

Clinical Pearls in Migraine Management

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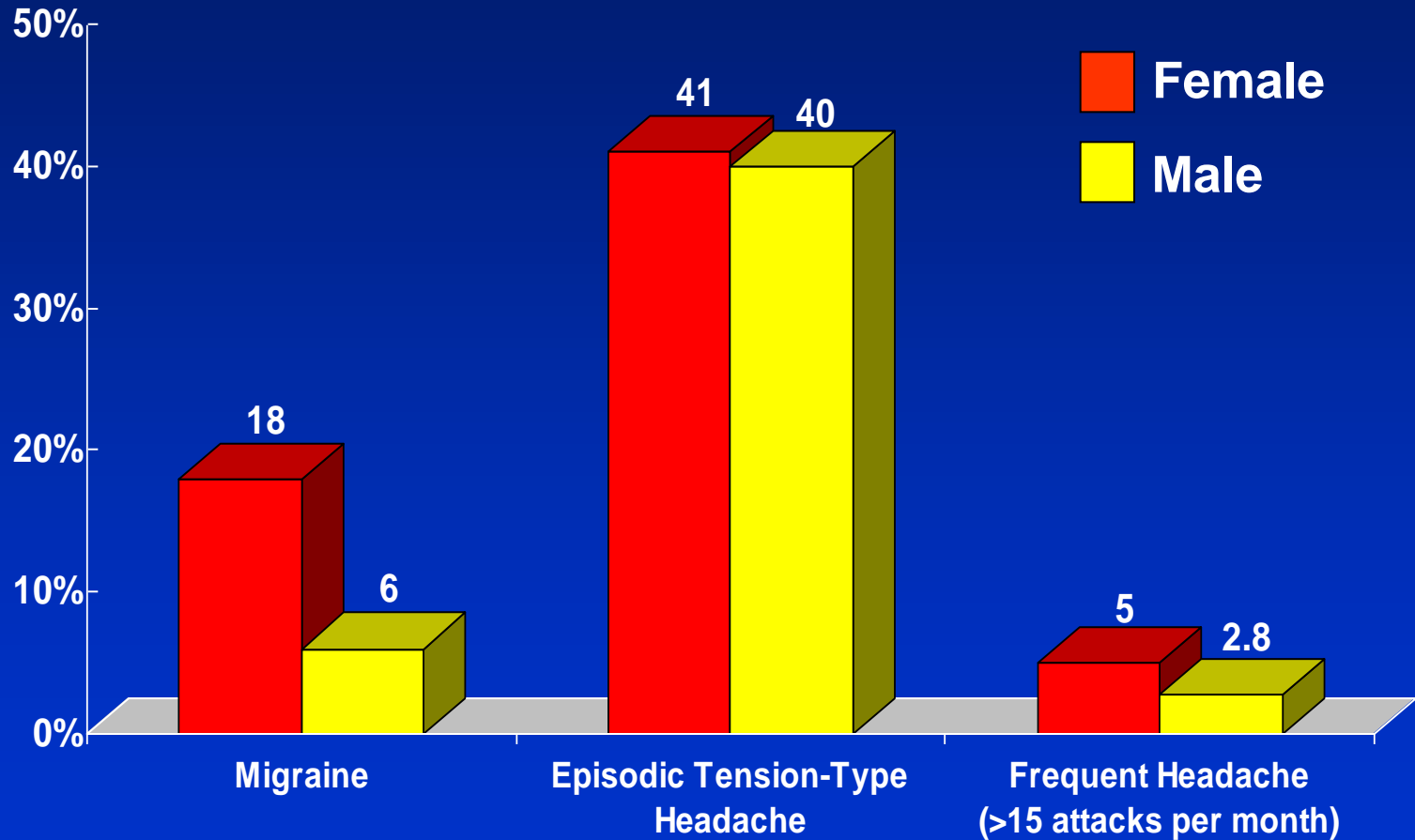


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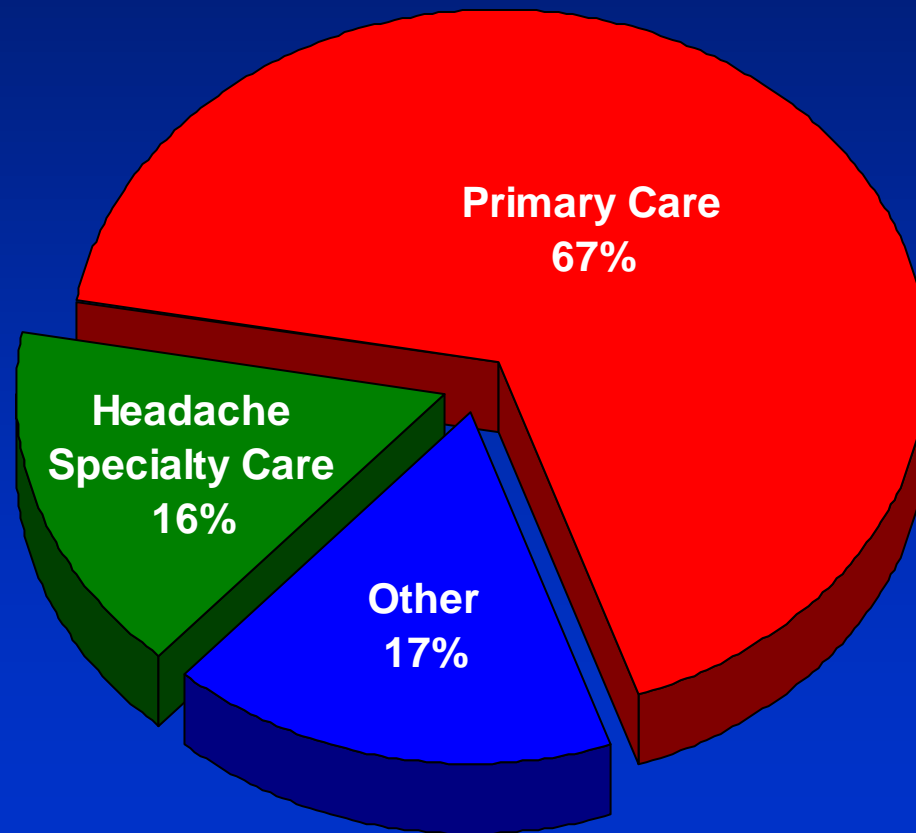
One-year Prevalence of Common Headache Disorders



Lipton RB, Stewart WF. *Neurology*. 1993.
Schwartz BS et al. *JAMA*. 1998.
Scher AI et al. *Headache*. 1998.

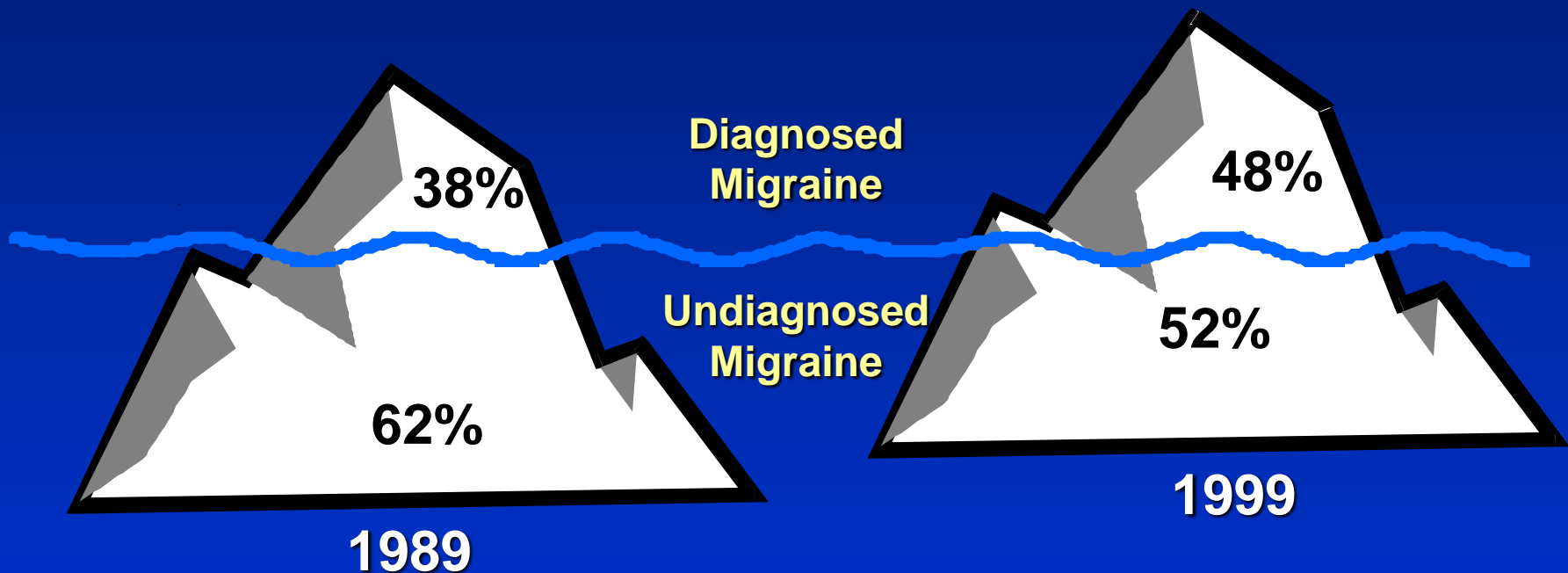


Where Do Migraine Sufferers Seek Medical Care?



Medically Diagnosed Migraine the Tip of the Iceberg

The Migraine Iceberg is Rising



- 14.6 million migraine sufferers remain undiagnosed
- 53% have headache-related disability



Diagnostic Criteria of Migraine (IHS, 2004)

≥ 5 attacks lasting 4-72 hours

≥ 2 of the following 4

Unilateral

Pulsating

Moderate or Severe intensity

Aggravation by routine physical activity (e.g. walking or climbing stairs)

≥ 1 of the following

Nausea and /or vomiting

Photophobia and Phonophobia

Not attributable to another disorder



The Migraine Spectrum

Common types

- Migraine without aura
- Migraine with aura
- Migraine aura without headache

Uncommon types

- Basilar migraine
- Hemiplegic migraine
 - familial (CACNA1A gene, chromosome 19)
 - Sporadic (ATP1A2 gene on chromosome 1)
- Migrainosus infarction
- Persisting aura without infarction



Three Item Identification of Migraine Screener (ID Migraine)

	Sensitivity	Specificity	Positive Predict Value
Disability (>1 d in past 3 m.)	0.87	0.52	
Nausea	0.60	0.81	
Photophobia	0.75	0.74	
<hr/>			
Dx. of Migraine	0.81	0.75	0.93



Migraine

Characteristics (2/4)

- Unilateral (40% bilateral or generalized)
- Throbbing (50% non-pulsating)
- Moderate-severe intensity (~20% mild)
- Pain worsened by exertion (>95%)

Associated symptoms (1/2)

- Nausea (86% – 95%)
- Vomiting (47% – 62%)
- Photophobia (82% – 95%)
- phonophobia (61% – 98%)



Migraine vs. Tension Headache (IHS, 2004)

Migraine

≥ 5 attacks lasting 4-72 hours

≥ 2 of the following 4

Unilateral

Pulsating

Moderate or Severe intensity

Aggravation by routine physical activity

≥ 1 of the following

Nausea and /or vomiting

Photophobia and Phonophobia

Not attributable to another disorder

Tension

≥ 10 attacks lasting 30 min-7 days

≥ 2 of the following 4

Bilateral

Not pulsating

Mild or moderate intensity

Not aggravated by routine physical activity

Both of the following

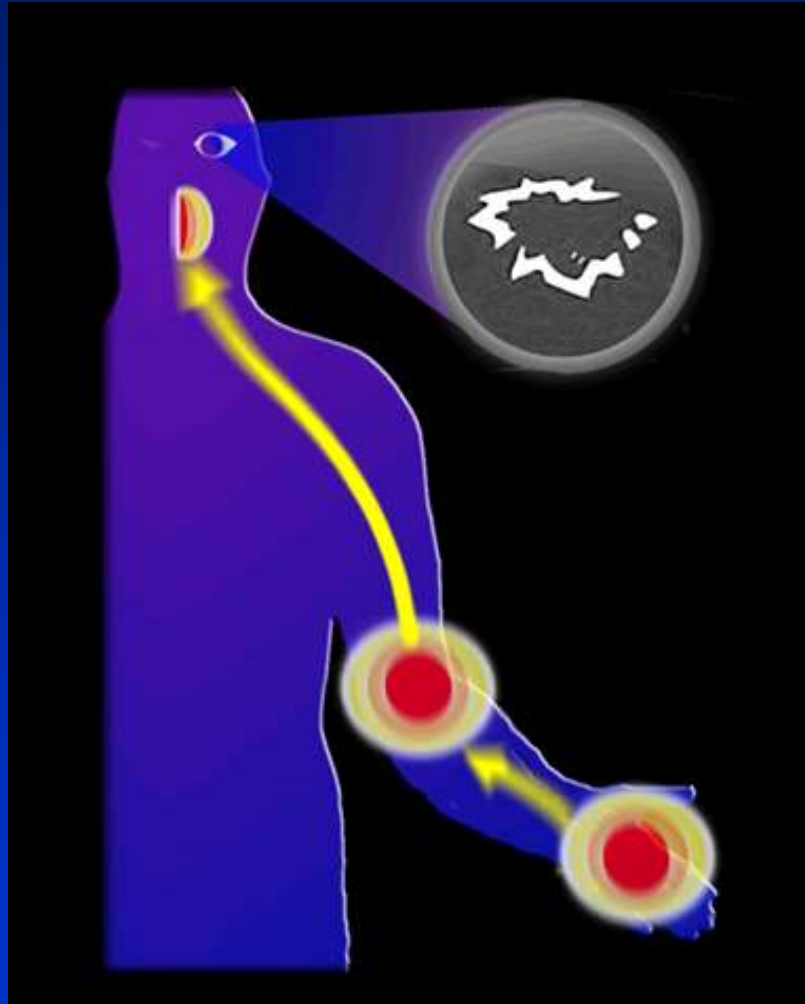
No nausea or vomiting

No more than one of photophobia or phonophobia

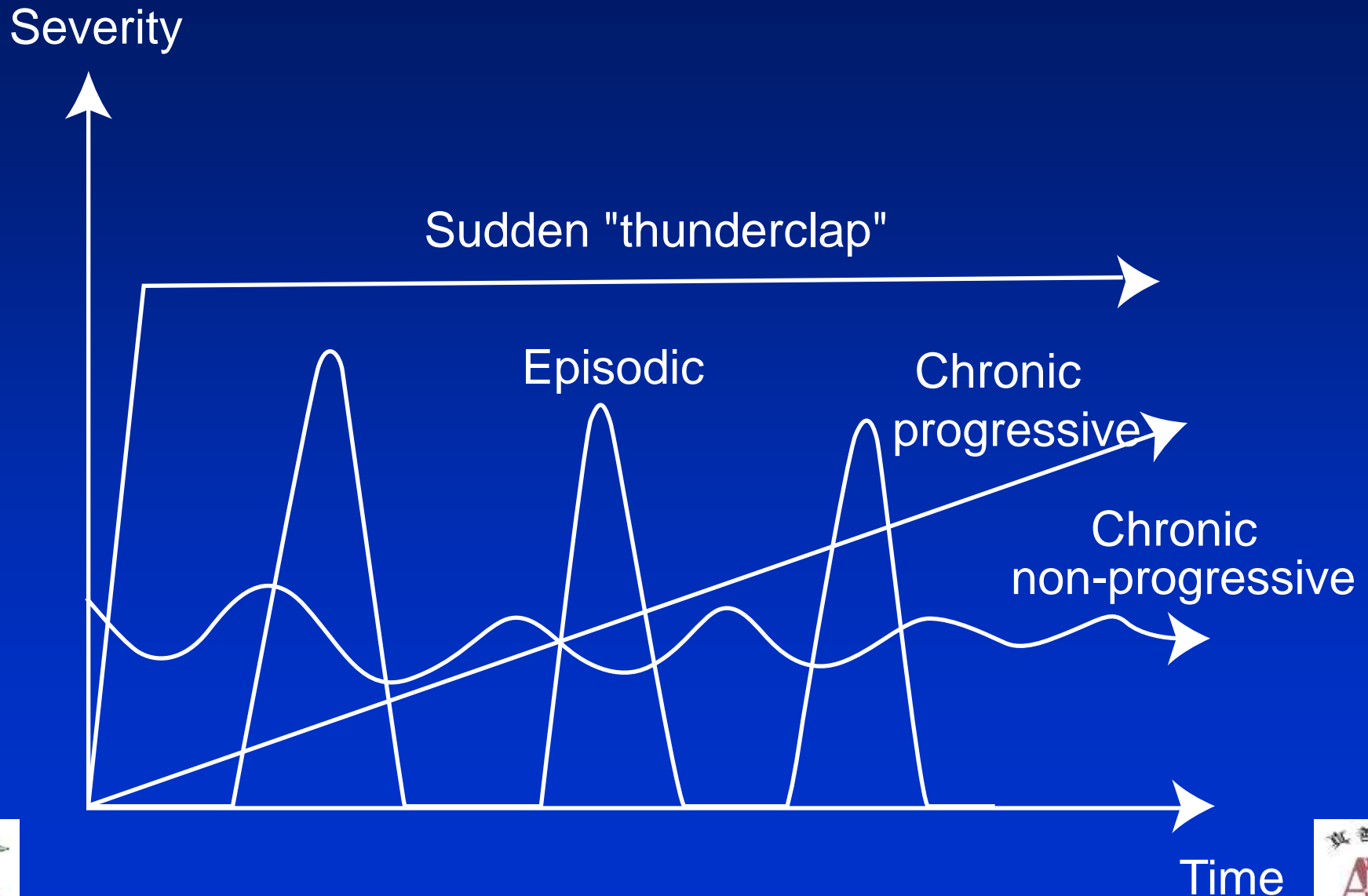
Not attributable to another disorder



Migraine Aura



Common Headache Patterns



Courtesy from David Rothner, MD



Worrisome Headache

Systemic symptoms (fever, weight loss) or Secondary risk factors (HIV, systemic cancer)

Neurologic symptoms or abnormal signs (confusion, impaired alertness, or consciousness)

Onset: sudden, abrupt

Older: new onset and progressive headache, especially in middle-age > 50 (giant cell arteritis)

Previous headache history: first headache or different (change in attack frequency, severity, or clinical features)



Neuroimaging Non-acute Headache / Normal Neurological Examination

Headache Type (# Studies)	n	Significant Abnormality	Prevalence (%)
Migraine (11)	1086	2	0.18
TTH (2)	83	0	0.0
Unspecified (10)	2788	49	1.2



Diagnosis Testing

CT and MRI

- In patients with recurrent migraine, neither CT nor MRI is warranted except in cases where:
 - Recent substantial change in headache pattern
 - History of seizures
 - Focal neurological symptoms or signs
- Role of CT or MRI in patients with non-migraine headache is unclear
- Consensus expert opinion
 - MRI is more sensitive



Disorders Not Excluded By Normal CT

Vascular

- Dural venous sinus thrombosis
- Arterial dissection
- CNS vasculitis
- Temporal arteritis

Infectious

- Encephalitis
- Meningitis
- Sinusitis (Sphenoid)

Tumor

- Posterior fossa lesion (tumor, Chiari malformation)
- Infiltrative CNS glioma
- Pituitary tumor/apoplexy
- Leptomeningeal cancer

Other

- Posterior fossa lesion (tumor, Chiari malformation)
- Low-pressure headache syndrome (CSF leak)
- Isodense subdural hematomas

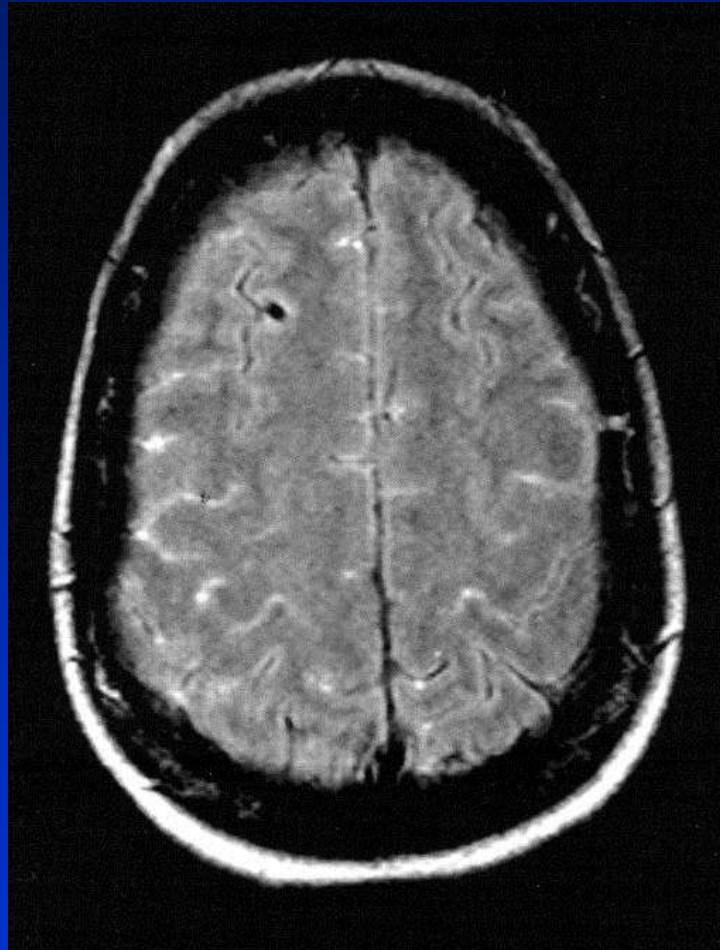


Lumbar Puncture

- The first unusually severe headache
- Thunderclap headache with negative CT head
- Subacute progressive headache
- Headache associated with fever, confusion, meningismus or seizures
- High or low CSF pressure suspected (even if papilledema is absent)



Acute Subarachnoid Hemorrhage



Silberstein SD et al. *Headache in Clinical Practice*. 2002.



Sensitivity of CT Scan in SAH

Time After Headache Onset	Probability (%)
Day 0	95
Day 3 *	80
1 Week	50
2 Weeks	30
3 Weeks	~ 0

Van Gijn J, van Dongen KT. *Neuroradiology*. 1982.
Kassel NF et al. *J Neurosurg*. 1990.
Silberstein SD. *Headache in Primary Care*. 1999



Migraine Triggers

Physical exertion

Diet

Hormonal changes

Head trauma

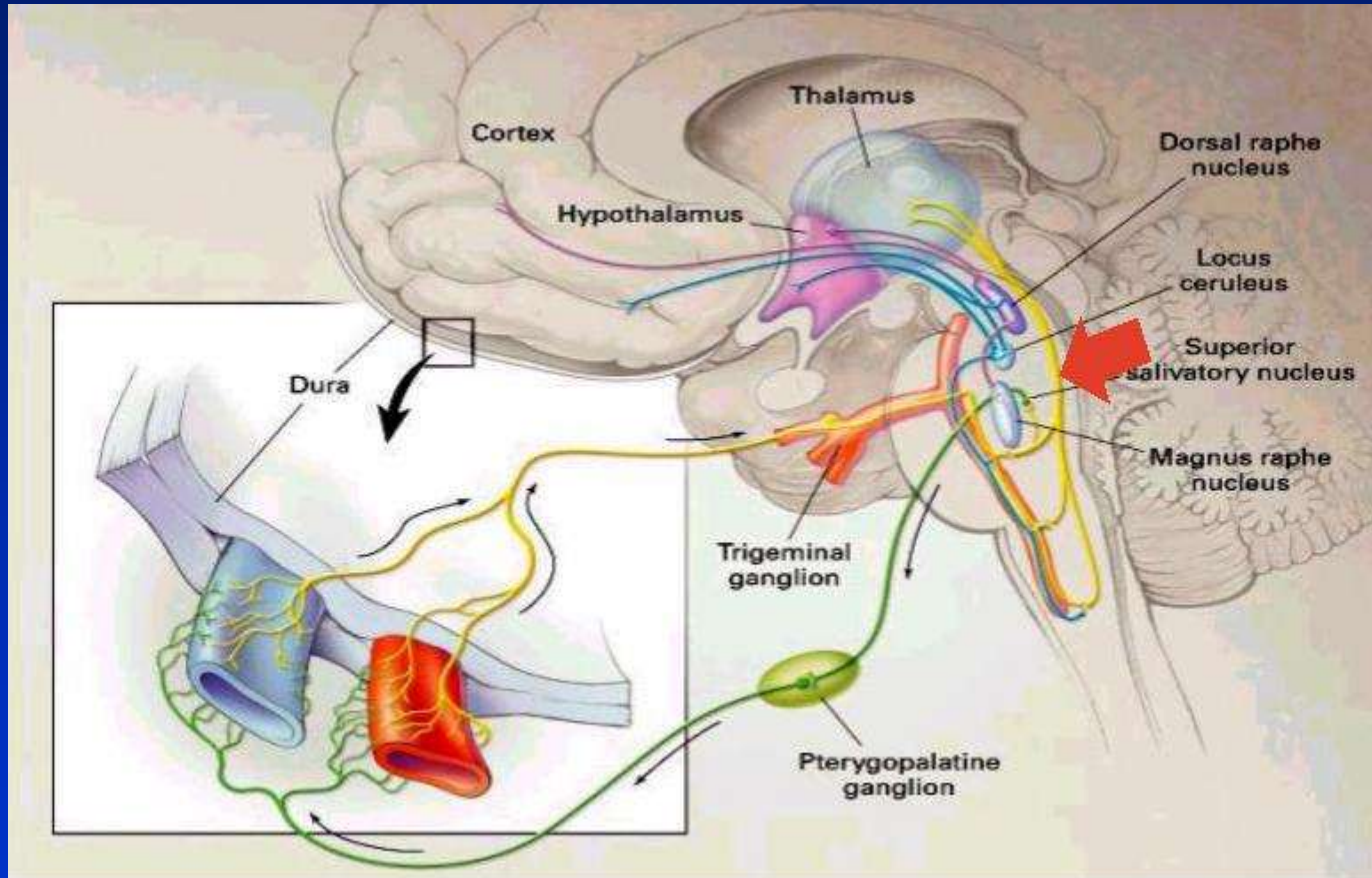
Stress and anxiety

Sleep deprivation or excess

Environmental factors



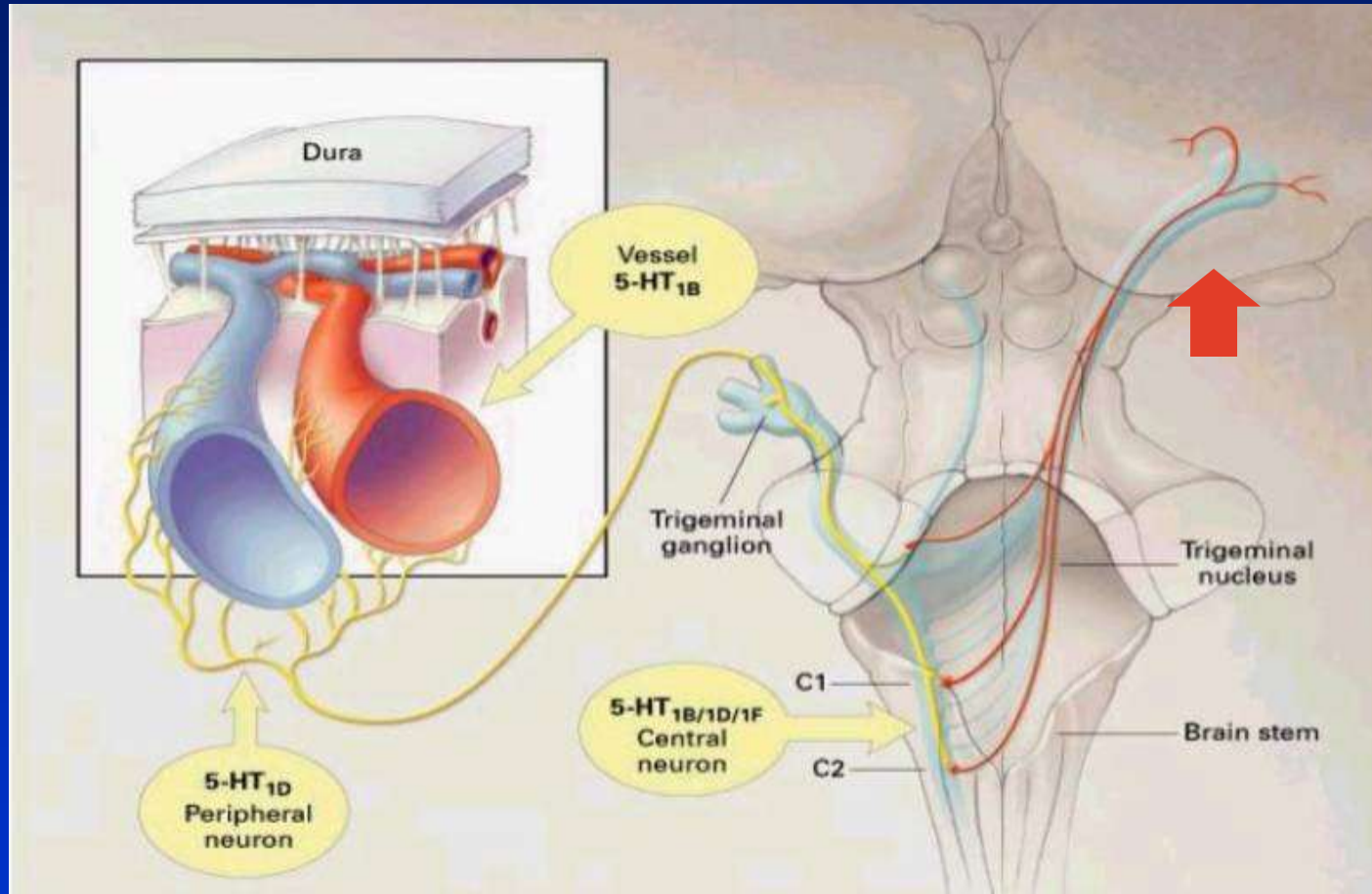
Pathophysiology of Migraine



Goadsby, PJ, et al. *New England Journal of Medicine*. 2002.



Central Neural Processing: Targets For Acute Treatments



Goadsby, PJ. *New England Journal of Medicine*. 2002.



Clinical Phenomenon of Central Sensitization in Migraine Patients

- 1) 75% migraine patient develop allodynia
- 2) Onset: 1 hr, ipsilateral head, mediated by 2nd order neuron (TNC)
- 3) At 2 hr: contralateral head and extremities, mediated by 3rd order neuron (medial thalamus)
- 4) Max: 2-4 hr after headache onset
- 5) Allodynia can last up to 2 days



Burstein R, et al. Brain. 2000.

Personal communication with Dr. Burstein.



Clinical Application of Central Sensitization in Migraine Treatment

- **Early use of triptan:**
 - Use triptan 5-20 min within headache onset, to prevent the development of allodynia.
- **Predictive:**
 - **Migraine with allodynia:**
 - 88% remains pain at 2h after the triptan use
 - Associated with higher migraine recurrence
 - **Migraine w/o allodynia:**
 - 93% pain free at 2 hr after the triptan use



Allodynia and Timing of Triptan Therapy

	With Cutaneous Allodynia at the time of treatment	Without Cutaneous Allodynia at the time of treatment
	32 Attacks	32 Attacks
Aborted by Triptans, with sustained pain-free response	2 (6%)	30 (94%)
Clinical Implication	Treat earlier (5-20 minutes after H/A onset) before allodynia (central sensitization develops)	Treat at any time during the attacks

Burstein R et al. AHS meeting, Hawaii, 2003.

Silberstein SD, Medscape, 2005.

Burstein R. et al. Brain 2000.



Comparison of Triptans: Pharmacokinetic Characteristics

Variable	Sumatriptan	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Zolmitriptan
Half-life (hr)	2.0	3.5	5.0	25.0	5.0-6.3	2.0	3.0
Time to maximal concentration (hr)							
During attacks	2.5	2.0-3.0	2.8	3.0	---	1.0	4.0
At other times	2.0	1.4-3.8	1.4-1.8	3.0	2.0-3.0	1.0	1.8-2.5
Oral bioavailability (%)	14	69	50	24-30	63-74	40	40
Metabolism and excretion							
Primary route	MAO	CYP450 and MAO	CYP3A4	Renal, 50%	Renal, 70%	MAO	CYP450
Secondary route	---	---	---	---	CYP450	---	MAO

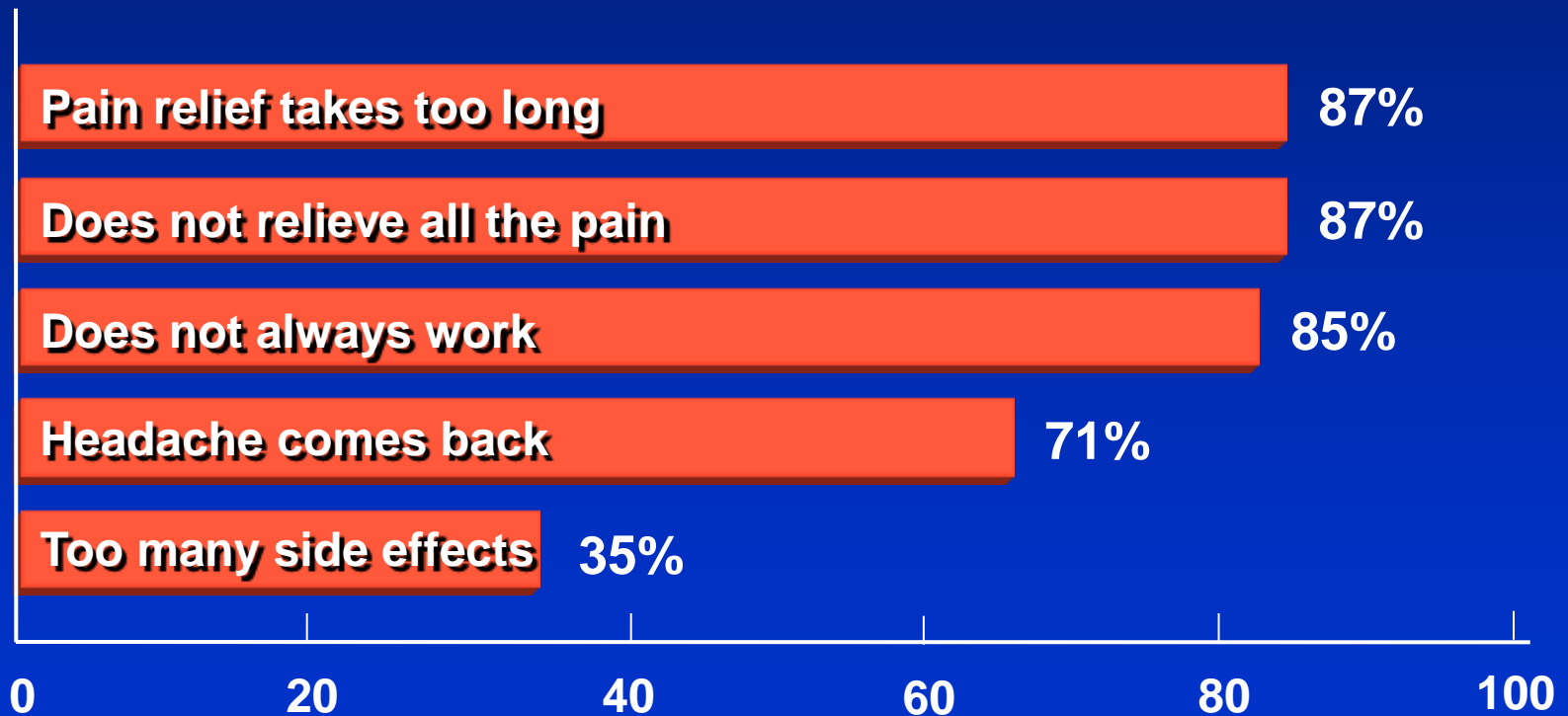
Data are derived from multiple studies. MAO denotes monoamine oxidase, CYP450 cytochrome P450, and CYP3A4 the 3A4 isoform of cytochrome P450.



Under-treatment of Migraine

Only **29%** of migraine sufferers in the US are very satisfied with their usual acute treatment

Reasons for Dissatisfaction



Lipton RB, Stewart WF. Headache. 1999.



Approach to Difficult Headache Problems

Problem

Strategy

- | | |
|---|---|
| <ul style="list-style-type: none">• Lack of response | Treat earlier, increase dose, add metoclopramide or NSAID, change formulation or triptan. Add preventive. |
| <ul style="list-style-type: none">• Headache recurrence | Treat earlier, add NSAID, increase dose, change triptans (consider naratriptan or frovatriptan), or switch to DHE |
| <ul style="list-style-type: none">• Elderly | Use acetaminophen, opioids, atypical neuroleptics |
| <ul style="list-style-type: none">• Pregnancy | Use acetaminophen, opioids, flexeril, corticosteroids, riboflavin, nerve block |
| <ul style="list-style-type: none">• Adverse effects | Switch triptans, use a different class of agents altogether |



Summary – Selective Prevention drugs

	Efficacy		Contraindications or Cautions	Indications
	Migraine (1-4 Scale)	CDH (1-3 Scale)		
Amitriptyline	4	3	Urinary retention	Depression, Insomnia
Valproic Acid	4	3	Liver disease	Mood disorders
Topiramate	4	3	Kidney stone	Obesity, Seizure
Propranolol	4	2	Asthma, CHF	Hypertension, Angina
Verapamil	2	2	Hypotension,	Hypertension, Angina Constipation, Basilar migraine
Fluoxetine	2	2	Mania	Depression, OCD
Riboflavin	2	-	-	Fear of drugs
Naproxen	2	-	PUD	Arthritis, Myofacial pain
Baclofen	+	-	Confusion	Muscle spasm, Insomnia
Botox	+	+	Hypersensitivity	Refractory or contraindicated to drugs
Memantine/Namenda	+	+	Hypersensitivity seizure, renal impairment	refractory migraine



Comparison of Migraine Prevention Therapies

Drugs	Size No.	Dose	Frequency Reduction (%)		Responder Rate (%)	
			Drug	Placebo	Drug	Placebo
VPA ¹	176	500mg	38	8	44	21
		1000mg	42	↓	↓	↓
		1500mg	36	↓	↓	↓
TPX ²	480	50mg	31	21	36	23
		100mg	53	↓	54	↓
		200mg	55	↓	52	↓
Elavil ³	72	100mg			55	34
Inderal	80	80mg	38	20	48	24
Timolol ⁴	↓	10mg	43	↓	44	↓
Neurontin ⁵	145	2400mg			36	14

1. Klapper J. Cephalalgia 1997; 2. Silberstein SD et al. Migraine Trust International Research Symposium. London 2002.; 3. Cluch JR et al. Neurology 1976.; 4. Tfelt-Hansen P et al. Acta Neurol Scand. 1984.; 5. Mathew N et al. Headache 2001.



Memantine in the Prevention of refractory migraine

- N= 28, retrospective review
- Refractory migraine (episodic migraine or transformed migraine, failed > 2 trials of preventive therapy)
- 10-20 mg/day for 3 months
- Outcome:
 - Monthly baseline headache days: 21.8 vs. 16.1
 - Days with severe headache pain: 7.8 vs. 3.2
 - Disability score: 54.9 vs. 36.6



BTX – A for Migraine Prevention

(Prospective, Double-blind, Placebo-controlled Studies)

Author(s)	Year	n	Total Dose	Results
Silberstein SD et al	2000	123	25 or 75 U	Significant reduction in migraine frequency.
Brin MF et al	2000	56	Dose variable	Significant reduction in migraine frequency, severity, and duration
Relja MA & Klepac N	2003	32	200 U	Significant reduction in Migraine-related disability and consumption of abortive Medications.
Barrientos N et al	2003	30	50 U	Significant reduction in migraine frequency, number of days with migraine, acute analgesic use.
Diener HC et al	2010	705	155-195 U	Significant reduction in head days, migraine days, frequency of moderate/severe headache, pain medicine and triptan intake

Diener HC et al. Cephalgia. 2010

Ashkenazi A & Silberstein SD. Annu.Rev.Med. 2004; Silberstein SD et al. Headache. 2000;

Brin MF et al. Cephalalgia. 2000; Relja MA & Klepac N. Neurology. 2003;

Barrientos N & Chana P. 12th International Headache Research Seminar. 2003

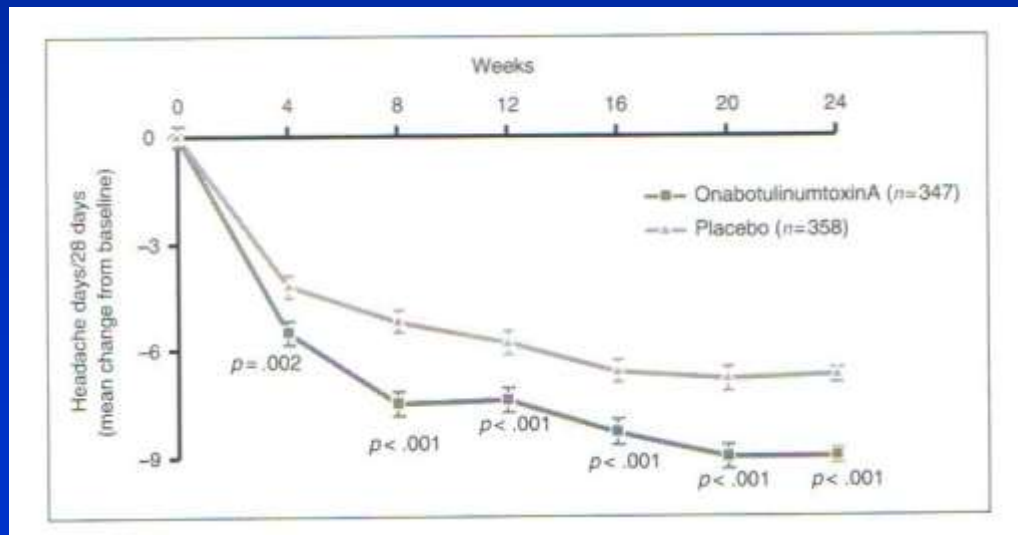
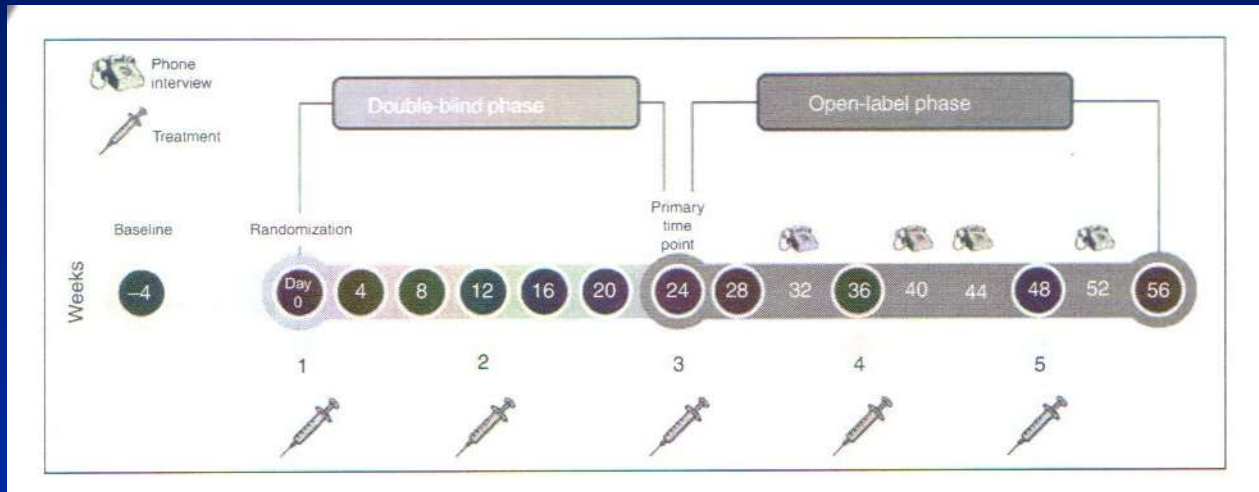


Onabotulinumtoxin A for Treatment of Chronic Migraine

- FDA approved as prophylactic treatment option for adult chronic migraine sufferers in 2010.
- PREEMPT 2 Study (The Phase III Research Evaluating Migraine Prophylaxis Therapy. Diener HC et al. 2010)
 - DB-RC for 24 weeks,
 - Injection of 155-195U on week 0, 12, 24 to corrugator, procerus, frontalis, temporalis, occipitalis, cervical paraspinal and trapezius muscles



Diener HC et al. Cephalalgia 2010



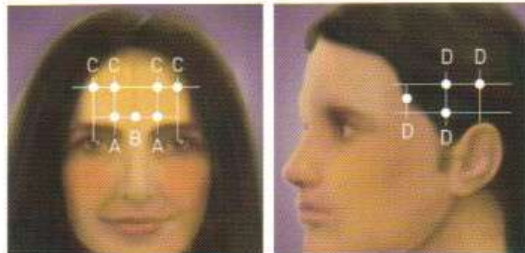
Diener HC et al. Cephalalgia 2010

Endpoint	OnabotulinumtoxinA (n = 347)	Placebo (n = 358)	Mean intergroup difference	p value
Change from baseline in frequency of headache days ^{*†}	-9.0	-6.7	-2.3 (-3.25, -1.31)	<.001
Change from baseline in frequency of migraine days ^{†‡}	-8.7	-6.3	-2.4 (-3.31, -1.36)	<.001
Change from baseline in frequency of moderate/severe headache days [†]	-8.3	-5.8	-2.5 (-3.37, -1.48)	<.001
Change from baseline in cumulative total headache hours on headache days [†]	-132.4	-90.0	-42.4 (-58.23, -21.05)	<.001
% Patients with severe (≥ 60) HIT-6 score ^{†§}	66.3	76.5	-10.2 (-16.9, -3.6)	.003
Change from baseline in frequency of headache episodes [†]	-5.3	-4.6	-0.7 (-1.65, -0.33)	.003
Change from baseline in total HIT-6 scores ^{†§}	-4.9	-2.4	-2.5 (-3.54, -1.55)	<.001
Change from baseline in frequency of acute headache pain medication intakes (all categories)	-9.9	-8.4	-1.5 (-3.77, 0.49)	.132
Change from baseline in frequency of triptan intake	-3.0	-1.7	-1.3 (-2.24, -0.6)	<.001

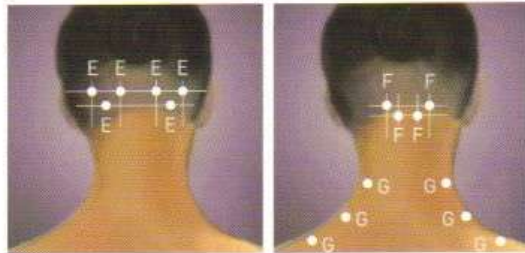
HIT, Headache Impact Test. *Primary efficacy endpoint. †Significant between-group differences favouring onabotulinumtoxinA. ‡International Classification of Headache Disorders, II 1.1 (migraine without aura), 1.2 (migraine with aura), 1.6 (probable migraine) (1). §Scores of 36–49 indicate little or no impact; 50–55, some impact; 56–59, substantial impact; ≥ 60 , severe impact. ||The 95% confidence intervals and p values are adjusted for baseline and for medication overuse stratification.



Botox Injection – Fixed Site , Fixed Dose



A. Corrugator: 5 Units each side
 B. Procerus: 5 Units (1 site)
 C. Frontalis: 10 Units each side
 D. Temporalis: 20 Units each side



E. Occipitalis: 15 Units each side
 F. Cervical paraspinal: 10 Units each side
 G. Trapezius: 15 Units each side

BOTOX® Dosing by Muscle for Chronic Migraine

Head/Neck Area

Head/Neck Area	Recommended Dose (Number of Sites ^a)
Frontalis ^b	20 Units divided in 4 sites
Corrugator ^b	10 Units divided in 2 sites
Procerus	5 Units in 1 site
Occipitalis ^b	30 Units divided in 6 sites
Temporalis ^b	40 Units divided in 8 sites
Trapezius ^b	30 Units divided in 6 sites
Cervical paraspinal muscle group ^b	20 Units divided in 4 sites
Total dose	155 Units divided in 31 sites

^aEach intramuscular (IM) injection site = 0.1 mL = 5 Units BOTOX®

^bDose distributed bilaterally.

