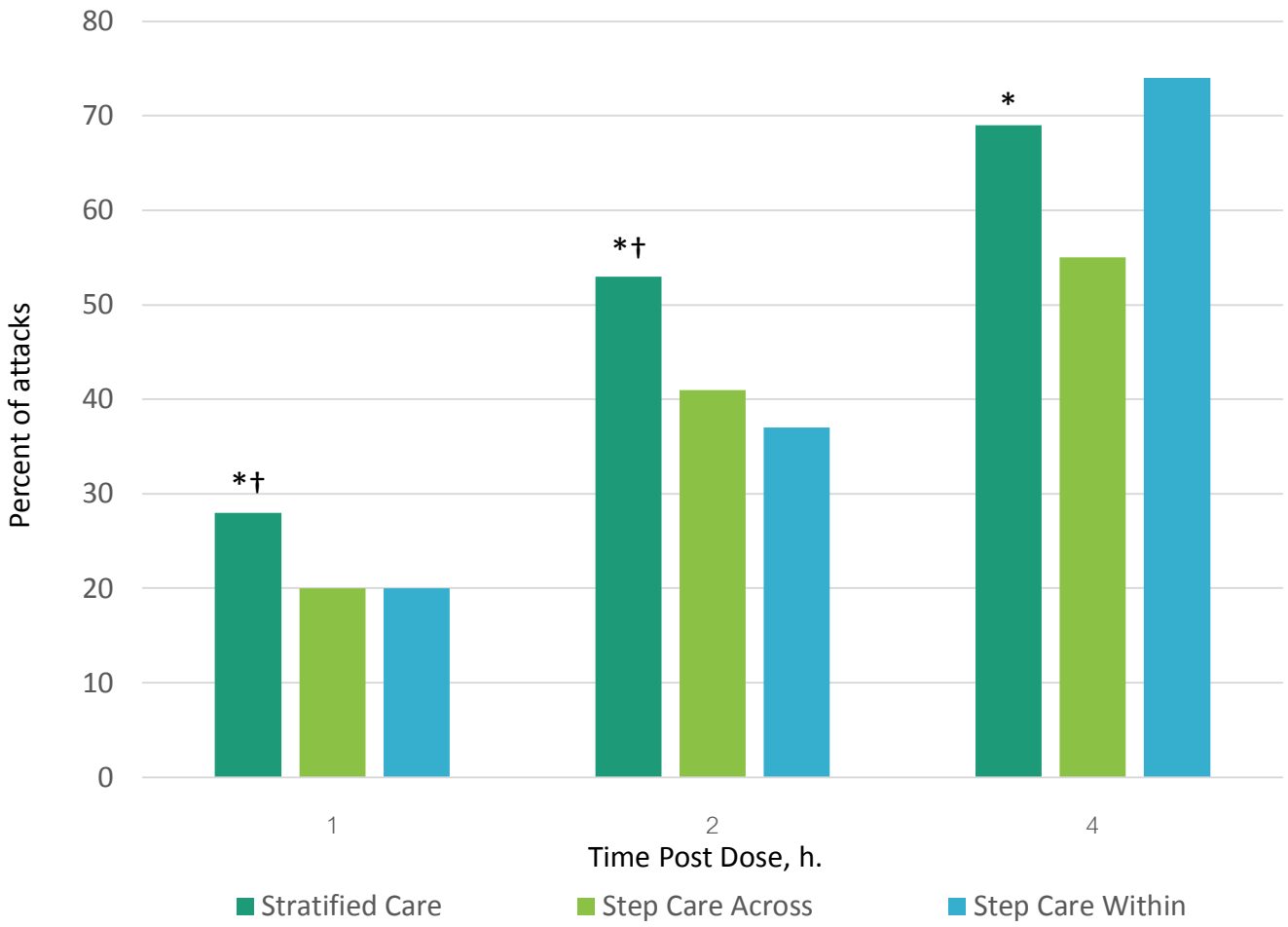
Sinclair et al. **Prac Neurol** 2015;15:411-423

Step care vs. stratified care for acute migraine



Lipton et al. **JAMA.** 2000;284:2599-2605

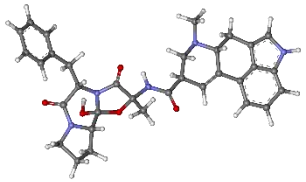
Step care vs. stratified care for acute migraine



Headache response at 1, 2, and 4 hours: statistically significantly more attacks in the stratified care treatment group had a 1-, 2-, and 4-hour headache response compared with the step care across attacks treatment group. Statistically significantly more attacks in the stratified care treatment group showed a 1- and 2-hour headache response compared with the step care within attacks group. This difference was not maintained at 4 hours because patients escalated to zolmitriptan, 2.5 mg, if they did not have a 2-hour headache response. *P*<.001 for stratified care vs step care across attacks (*) and for stratified care vs step care within attacks (†).

Lipton et al. **JAMA.** 2000;284:2599-2605

Ergotamine preparation

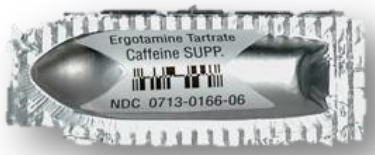


Ergotamine

sublingual

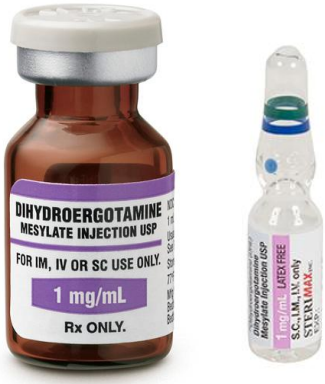
Ergotamine + caffeine

oral



Rectal suppository

Dihydroergotamine



injection

Nasal spray

Recommendations for the use of ergotamine

Recommendation	Limitations and comments
Which patients?	
• Patients requiring migraine-specific therapy	• When a migraine-specific therapy is indicated, a triptan is a better choice than ergotamine for most patients
• Patients established on ergotamine	• Patients established on ergotamine who are responding satisfactorily, with no contraindications to its use and with no signs of dose escalation, should not usually be switched to a triptan
Special cases	
• Patients with very long attacks	• Attacks lasting > 48 h may be usefully treated with ergotamine
• Patients with frequent headache recurrence	• Headache recurrence is probably less likely with ergotamine
Frequency of dosing: 1/week or 6/month	• A major problem with ergotamine is ergotamine-induced headache and rebound headache associated with frequent use. This can be limited by restricting ergotamine consumption and encouraging use of a preventative medication as headache becomes more frequent.
	• May be modified to four consecutive doses for menstrual migraine
	• May be modified for use in cluster headache
Dose per attack: single dose (0.5–2 mg)	Ergotamine should be dosed at one time as early as practicable in the attack at a dose that produces a response with as few side-effects as possible. It is useful to test this dose for tolerability for nausea between attacks
Preferred route: rectal	Although still useful orally, ergotamine is generally better used, provided it is acceptable to the patient, by the rectal route because of improved absorption. Where it is available, the ergotamine puffer is preferred to the oral route for the same reasons

Tfelt-Hansen et al. **Brain** 2000;123;Pages 9–18,

Recommendations for the use of DHE

1. Long migraines with multiple recurrences
2. Long migraines, specifically including menstrually related migraines.
3. Migraine upon awakening
4. Moderate to severe levels of pain, in the presence of allodynia
5. Status migrainosus (a migraine lasting longer than 72 hours)
6. As a bridge to wean a patient out of medication overuse headache.
7. Patient with nausea and vomiting

Selected therapies for acute migraine

Class	Specific treatments	Reported mean therapeutic effects	Common or serious adverse effects
Triptans	Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan	Pain relief by 2 hr, 16-51%; pain-free by 2 hr, 9-32%; free of headache for 24 hr, 9-27%	Chest or facial muscle tightness, lightheadedness, contraindicated in patients with coronary disease
Ergots	DHE nasal spray, DHE injection	Pain relief by 2 hr, 20-40% (for DHE nasal spray; limited evidence)	Nausea, dizziness, contraindicated in patients with peripheral vascular disease or coronary disease
Acetaminophen		Pain relief by 2 hr, 19%; pain-free by 2 hr, 9-%	Minimal with intermittent use
NSAIDs	Aspirin, Diclofenac, ibuprofen, ketorolac, naproxen,	Pain relief by 2 hr, 17-29%; pain-free by 2 hr, 7-20%	Gastric irritation, excessive bleeding
Combinations	Acetminophen-aspiri-caffeine, sumatriptan-naproxen	Pain relief by 2 hr, 10-17% (limited evidence); pain-free by 2 hr, 20-30%	Same as with NSAIDs and triptans
Antiemetics	Chlopromazine, metochlopramide, prochlorperazine	Pain relief by 2 hr with oral metochlopramide (plus aspirin or acetaminophen), 23%; pain-free by 1-2 hr with intravenous delivery in ER, 24-67%	Sedation, restlessness (akathisia), dystonic reactions
CGRP receptors antagonists	Rimegepant, ubrogepant	Pain-free by 2 hr, 14-18%	None reported; safety studies are ongoing

Charles A. **N Engl J Med** 2017; 377:553-561

Abortive medication stratification by headache severity

Moderate	Severe	Extremely Severe
NSAIDs	Naratriptan	DHE (IV)
Isometheptene	Rizatriptan	Opioids
Ergotamine	Sumatriptan (SC,NS)	Dopamine antagonists
Naratriptan	Zolmitriptan	
Rizatriptan	Almotriptan	
Sumatriptan	Frovatriptan	
Zolmitriptan	Eletriptan	
Almotriptan	DHE (NS/IM)	
Frovatriptan	Ergotamine	
Eletriptan	Dopamine antagonists	
Dopamine antagonists		

Treating status migrainosus

1. Intravenous Dihydroergotamine (DHE).
    - Premedication with anti-nausea medication such as ondansetron or metoclopramide. Then administer 1 mg DHE q 8 hours for 5-20 doses- (.5 mg if < 25 kg)
2. IV Valproate
    - 1 gram IV Valproate in Normal Saline drip over 15 minutes (200 ml/hr)
3. Metoclopromide
    - 10 mg IV Metoclopromide in 200 cc Normal Saline
4. Triptans ± NSAIDs

Acute management of migraine – National Institute of Health and Care Excellence guidelines

1. Combination therapy:
   - triptan + non-steroidal anti-inflammatory drug (NSAID) or paracetamol + antiemetic
2. Single agent
   - Triptan ± antiemetic
   - NSAID ± antiemetic
   - paracetamol ± antiemetic

NSAID

- Aspirin 600–900 mg (ideally effervescent)
- Ibuprofen 600–800 mg
- Naproxen 500–1000 mg
- Diclofenac 50–75 mg (or 100 mg suppository)
- Tolfenamic acid 200 mg

Antiemetics

For nausea and/or as a prokinetics such as

- Domperidone 10 mg up to three times a day (or 60 mg suppository)
- Metoclopramide 10 mg
- Prochlorperazine 3–6 mg as buccal preparation

Sinclair et al. **Prac Neurol** 2015;15:411-423

Migraine – Preventive medication

Preventive medication – goal

- Reduce attack frequency, severity, and/or duration
- Improve responsiveness to acute attacks
- Reduce disability

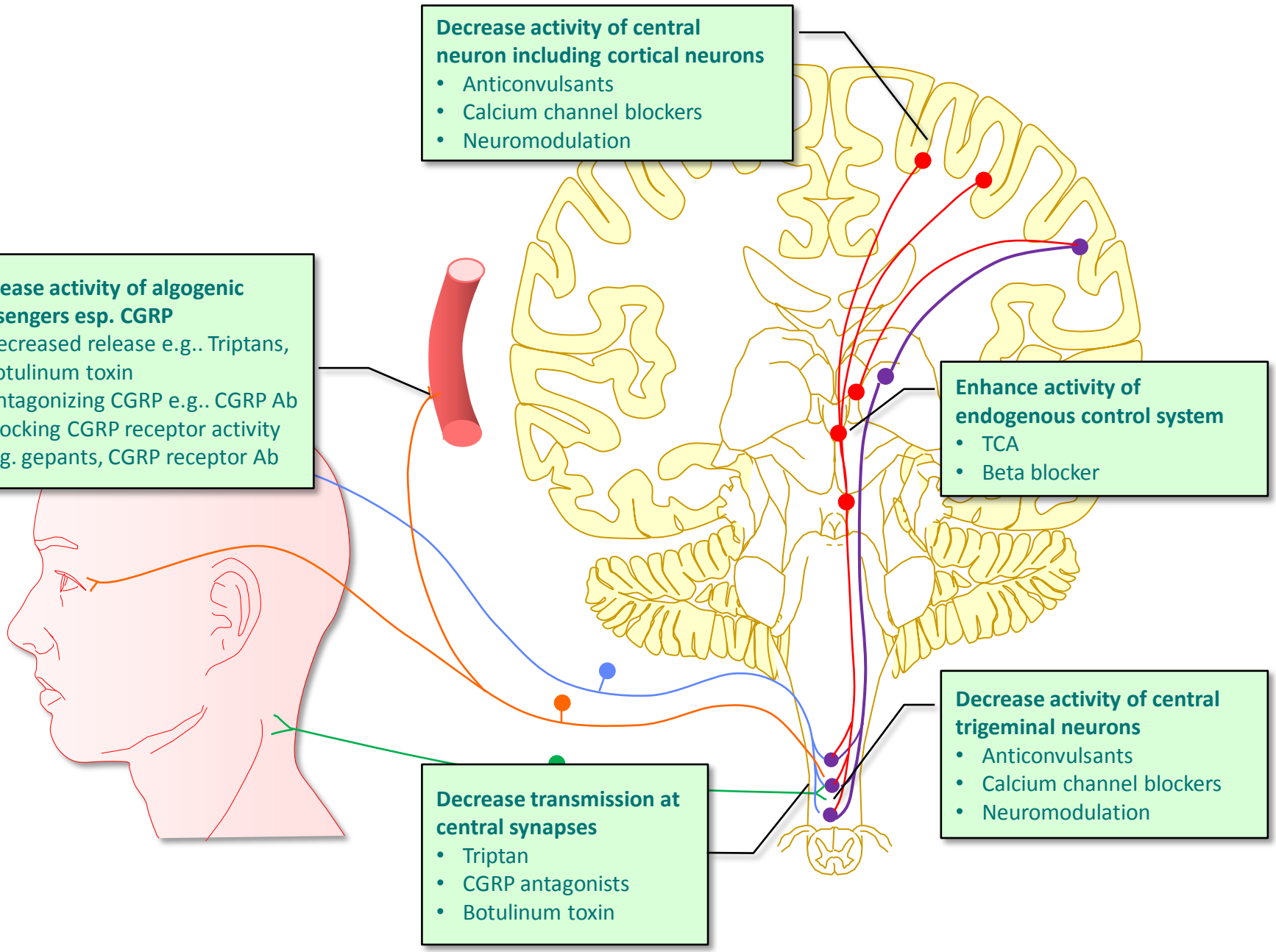
Preventive therapies – when

- Frequency > 2 per month
- Duration > 24 hours
- The headaches cause major disruptions in the patient's lifestyle, with significant disability that lasts 3 or more days
- Abortive therapy fails or is overused
- Symptomatic medications are contraindicated or ineffective
- Use of abortive medications more than twice a week
- Migraine variants such as hemiplegic migraine or rare headache attacks producing profound disruption or risk of permanent neurologic injury

1. Use medications with the best evidence-based efficacy and fewest adverse events.
2. Take coexisting conditions into account:
   - Select a drug that will treat all conditions, if possible.
   - Be sure that the coexistent disease is not a contraindication to the migraine treatment.
   - Be sure that the treatments used for coexistent conditions do not exacerbate migraine.
   - Beware of drug interactions.
3. Start low, increasing the dose slowly until clinical benefits are achieved in the absence of, or until limited by, adverse events.

4. Give the selected drug an adequate trial at adequate doses (2-3 months).
5. Avoid interfering medications, e.g., overuse of medications for acute treatment.
6. A long-acting formulation may improve compliance.
7. Monitor the patient's headache through a headache diary.
8. Re-evaluate therapy. If headaches are controlled at 6 months, consider tapering or discontinuing treatment

Potential therapeutic target for preventive therapy



AAN/AHS Summary of evidence-based guideline for episodic migraine prevention in adults

Drug	Strong (A)	Moderate (B)	Weak (C)	Insufficient (U)
Angiotensin Receptor Blockers			Candesartan Telmisartan (C-)	
Ace Inhibitors			Lisinopril	
Alpha Agonists			Clonidine Guanfacine	
Antithrombotics				Acenocoumarol Coumadin
Antidepressants		Amitriptyline Venlafaxine Clomipramine (B-)		Fluoxetine Fluvoxamine Protriptyline
Antiepileptic Drugs	Divalproex sodium Sodium valproate Topiramate Lamotrigine (A-)		Carbamazepine Oxcarbazepine (C-)	Gabapentin
Beta-blockers	Metoprolol Propranolol Timolol	Atenolol Nadolol	Nebivolol Pindolol Acebutolol (C-)	bisoprolol
Calcium-channel Blockers				Nicardipine Nifedipine Nimodipine Verapamil
Triptans	Frovatriptan (for MAM)	Naratriptan Zolmitriptan (for MAM)		
Other agents			Clonazepam (C-) Nabumetone (C-)	Acetazolamide Cyclandelate Picotamide

Selected preventive therapies for migraine

Class	Specific treatments	Reported mean monthly therapeutic effects	Common or serious adverse effects
Tricyclic antidepressants	Amitriptyline, nortriptyline	Data not available	Dry mouth, sedation, weight gain, urinary retention
Beta-blockers	Metoprolol, nadolol, propranolol, timolol	Headache days, -0.4 (meta-analysis for propanolol)	Hypotension, exercise intolerance, sexual dysfunction
Anticonvulsant agent	Topiramate	Episodic migraine days, -1.1 to -1.3; chronic migraine days, -1.5 to -3.3	Paresthesia, weight loss, cognitive dysfunction, depression
Anticonvulsant agent	Divalproex sodium	Migraine days, -2.6; migraine attacks, -0.6 to 3.4	Tremor, weight gain, hair loss, fetal neural tube defect
Angiotensin Receptor Blocker	Candesartan	Headache days, -0.7 to -1.7 migraine days, -0.6 to 1.1	Dizziness
Calcium blocker	Flunarizine	Migraine attacks, -1.2 to -1.8	Sedation, weight gain, depression
Non-prescriptive therapies	CoQ10, magnesium, melatonin, petasites, riboflavin	Migraine attacks, -1.1 with CoQ10, -0.5 to -0.9 with magnesium; -0.8 with petasites or riboflavin	Diarrhea with magnesium
Botulinum toxin	Onabotulinumtoxin A	Chronic migraine headache days, -1.4 to -2.3; migraine days, -1.5 to -2.4	Muscle weakness, headache
CGRP antibody	Eptinezumab, erenumab, fremanezumab, galcanezumab	Episodic migraine headache days, -1.0 to -1.2; high frequency episodic migraine days, -2.8; days with chronic migraine headache, -2.5; hr with chronic migraine headache, -30.4	Injection-reactions; safety studies are on-going

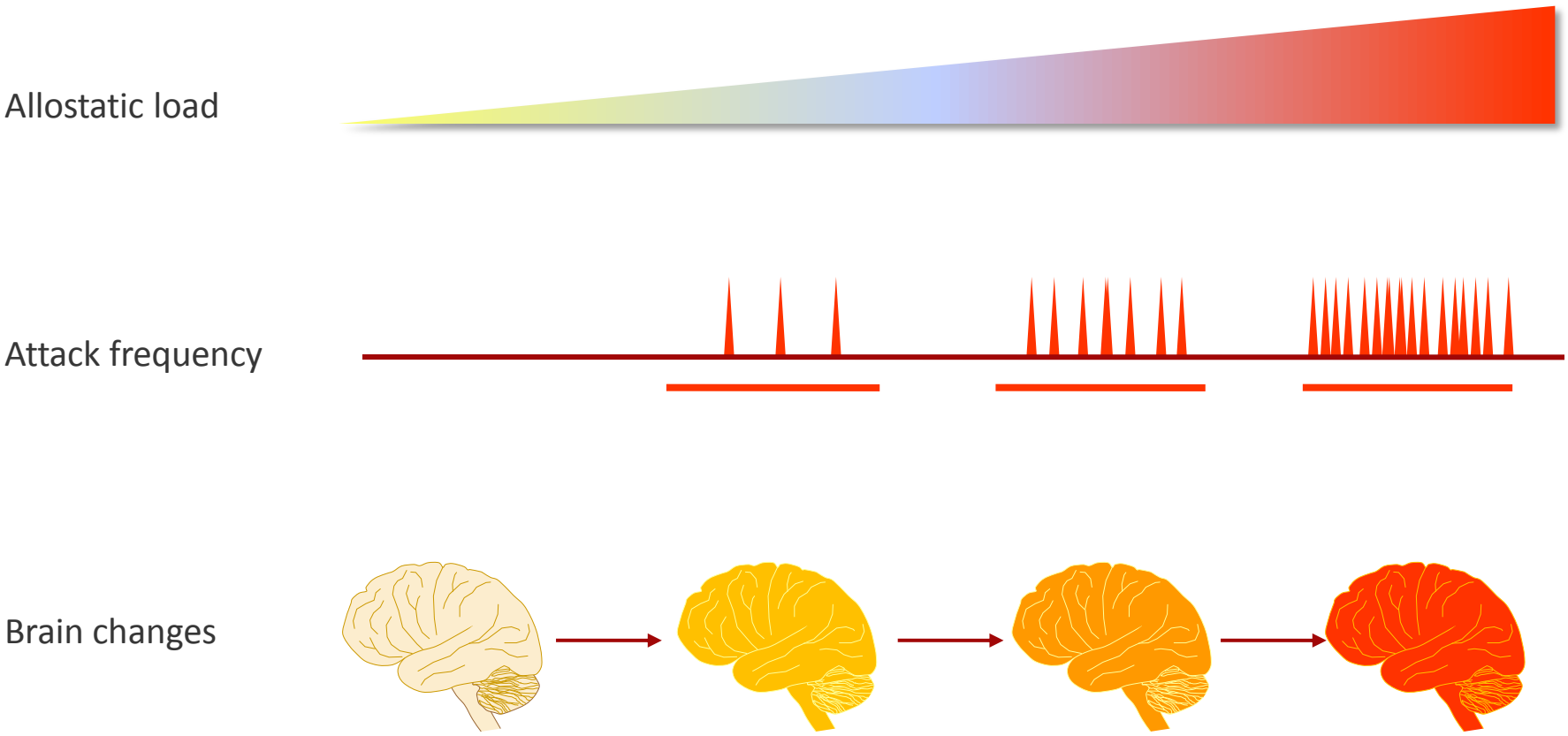
Charles A. **N Engl J Med** 2017; 377:553-561

Preventive medication for comorbid conditions

Comorbid Condition	Medication
Hypertension	Beta blockers
Angina	Beta blockers
Stress	Beta blockers
Depression	Tricyclic antidepressants, SSRIs
Overweight	Topiramate
Underweight	Tricyclic antidepressants
Epilepsy	Valproic acid, topiramate
Mania	Valproic acid

Refractory chronic migraine

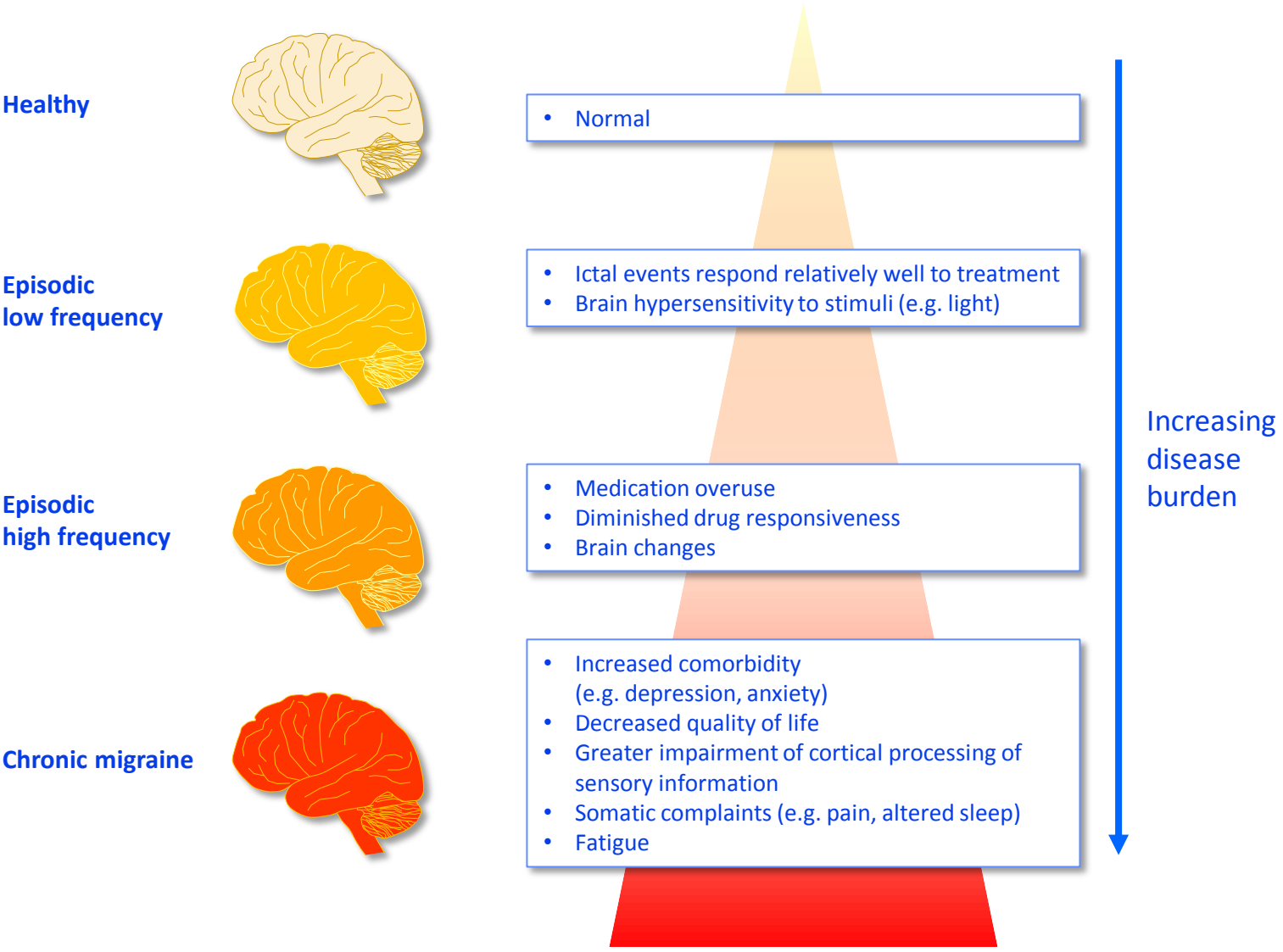
Migraine frequency and allostatic load



Migraines may be episodic or chronic based on the number of headache days per month. With increasing frequency, there are increasing effects on brain function and structure. These changes reflect increasing allostatic load

Borsook et al. Neuron 2012;73:219–234

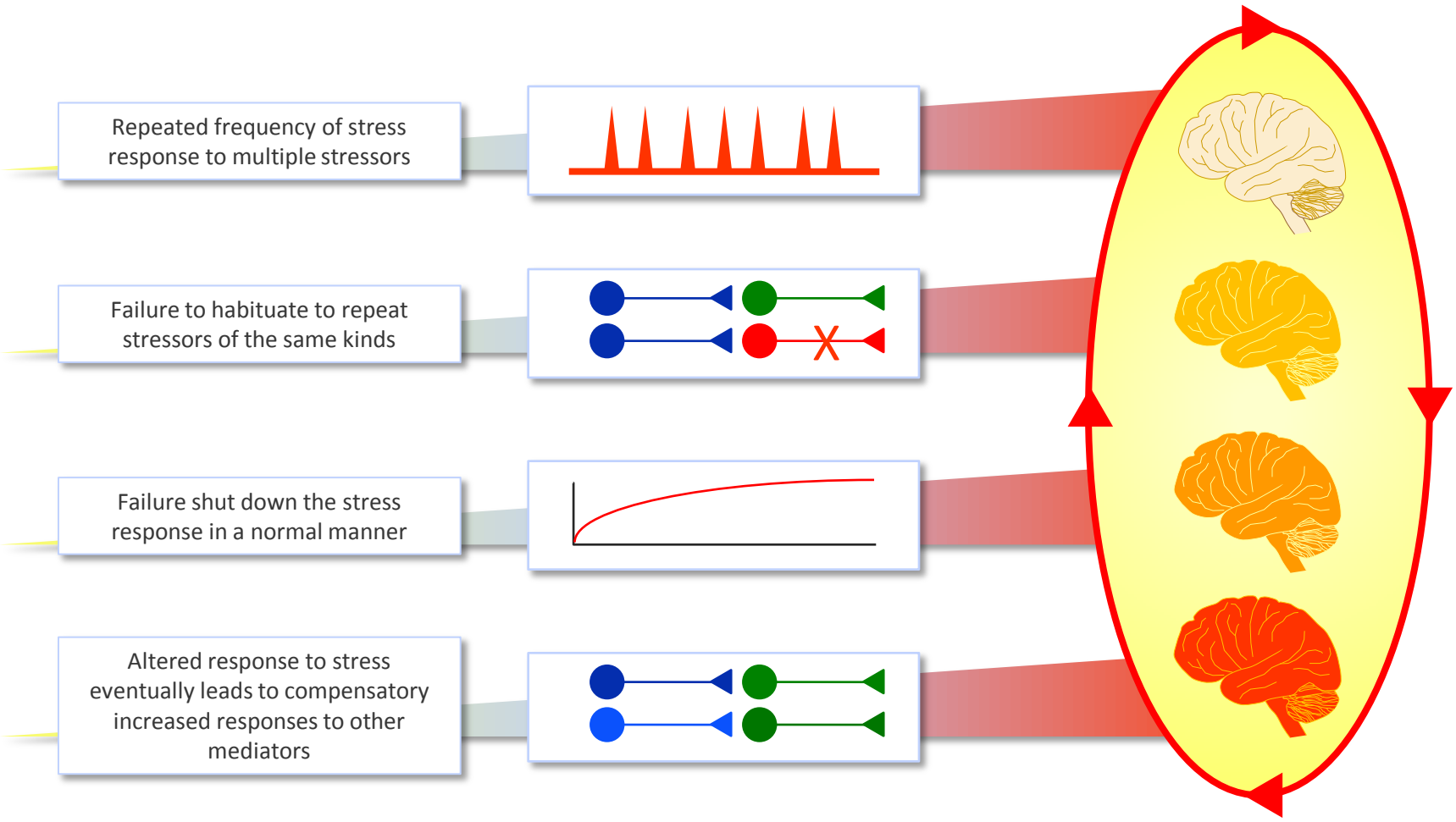
Migraine disease state and increasing allostatic load



The figure shows examples of increased burden of disease as a consequence of increased migraine frequency. The changes affect both brain and body processes. Disease burden may be defined as the personal cost of migraine in terms of medical, economic, social, financial, personal, or family costs.

Borsook et al. Neuron 2012;73:219–234

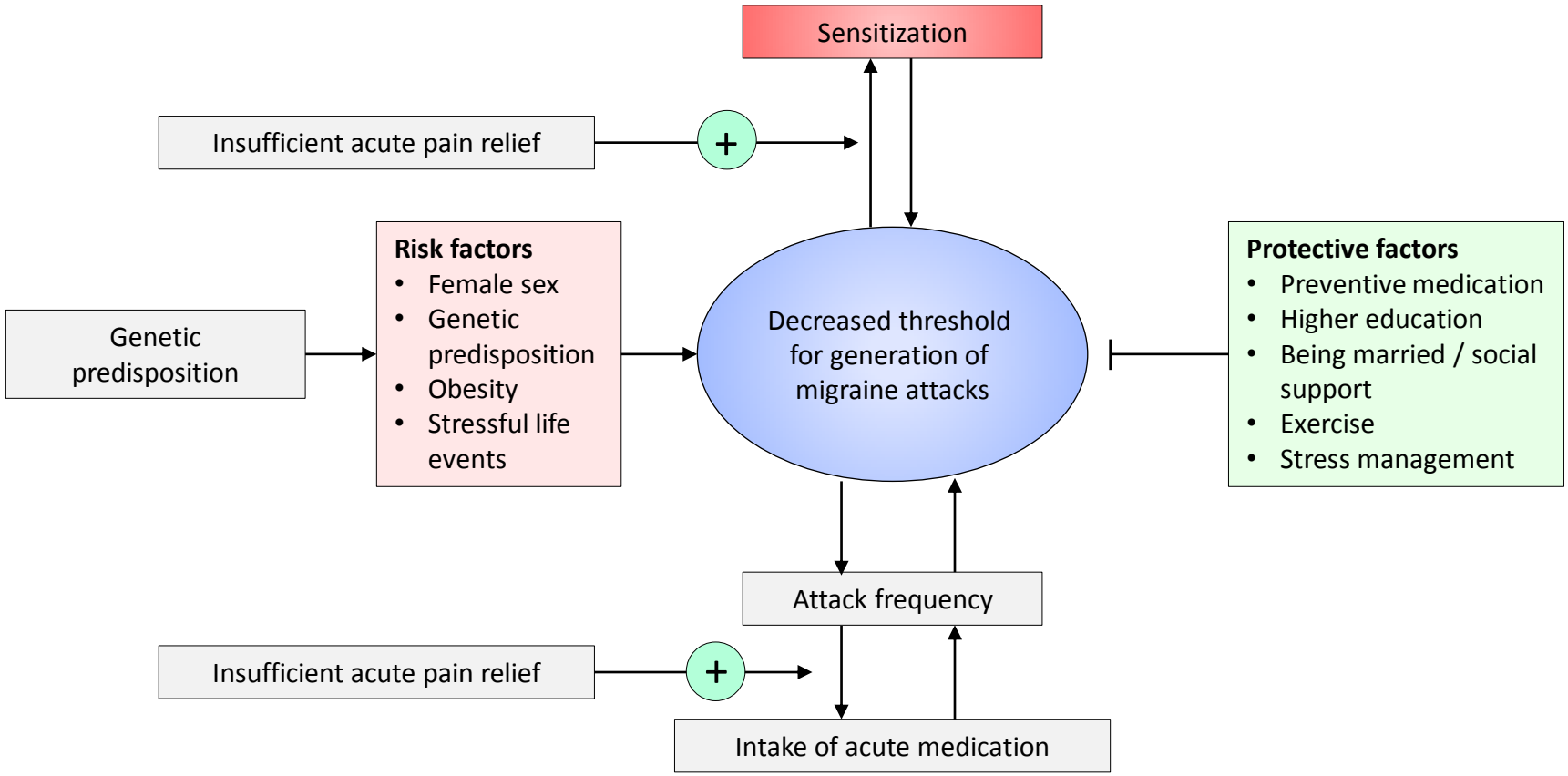
Four major processes contribute to allostatic load in migraine



Four major processes contribute to allostatic load in migraine: (1) migraine attacks produce repeated stress; (2) the brain fails to habituate to stimuli; (3) dysregulation of normal adaptive responses, in which components of the stress response may fail to shut down normally, occurs; and (4) compensatory increased responses may occur (e.g., photophobia) during ictal and interictal states. All of these processes act on the brain system to increase the allostatic load. The process is further aggravated by the bidirectional effects of migraine on systemic processes that contribute to alterations in brain processing.

Borsook et al. Neuron 2012;73:219–234

Multiple factors contribute to migraine chronification



Genetic and nongenetic risk factors contribute to the threshold for the generation of migraine attack. Insufficient acute pain relief leads to senstization, which can further lower migraine attack threshold. Increased migraine attack frequency itself also lowers attack threshold; moreover, it increases the intake of acute medication, which can decrease the efficacy of acute pain relief and further predispose to migraine chronification. By contrast, preventive medication and protective factors related to behaviour and lifestyle heighten the threshold and thereby inhibit migraine chronification.

May and Schulte. **Nature Reviews | Neurology** 2016;12:455-64

Intractable migraine (Goadsby 2006)

Primary Diagnosis	ICHD-II migraine or chronic migraine
Refractory	Failed an adequate trial of regulatory approved and conventional treatments according to local national guidelines In migraine, failure of at least 4 classes, where 3 should come from 1 to 4 1. Beta-blockers 2. Anticonvulsants 3. Calcium channel blockers 4. Tricylic antidepressants 5. Other treatments with at least 1 positive randomized controlled trial 6. Nonsteroidal anti-inflammatory drugs 7. Metabolic enhancers, such as vitamin B2 or coenzyme Q10
Adequate trial	Appropriate dose, appropriate length of time Consideration of medication overuse
Failed	No therapeutic or unsatisfactory effect Intolerable side effects Contraindications to use

Refractory Headache Special Interest Section (RHSIS) criteria (AHS 2008)

Primary Diagnosis	ICHD-II migraine or chronic migraine
Refractory	Headaches cause significant interference with function or quality of life despite modification of triggers, lifestyle factors, and adequate trials of acute and preventive medicines with established efficacy Failed adequate trials of preventive medicines, alone or in combination, from at least 2 of 4 drug classes: a. Beta blockers b. Anticonvulsants c. Tricyclics d. Calcium channel blockers Failed adequate trials of abortive medicines from the following classes, unless contraindicated: a. Both a triptan and DHE intranasal or injectable formulation b. Either nonsteroidal anti-inflammatory drugs or combination analgesics
Adequate trial	Period of time during which an appropriate dose of medicine is administered, typically at least 2 months at optimal or maximum-tolerated dose, unless terminated early due to adverse effects
Modifiers	With or without medication overuse, as defined by ICHD-2 With significant disability, as defined by MIDAS ≥11

EHF proposed criteria for refractory chronic migraine

A. ICHD-III β chronic migraine

No medication overuse

B. Prophylactic migraine medications in adequate dosages used for at least 3 months each.

C. Contraindications or No effect of the following preventive medication with at least 3 drugs from the following classes:

- Beta blockers
  - Propranolol up to 240 mg/d
  - Metoprolol up to200mg
  - Atenolol up to100mg
  - Bisoprolol up to10mg
- Anticonvulsants
  - Valproate acid up to 1,5 g/d
  - Topiramate up to 200 mg/d
- Tricyclics
  - Amitriptyline up to 150 mg/d
- Others
  - Flunarizine up to 10 mg/d
  - Cardesartan 16 mg/d
- Onabotulinumtoxin A
  - 155 - 195 U according to the PREEMPT protocol

D. Adequate treatment of psychiatric or other comorbidities by multidisciplinary team, if available.

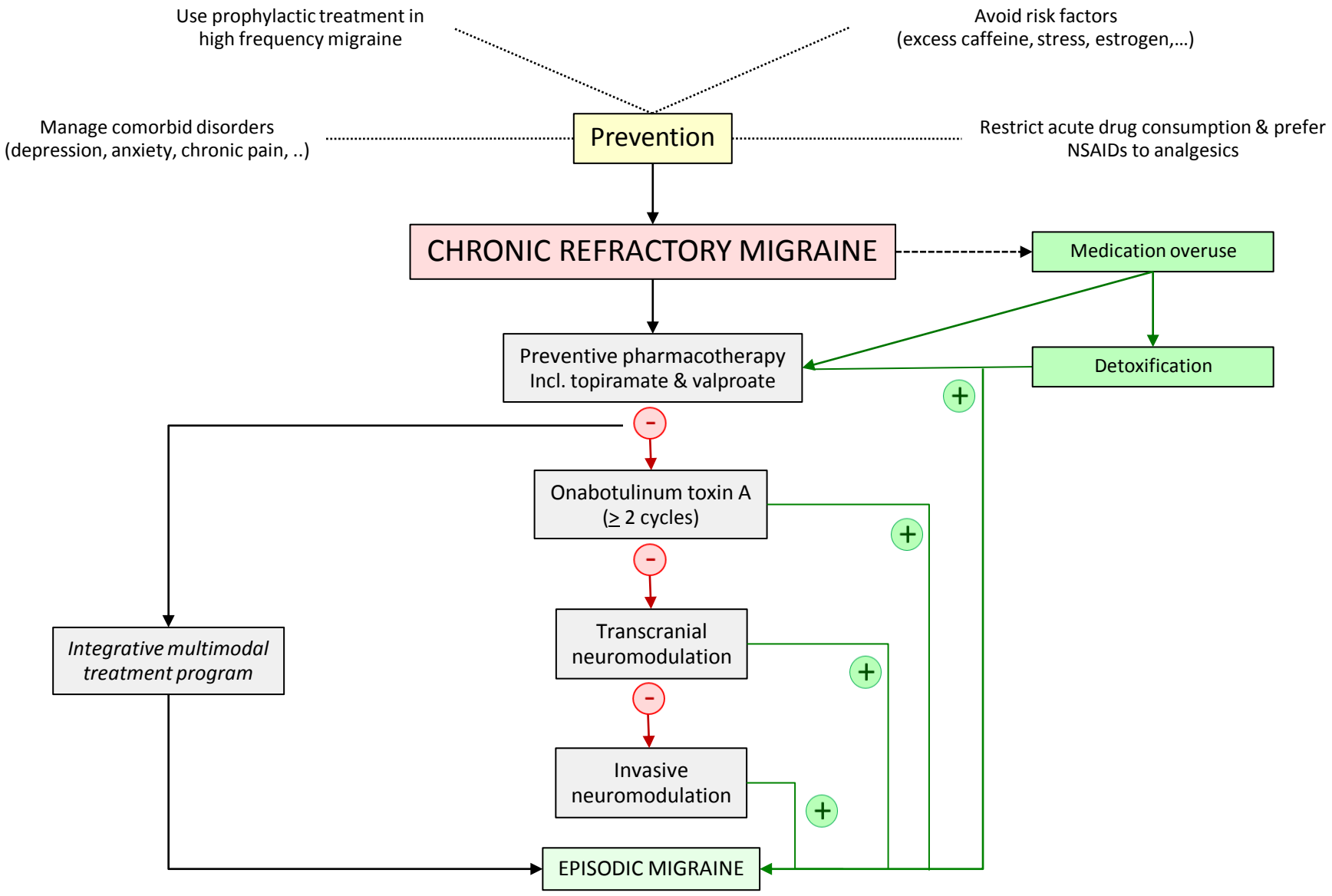
The Journal of Headache and Pain 2014;15:47 DOI: 10.1186/1129-2377-15-47

Refractory migraine headache severity scale

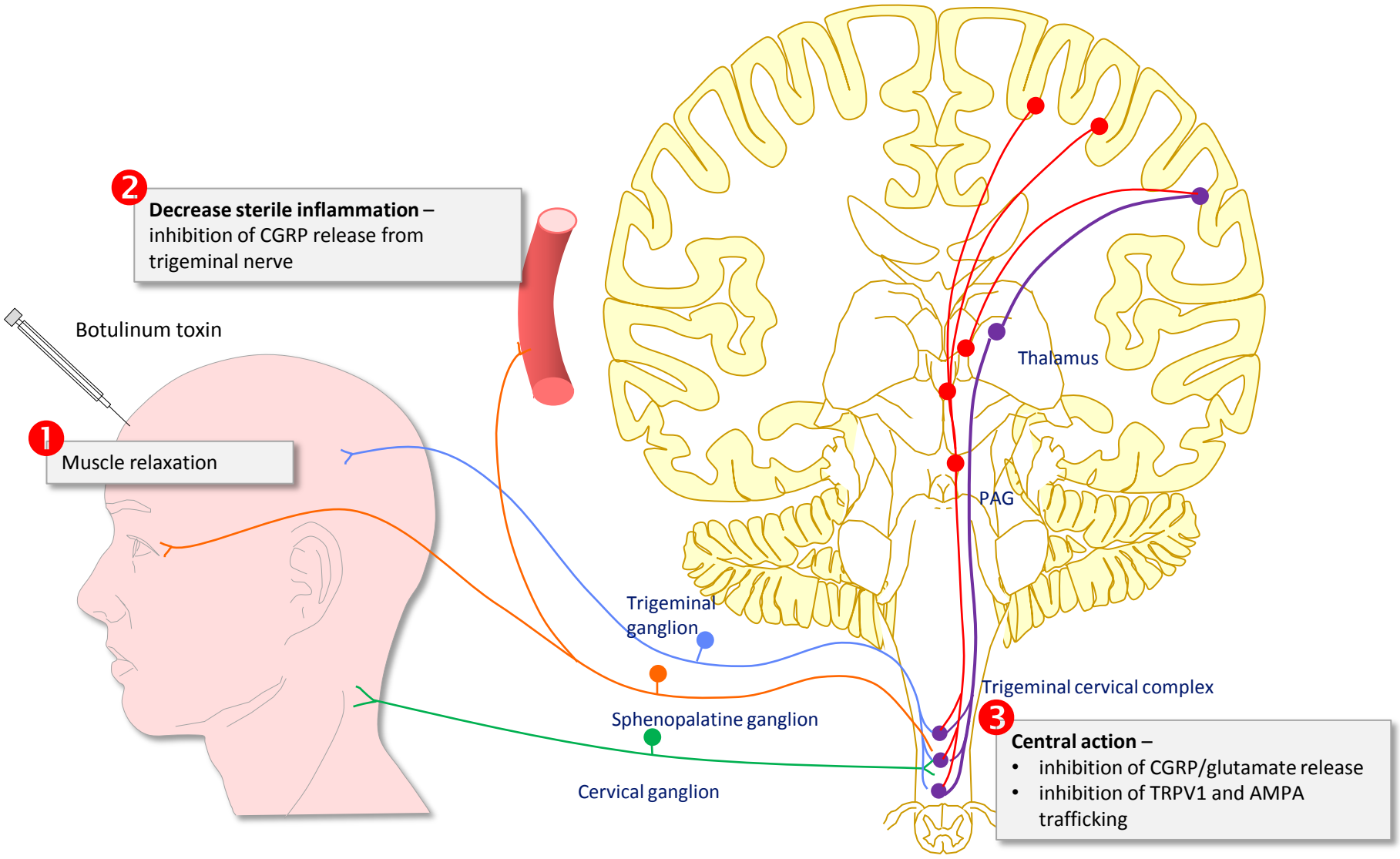
Criteria	Point
Refractory to preventive agents	2
Refractory to abortive agents	2
Duration > 10 years of chronic migraine	1
Headaches per month: 25+ days (on average)	1
Have 2 medical conditions: • Irritable bowel syndromes • Fibromyalgia • Temporal mandibular dysfunction • Chronic pelvic pain • Painful bladder syndrome • Chronic fatigue	1
Psychiatric comorbidities: • Severe axis I (affective disorder) or • Severe axis II (personality disorder)	1
Disability (work and/or home)	1
Medication overuse headache	1

2-4 points, mild; 5-7 points, moderate; 8-10 points, severe

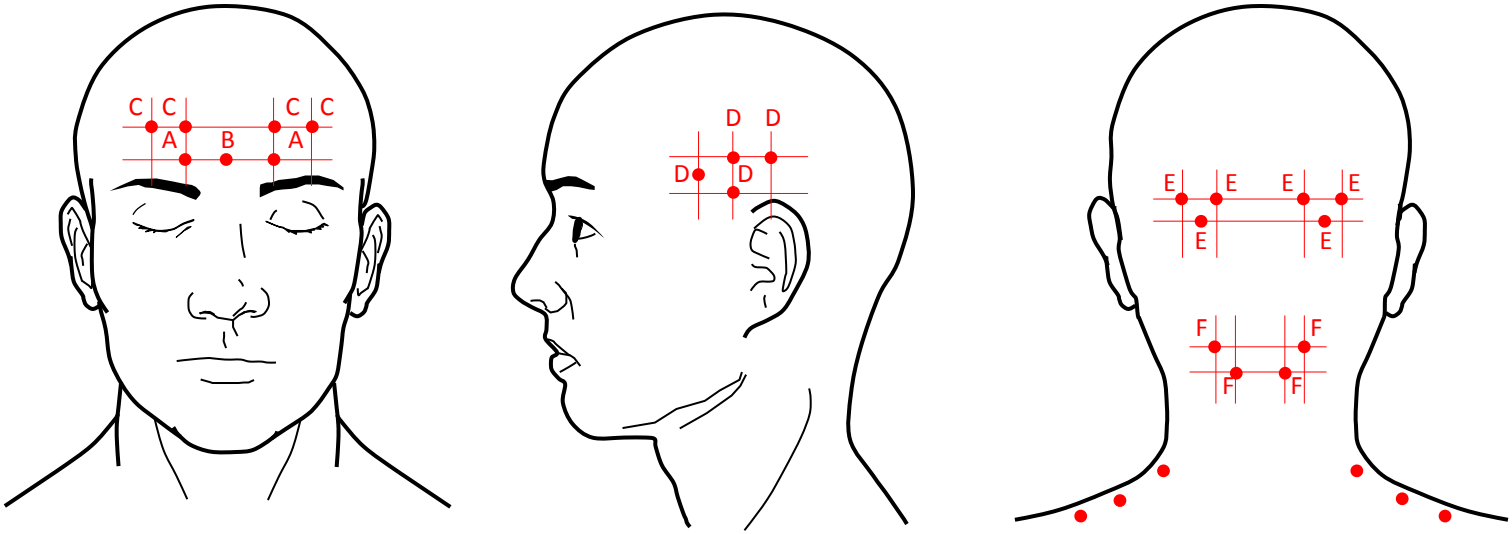
Guideline for management of refractory chronic migraine



Speculative mechanism(s) of botulinum toxin in migraine



Recommended injection sites for chronic migraine



A. Corrugator 5 U each side
B. Procerus 5 U (one site)
C. Frontalis 10 U each side

D. Temporalis 20 U each side

E. Occipitalis 10 U each side
F. Cervical paaspinal 10 U each side
G. Trapezius 15 U each side

Recommended injection sites for chronic migraine using fixed-site, fixed-dose injection site locations.

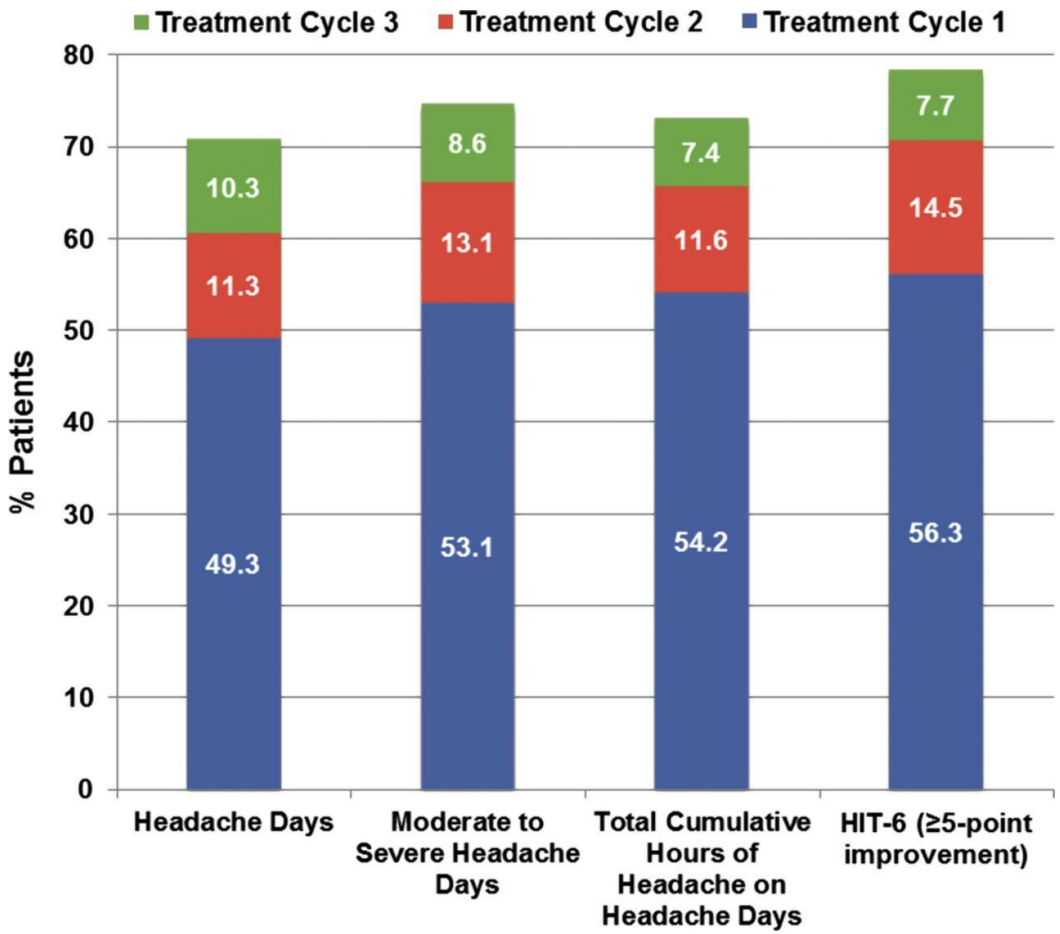
Blumenfeld et al. **Headache** 2010 ;50:1406–1418

Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) study design

≥50% First-time responders, variable	OnabotulinumtoxinA (n=688)		
	Treatment cycle 1	Treatment cycle 2	Treatment cycle 3
Frequency of headache days, n (%)	339 (49.3)	78 (11.3)	71 (10.3)
95% CI	45.5% to 53.0%	9.0% to 13.7%	8.1% to 12.6%
Frequency of moderate/severe headache days, n (%)	365 (53.1)	90 (13.1)	59 (8.6)
95% CI	49.3% to 56.8%	10.6% to 15.6%	6.5% to 10.7%
Total cumulative hours of headache on headache days, n (%)	373 (54.2)	80 (11.6)	51 (7.4)
95% CI	50.5% to 57.9%	9.2% to 14.0%	5.5% to 9.4%

Silberstein SD, et al. J Neurol Neurosurg Psychiatry 2014;0:1–6. doi:10.1136/jnnp-2013-307149

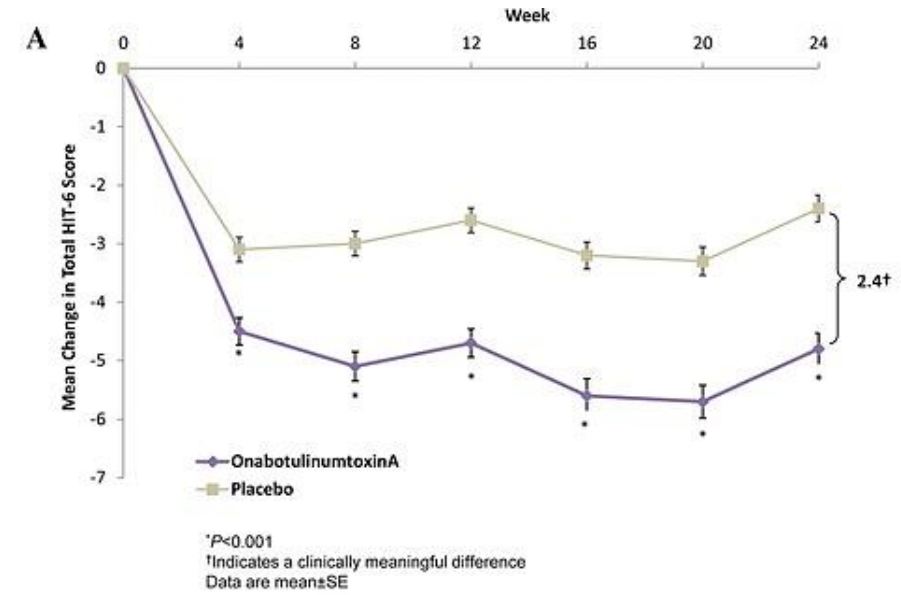
Efficacy of botulinum toxin A in migraine



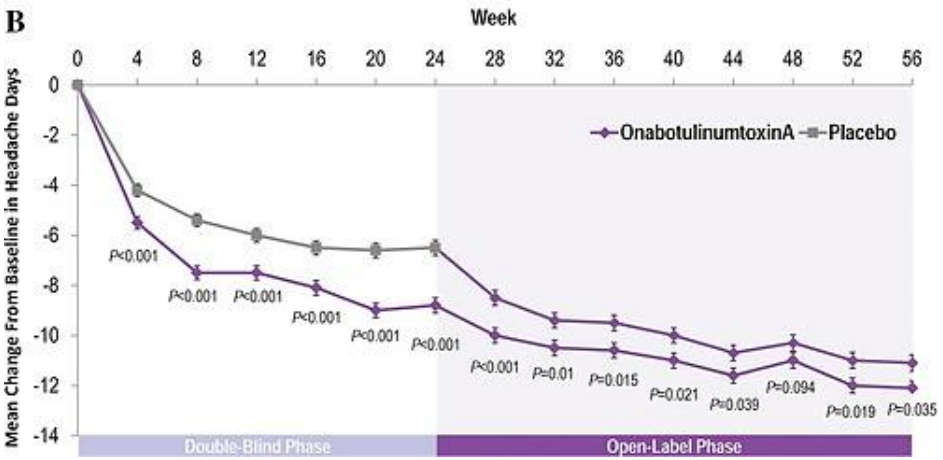
Per cent of first-time responders* with a ≥50% improvement from baseline in treatment cycles 1, 2 and 3 for multiple headache outcome measures (HIT, Headache Impact Test). *First-time responders for a given time point are patients who never responded at any previous time points.

Silberstein SD, et al. J Neurol Neurosurg Psychiatry 2014;0:1–6. doi:10.1136/jnnp-2013-307149

Efficacy of botulinum toxin A in migraine



A) Mean change from baseline in total Headache Impact Test-6 (HIT-6) score with significant reductions in headache impact from weeks 4 through 24 for onabotulinumtoxinA relative to placebo (P < 0.001).



B) Efficacy of onabotulinumtoxinA for CM: primary efficacy parameter in the pooled data from PREEMPT 1 and PREEMPT 2 of the mean change from baseline to each 4-week period through week 56 among patients who completed all five treatment cycles in the frequency of headache days (mean ± standard error).

Lipton et al. **Neurology** 2011;77:1465-1472.

Outline

- Migraine is underdiagnosed; recurrent headache that is associated with sensitivity to light, nausea, or a reduced ability to function is most likely migraine, regardless of other headache characteristics.
- Management should include establishing an accurate diagnosis, identifying and modifying potential exacerbating factors (including medications), developing a plan for the treatment of acute attacks, and determining whether preventive therapy is warranted.
- Therapies for acute migraine should be taken as early as possible after the onset of a migraine attack.
- Preventive should be considered on the basis of the frequency and severity of attacks, response to medications for acute migraine, and coexisting conditions.
- Recent clinical trials support the efficacy of new therapies targeting calcitonin gene–related peptide (CGRP) for the treatment of acute migraine and for migraine prevention.

THANK YOU

Pharmacological Management in HEADACHE