Migraine in the ED/UC – Which Drugs - Why and When

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Disclosure

I have no financial interests or relationships to disclose.

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Learning Objectives

1. Understand the current theories of migraine pathogenesis
2. Correctly and confidently employ any number of proven abortive therapies ideal in the ED/UC
3. Become familiar with the newer agents (gepants and ditans) and why they are not appropriate for ED/UC at this time

3

The Case… CC: 28 yo Female, Hx of Migraine HA's Persistent HA x 4 Days

HPI: Unilateral throbbing headache. Now 10/10. Is nauseated/vomiting
PMHx: migraine HA, approx. "a couple of times a year"
Minimal, transient improvement with Tylenol and Advil
Neg(-)'s: no trauma, no nuchal rigidity, no fever, no neuro deficits, no bleeding disorder, no visual changes. Not maximal intensity at onset
Meds: none other than above. IUD present
SHx: (-) smoke, (-) ETOH, married
FHx: mother (+) hx of migraine, father – (+) DVT
ROS: neg(-) except for those in HPI
PE: VSS, afebrile, 70kg, no abnormal physical findings

Does this patient need a "work up"? Any red flags?

4

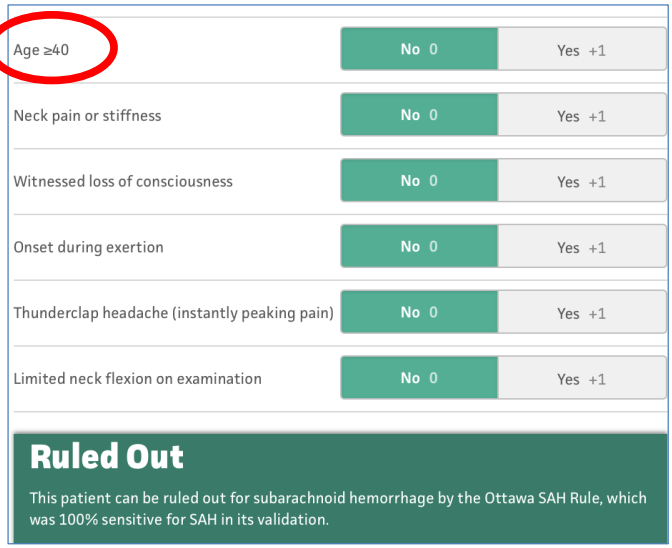
Compare and Contrast Key Features (for Severe Acute HA)

Red flags/Key features

• **Age > 50.**	**vs**	**Age < 50**
• **Sudden onset**	**vs**	**Gradual**
• **Progressive**	**vs**	**No progression**
• **Worse with position/ exertion**	**vs**	**Not present**
• **Predisposition** *(malignancy, meds, immunocompromise)*	**vs**	**Not present**
• **Neck stiffness**	**vs**	**None**
• **Fever**	vs	**None**

5

The Ottawa Subarachnoid Hemorrhage Rule



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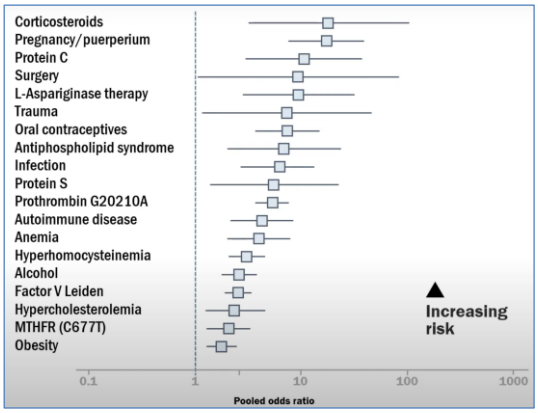
Risk Factors for:

Central venous thrombosis



Idiopathic Intracranial Hypertension

A. Demographic/Risk factors:
   1. Young women: age 20-44, mean 30
   2. Obese

B. Headache: 84-92%: diffuse, -worse in am, Valsalva

C. Vision Changes: common

D. Pulse synchronous tinnitus - 52%

E. Papilledema: 85-95%

F. Lumbar puncture: > 25cm H2O

7

Diagnostic Framework: 3rd International Classification of HA Disorders (2018)

Primary Headache Syndromes (Generally present as chronic and episodic)		Secondary Headache (Generally present as an abrupt single episode and/or new onset in older age)		
Common	**Uncommon**	**Mass-occupying lesions**	**Other CNS pathology**	**Disorders primarily external to the CNS**

Tension-type headache
 	
Migraine headache
• Migraine without aura (a.k.a. "common migraine")
• Migraine with aura
  ▪ Typical aura (a.k.a. "classic migraine")
  ▪ Retinal migraine
  ▪ Hemiplegic migraine
  ▪ Basilar-type migraine (i.e. with brainstem aura)
	Trigeminal autonomic cephalagias
	• Cluster headache
	• Paroxysmal hemicrania
	• Short-lasting unilateral neuralgiform headache attacks (SUNCT)
	
	Primary thunderclap headache
	
	Trigeminal neuralgia*
		Hemorrhage
		• Epidural (EDH)
		• Subdural (SDH)
		• Subarachnoid (SAH)
		• Intraparenchymal (IPH)
		• Intraventricular (IVH)
		
		Tumor
		• Primary brain
		• Metastatic to brain
		
		Brain abscess
			Meningitis/Encephalitis
			
			Venous sinus thrombosis
			
			Arterial dissection
			
			Reversible cerebral vasoconstriction syndromes (RCVS)
			
			Idiopathic intracranial hypertension (a.k.a. pseudotumor cerebri)
			
			Post lumbar puncture headache
			
			Post head trauma
			
			Ischemic stroke/TIA
				Systemic infection (e.g. severe URIs, sinusitis, etc...)
				
				Hypertensive emergency
				
				Acute narrow-angle glaucoma
				
				Vasculitis (e.g. temporal arteritis)
				
				Obstructive sleep apnea
				
				Preeclampsia / eclampsia
				
				Carbon monoxide poisoning
				
				Substance use (e.g. alcohol) or withdrawal (e.g. caffeine)
				
				Medication side effect
				• Nitrates
				• Analgesic overuse

* Headache experts usually classify trigeminal neuralgia as a "painful cranial neuropathy" rather than a true primary headache syndrome

8

Diagnostic Framework: 3rd International Classification of HA Disorders (2018)

Primary Headache Syndromes (Generally present as chronic and episodic)		Secondary Headache (Generally present as an abrupt single episode and/or new onset in older age)		
Common	Uncommon	Mass-occupying lesions	Other CNS pathology	Disorders primarily external to the CNS
Tension-type headache Migraine headache • Migraine without aura (a.k.a. "common migraine") • Migraine with aura ▪ Typical aura (a.k.a. "classic migraine") ▪ Retinal migraine ▪ Hemiplegic migraine ▪ Basilar-type migraine (i.e. with brainstem aura)	Trigeminal autonomic cephalagias • Cluster headache • Paroxysmal hemicrania • Short-lasting unilateral neuralgiform headache attacks (SUNCT) Primary thunderclap headache Trigeminal neuralgia*	Hemorrhage • Epidural (EDH) • Subdural (SDH) • Subarachnoid (SAH) • Intraparenchymal (IPH) • Intraventricular (IVH) Tumor • Primary brain • Metastatic to brain Brain abscess	Meningitis/Encephalitis Venous sinus thrombosis Arterial dissection Reversible cerebral vasoconstriction syndromes (RCVS) Idiopathic intracranial hypertension (a.k.a. pseudotumor cerebri) Post lumbar puncture headache Post head trauma Ischemic stroke/TIA	Systemic infection (e.g. severe URIs, sinusitis, etc…) Hypertensive emergency Acute narrow-angle glaucoma Vasculitis (e.g. temporal arteritis) Obstructive sleep apnea Preeclampsia / eclampsia Carbon monoxide poisoning Substance use (e.g. alcohol) or withdrawal (e.g. caffeine) Medication side effect • Nitrates • Analgesic overuse

* Headache experts usually classify trigeminal neuralgia as a "painful cranial neuropathy" rather than a true primary headache syndrome

9

How Do You Want to Treat This Patient in the ED/UC Now?

10

Migraine Headache: The "Cocktail"

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- An NSAID (ketorolac 15-30mg IV)
- Dopamine antagonist
  - prochlorperazine (Compazine) 10 mg IV
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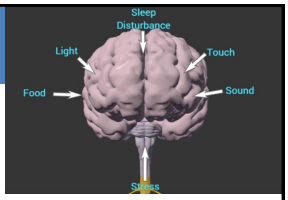
- Diphenhydramine (Benadryl 12.5-25 mg IV)
- Steroid (Dexamethasone 8-24 mg IV)

B. And why?

11

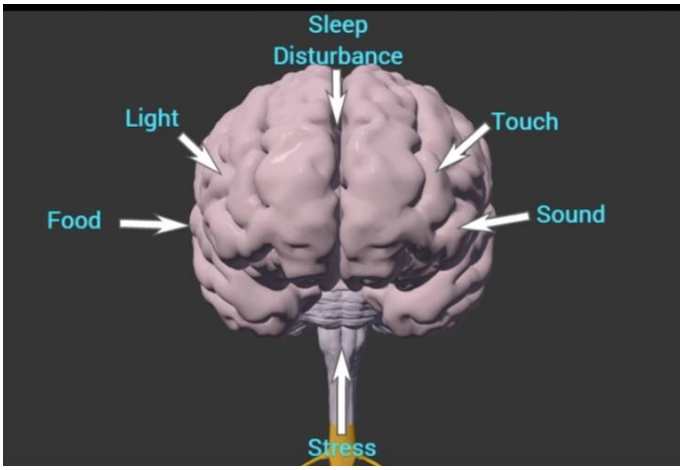
Pathogenesis of Migraine: Theories



I. Vasodilation → Dilatation of intracranial blood vessels

12

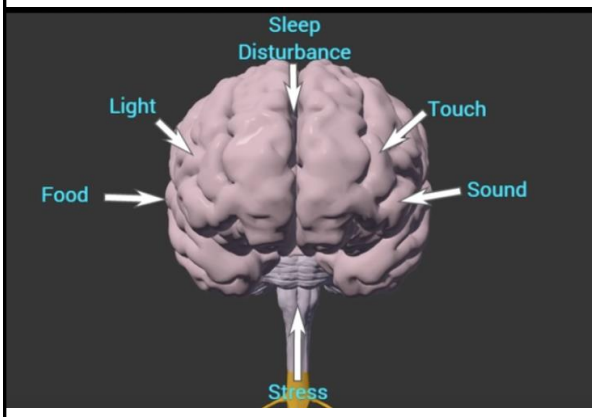
Migraine Headache: What Is the Cause?



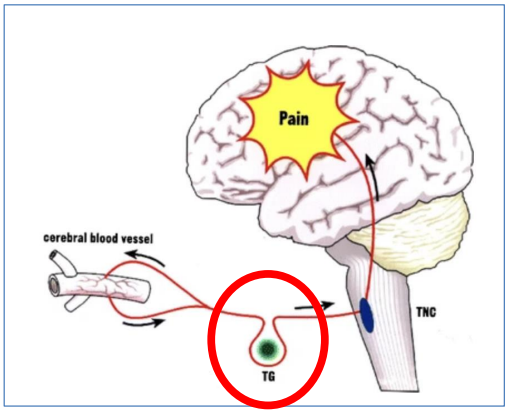
+ genetics

13

Migraine Headache: What Is the Cause?

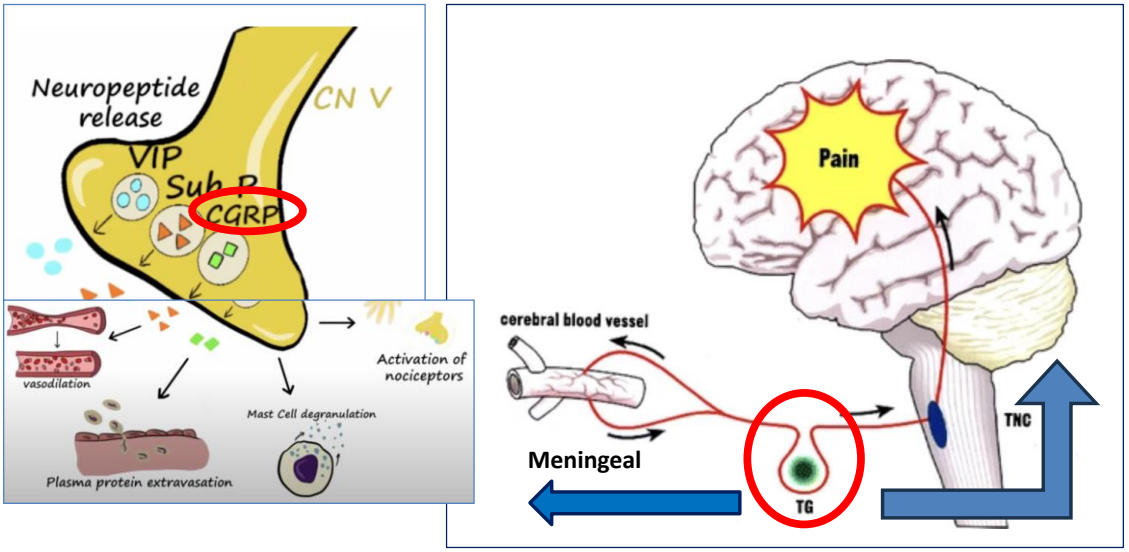


Trigeminal vascular system



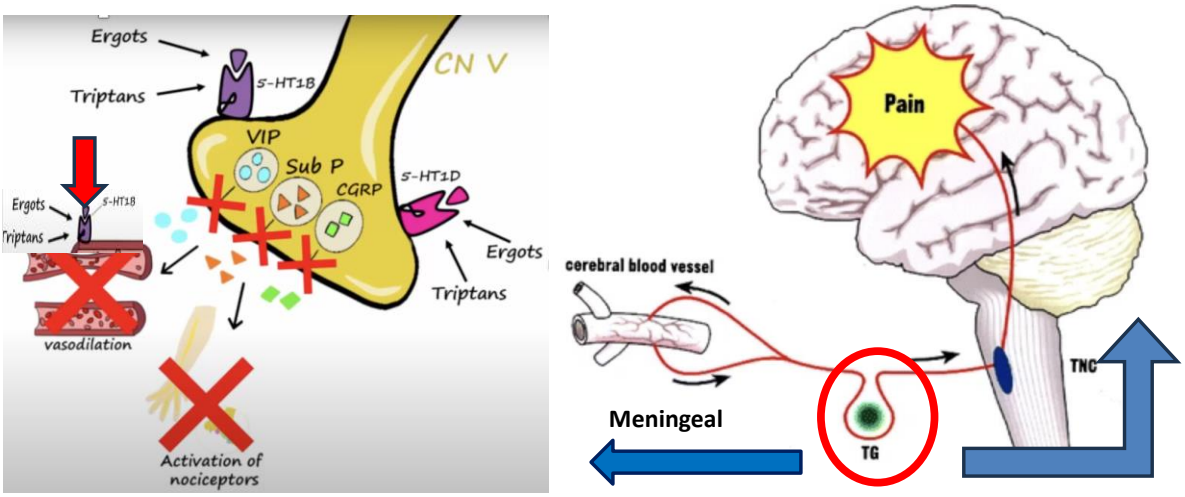
14

Trigeminal Vascular System



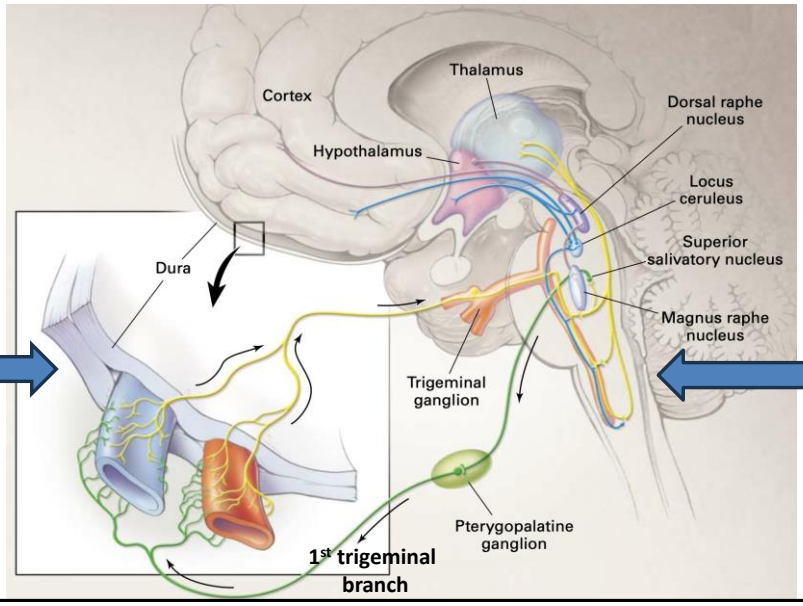
15

Trigeminal Vascular System



16

Trigeminal Vascular System

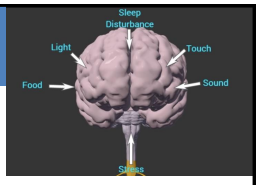


COX-1 & COX-2 Enzymes & Receptors In dura

COX-1 & COX-2 Enzymes & Receptors In brain stem

17

Pathogenesis of Migraine: Theories



I. Vasodilation

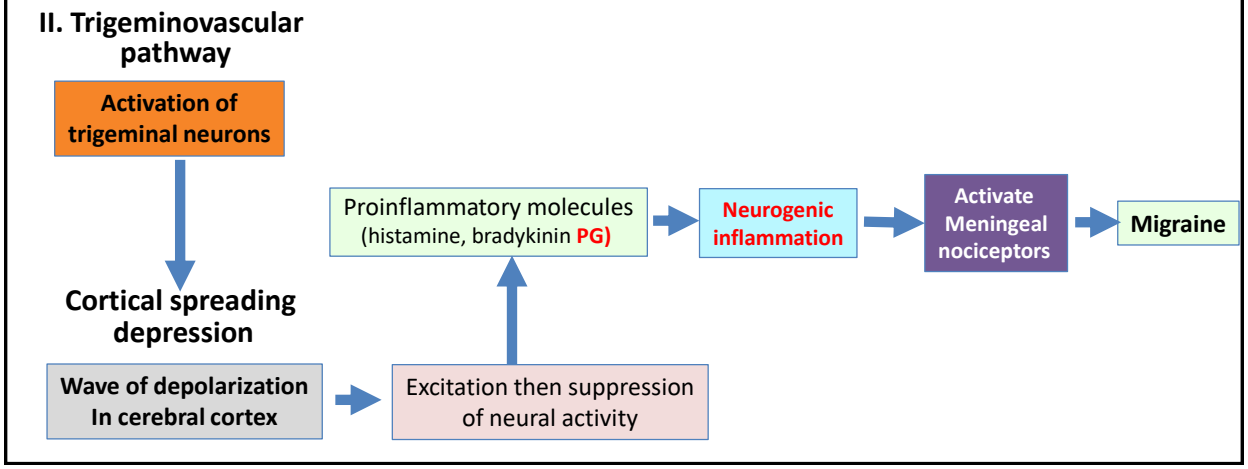
Dilatation of intracranial blood vessels

II. Trigeminovascular pathway

III. Cortical spreading depression

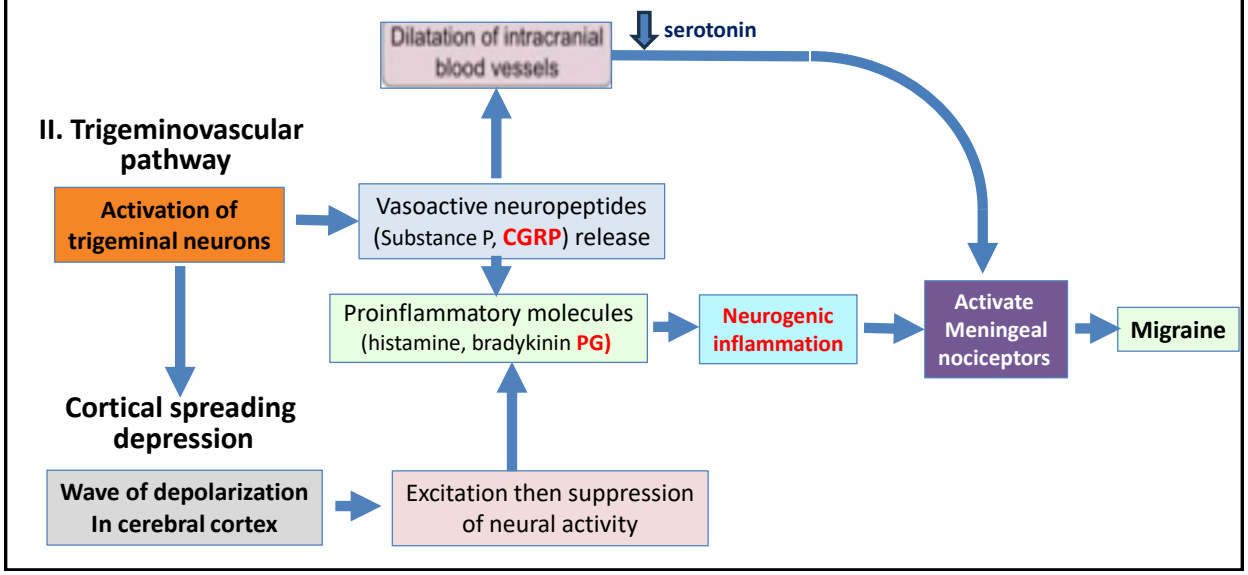
18

Pathophysiology of Migraine: Theories



19

Pathophysiology of Migraine: Theories



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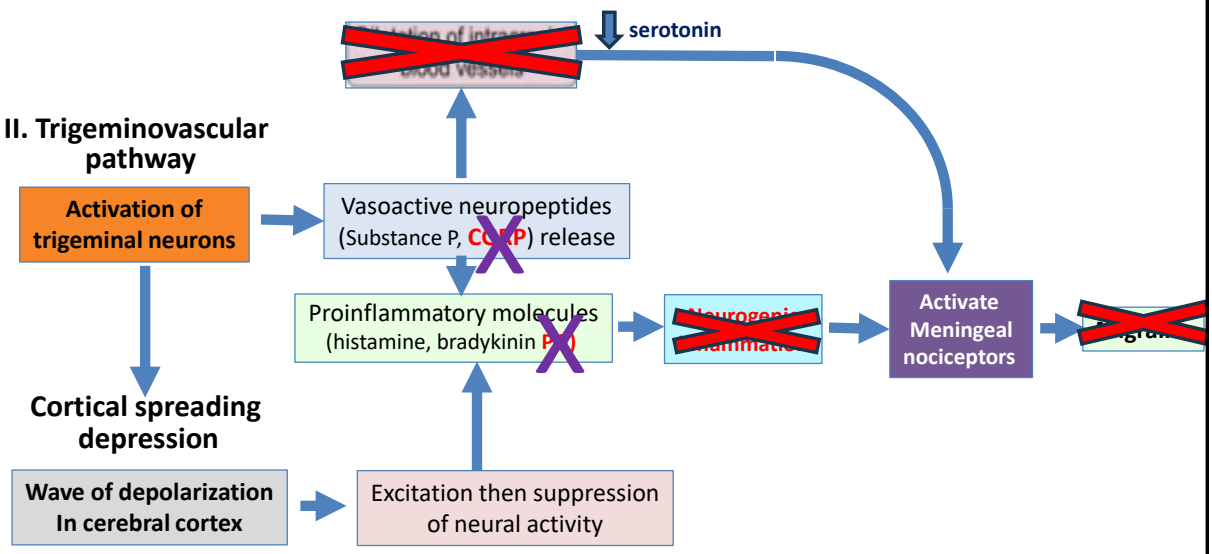
Pathophysiology of Migraine: Theories



21

Migraine Headache: The "Cocktail"

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- Steroid (Dexamethasone 10-24 mg IV)

B. And why?

➔Analgesia + Prostaglandin inhibition

22

Migraine Headache Rx: Ketorolac and NSAID's

Efficacy of ketorolac in the treatment of acute migraine attack: A systematic review and meta-analysis

Nurathirah MN, et al. *Acad Emerg Med.* 2022;29:1118–1131

13 trials, 944 patients

- ketorolac = phenothiazines (n=4) and metoclopramide (n=3) *(with less side effects)*
- ketorolac > sumatriptan, dexamethasone and valproic acid

23

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- ketorolac > sumatriptan, dexamethasone and valproic acid

- **ASA (13 placebo-controlled trials – 52% vs. 32% (Cochrane review)**
- **ibuprofen (9 trials) – NNT = 3 @ 2hrs; NNT = 2 @7 hrs**
- **Naproxen (4 trials) – NNT = 7 @ 2 hrs**

Pardutz A, et al. *Pharmaceuticals* **2010**, *3*, 1966-1987
Kirthi V, et al. Cochrane Database Syst Rev Apr 30;2013(4):CD008041

24

Migraine Headache: The "Cocktail"

A. What's in it?

- An analgesic (ketorolac 15-30mg IV)

B. And why?

➔Analgesia + Prostaglandin inhibition

What if… *"I'm allergic to NSAID's"*

25

Migraine Headache: The "Cocktail"

A. What's in it?

- ~~An NSAID (ketorolac 15-30mg IV)~~
- Acetaminophen 1000mg???

B. And why?

➔Analgesia + Prostaglandin inhibition

What if… *"I'm allergic to NSAID's"*

26

Acetaminophen Rx: Migraine – Mixed Results

Methods: RCT, double-blind, 351 patients
PO acetaminophen vs. placebo
Results: response rate @ 2 hours➔

Acetaminophen 58% vs. placebo 39%

Efficacy and Safety of Acetaminophen in the Treatment of Migraine

Results of a Randomized, Double-blind, Placebo-Controlled, Population-Based Study

Lipton RB, et al. Arch Intern Med 2000; 160: 3486

Methods: RCT, double-blind, 60 patients
IV acetaminophen vs. placebo

Results: no difference @ 2 hours

Evaluation of the efficacy of intravenous acetaminophen in the treatment of acute migraine attacks: a double-blind, placebo-controlled parallel group multicenter study

Leinisch, E, et al. *Pain* 117(3):p 396-400, Oct 2005.

Bottom line: Cochrane Review (11 studies, 2013) ➔ NNT 12

27

Migraine Headache: The "cocktail"

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- Dopamine antagonist
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B. And why?

➔Analgesia + Prostaglandin inhibition

28

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B. And why?

➔Analgesia + Prostaglandin inhibition

D2 receptor antagonists = ANTIEMETIC
? inhibit vasodilation?
? may ↑ serotonin?

29

Data for Phenothiazines and Metoclopramide

- **5 RCT's better than placebo**

The relative efficacy of phenothiazines for the treatment of acute migraine: a meta-analysis

Authors
AM Kelly, T Walcynski, and B Gunn.

Database of Abstracts of Reviews of Effects (DARE): 2009

- **1 RCT better than hydromorphone**

Randomized study of IV prochlorperazine plus diphenhydramine vs IV hydromorphone for migraine

Friedman BW, et al. Neurology 2017; 89: 20275-82

- **1 RCT better than sumatriptan**

PAIN MANAGEMENT/ORIGINAL RESEARCH

A Prospective, Randomized Trial of Intravenous Prochlorperazine Versus Subcutaneous Sumatriptan in Acute Migraine Therapy in the Emergency Department

Kostic MA et al. Ann Emerg Med 2010; 56: 1-6

30

Data for Phenothiazines and Metoclopramide

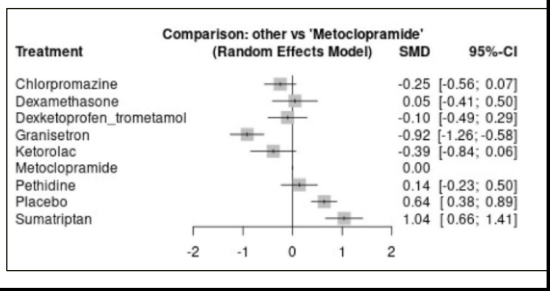
RESEARCH Open Access

The efficacy and safety of metoclopramide in relieving acute migraine attacks compared with other anti-migraine drugs: a systematic review and network meta-analysis of randomized controlled trials

Hanaa Abdelmonem[1], Hebatallah Mohamed Abdelhay[2], Gehad Taha Abdelwadoud[3], Amira Naser Mohammed Alhosini[2], Ahmed Eissa Ahmed[1], Samaher Walied Mohamed[4], Nada Mostafa Al-dardery[3], Mohamed Abd-ElGawad[1] and Mohamed Abdelmonem Kamel[1*]

BMC Neurology 2022

- **16 RCT's**
  - **8 trials: better than placebo**
  - **8 trials vs. competitors**



31

Prochlorperazine VS. Metoclopramide????

Table 1 Relevant papers

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Coppola *et al*, 1995, USA	70 Adult patients with migraine receiving either 10 mg of metoclopramide IV (24) or 10 mg prochloperazine IV (22) or a placebo (24).	Prospective double-blind RCT	Pain score at 30 min (10 cm scale) Clinical success (defined as patient satisfaction and either a decrease of 50% or more in pain or an absolute pain of 2.5 cm or less)	3.9 vs 1.1 vs 6.1 48% vs 82% vs 29% ($p<0.05$)	Outcome measured at 30 min
Jones *et al*, 1996, USA	86 Patients between 16 and 60 years old with migraine receiving 10 mg metoclopramide IM (n=28) vs 10 mg IM prochloperazine (28) vs placebo (29).	Prospective double-blind RCT	Reduction in median pain score at 60 min Rescue narcotics required	34% vs 67% vs 16% ($p<0.01$) 79% vs 57% vs 86% ($p=0.3$)	Non-consecutive patients
Friedman *et al*, 2008, USA	77 Adult patients with migraine receiving 20 mg metoclopramide IV (38) or 10 mg prochlorperazine IV (39) both accompanied by 25 mg diphenhydramine IV	Prospective double-blind RCT	Reduction in pain at 60 min (scale 0 to 10) Reduction in pain at 120 min (scale 0–10)	5.5 vs 5.2 (NSD) 5.9 vs 6.4 (NSD)	Not the common use dose of metoclopramide Prophylaxic use of diphenhydramine

IM, intramuscularly; IV, intravenously; RCT, randomised controlled trial.

2 of 3 RCT's favor prochlorperazine

Leger P. Emerg Med J, July 2013; 30: 595-6

32

Migraine Headache: The "Cocktail"

A. What's in it?	B. And why?
• An NSAID (ketorolac 30mg IV)	➔Analgesia + Prostaglandin inhibition
• Dopamine antagonist - prochlorperazine (Compazine) 10 mg IV - metoclopramide (Reglan) 10 -20 mg IV	
• Diphenhydramine (Benadryl 12.5-25 mg IV)	➔Rx: dystonia (akathisia)

33

Migraine Headache: The "Cocktail"

A. What's in it?	B. And why?
• An NSAID (ketorolac 30mg IV)	➔Analgesia + Prostaglandin inhibition
• Dopamine antagonist - prochlorperazine (Compazine) 10 mg IV ➔**36 - 44%** - metoclopramide (Reglan) 10 -20 mg IV➔**2 - 32%**	
• Diphenhydramine (Benadryl 12.5-25 mg IV)	➔Rx: dystonia (akathisia)

"I'm allergic to Compazine and Reglan"

34

Dopamine Antagonist – Alternatives

Haloperidol

- RCT 118 pts. Vs. placebo
2.5mg IV ➔ significant improvement[1]

- RCT 64 pts. Vs. metoclopramide
5mg IV ➔ equal efficacy
➔ less need for rescue med
➔ more restlessness (43% vs 10%)[2]

[1]McCoy JJ et al. J Emerg Med 2020; 59: 12-20
[2]Gaffigan ME, et al. J Emerg Med 2015; 49: 326-34

Droperidol

- RCT 395 pts. Vs. placebo
2.5–8.25mg IV ➔ significant improvement[1]

- RCT 168 pts. Vs. prochlorperazine IM
5mg IM ➔ equal efficacy[2]

- RCT 168 pts. Vs. prochlorperazine IV
2.5mg IV ➔ equal efficacy[3]

[1]Silberstein SB et al. Neurology 2003; 60: 315-21
[2]Miner JR, et al. Acad Emerg Med 2001; 8: 873-93
[3]Weaver CS et al. J Emerg Med 2004; 26: 145-50

35

Dopamine Antagonist – Alternatives

Olanzapine versus Droperidol for the Treatment of Primary Headache in the Emergency Department

Chandler H. Hill, MD, James R. Miner, MD, Marc L. Martel, MD

Acad Emerg Med 2008; 15: 806-15

Methods: prospective, randomized single blind trial

Results:	olanzapine 10mg IM	droperidol 5mg IM
	n= 44	n=40
-Mild/no pain @30 min	61%	67%

Olanzapine: dopaminergic and serotonergic antagonism.
*less QT prolongation, less extra-pyramidal symptoms

36

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B. And why?

➔Analgesia + Prostaglandin inhibition

D2 receptor antagonists = ANTIEMETIC
? inhibit vasodilation?
? may ↑ serotonin?

➔Rx: dystonia (akathisia)

➔ Prevent rebound

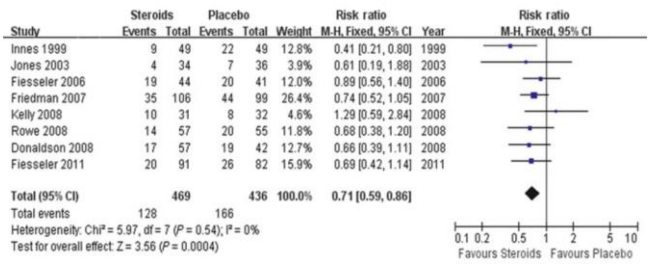
37

How Effective Is Dexamethasone in Preventing "Rebound"?

Table 1 Characteristics of studies included in the meta-analysis

Study	Patients (*n*)	Treatment/Comparison	Concomitant therapy	Follow-up (h)	Jadad score
Friedman 2007 [8]	205	DXM 10 mg iv/placebo	Metoclopramide and diphenhydramine iv	24	5
Innes 1999 [10]	98	DXM 24 mg iv/placebo	Standard abortive therapy	48–72	5
Jones 2003 [11]	70	DXM 20 mg iv or im/placebo	Standard abortive therapy	48	5
Fiesseler 2006 [12]	85	DXM 10 mg iv/placebo	Standard abortive therapy	24–48	4
Rowe 2008 [13]	112	DXM 15 mg iv/placebo	Standard abortive therapy	48–72	5
Donaldson 2008 [14]	99	DXM 24 mg iv/placebo	Standard abortive therapy	72	5
Kelly 2008 [16]	61	DXM 10 mg oral/placebo	Chlorpromazine or prochlorperazine iv	24	5
Fiesseler 2011 [17]	173	DXM 10 mg iv once or prednisone 40 mg oral for 2 days/corresponding placebo	Standard abortive therapy	24 –72	5

DXM, dexamethasone; iv, intravenously; im, intramuscularly.



NNT= 10

Huang Y, et al. Eur J Neurol 2013, 20: 1184-90

38

Breaking News...

RESEARCH ARTICLE

Randomized Trial Comparing Low- vs High-Dose IV Dexamethasone for Patients With Moderate to Severe Migraine

Friedman BW, et al Neurology 2023: e1448-1454

Methods: randomized, double-blind study, 2 NYC ED's

Results:

	metoclopramide 10mg + dexamethasone **4mg** (n=104)	metoclopramide 10mg + dexamethasone **16mg** (n=105)	
@48 hr no/mild HA	67%	75%	*(Absolute CI =8 95%CI: -4-21)*
No meds post-discharge	55%	60%	*(absolute CI = 4 95% CI -9-18)*

39

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B. And why?

➔Analgesia + Prostaglandin Inhibition

D2 receptor antagonists = ANTIEMETIC
? inhibit vasodilation?
? may ↑ serotonin?

➔Rx: dystonia (akathisia)

➔Prevent rebound

Is there an Alternative/Back up plan?

40

Migraine Headache: "Triptans"

- **Sumatriptan – 6mg SQ**
  - oral 25, 50,100mg
  - intranasal 10,20mg
- Frovatriptan 2.5mg
- Naratriptan 2.5mg
- Rizatriptan 5, 10mg
- Zolmitriptan 2.5, 5mg

Retains efficacy > 2 hours from symptom onset [1]

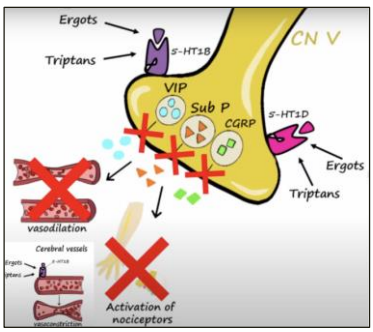
efficacy diminishes > 2 hours from symptom onset

[1]Linde M, et al Cephalgia 2006 26: 113-21
-20 patients with 2 migraine episodes

41

Migraine Headache: "Triptans"

- **Sumatriptan – 6mg SQ**
- Patients should be offered as first-line therapy in the ED[1]
- can be repeated in 2 hours if needed.
- Contraindications:
  - uncontrolled hypertension,
  - cerebrovascular, CV, PAD
  - ergot use within 24 hours.



[1]Cortel-Leblanc MA, et al. Ann Emerg Med 2023; 82: 732-751

42

Migraine Headache: "Triptans"

TABLE 6

Effectiveness of Sumatriptan (Imitrex) for Migraine Headache

Route of administration	Dose (mg)	Number needed to treat* Pain relief at 2 hours	Pain free at 2 hours
Intranasal	10	6	7
	20	4	5
Oral	25	4	6
	50	4	6
	100	4	5
Subcutaneous	4	2	3
	6	2	2

*—In patients with moderate to severe pain at baseline.

Summary of Triptan Medications for Migraine Headache

Medication	Formulation	Half-life (hours)	Cost*
Almotriptan (Axert)	6.25- and 12.5-mg tablets	3 to 4	$71 ($264) for 6 tablets
Eletriptan (Relpax)	20- and 40-mg tablets	4	$72 ($346) for 6 tablets
Frovatriptan (Frova)	2.5-mg tablets	26	$171 ($664) for 9 tablets
Naratriptan (Amerge)	1- and 2.5-mg tablets	6	$36 ($514) for 9 tablets
Rizatriptan	5- and 10-mg tablets (Maxalt)	2 to 3	$12 ($228) for 6 tablets
	5- and 10-mg orally disintegrating tablets (Maxalt-Mlt)	2 to 3	$17 ($228) for 6 tablets
Sumatriptan (Imitrex)	25-, 50-, and 100-mg tablets	2.5	$16 ($546) for 9 tablets
	6-mg injection	2.5	$29 ($185) for 1 vial (1 dose)
	5- or 20-mg nasal spray	2	$130 ($458) for 1 nasal spray (6 doses)
Zolmitriptan	2.5- or 5-mg tablets (Zomig)	3	$52 ($587) for 6 tablets
	2.5- or 5-mg orally disintegrating tablets (Zomig Zmt)	3	$46 ($589) for 6 tablets
	5-mg nasal spray	3	Generic not available ($420 for 6 doses)

*—Estimated retail cost based on information obtained at http://www.goodrx.com (accessed September 19, 2017). Generic price listed first; brand in parentheses.

MAYANS L, et al. Am *Fam Physician.* 2018;97(4):243-251

43

Migraine Headache: The "Cocktail"

A. What's in it?

- An NSAID (ketorolac 15-30mg IV)
- Dopamine antagonist
  - prochlorperazine (Compazine) 10 mg IV
  - metoclopramide (Reglan) 10 -20 mg IV
- Diphenhydramine (Benadryl 12.5-25 mg IV)
- Steroid (Dexamethasone 10-24 mg IV)

Alternative: Sumatriptan 6mg SQ

B. And why?

➔Analgesia + Prostaglandin inhibition

D2 receptor antagonists = ANTIEMETIC
? inhibit vasodilation?
? may ↑ serotonin?

➔Rx: dystonia (akathisia)

➔Prevent rebound

➔Bind 5HT receptors

44

What If the Patient Still Has Pain?

A. What's in it?

- An NSAID (ketorolac 15-30mg IV)
- Dopamine antagonist
  - prochlorperazine (Compazine) 10 mg IV
  - metoclopramide (Reglan) 10 -20 mg IV
- Diphenhydramine (Benadryl 12.5-25 mg IV)
- Steroid (Dexamethasone 10-24 mg IV)

Alternative: Sumatriptan 6mg SQ

B. And why?

➔Analgesia + Prostaglandin inhibition

D2 receptor antagonists = ANTIEMETIC
? inhibit vasodilation?
? may ↑ serotonin?

➔Rx: dystonia (akathisia)

➔Prevent rebound

➔Bind 5HT receptors

45

Differential diagnosis/Diagnostic Framework: 3rd International Classification of HA disorders (2018)

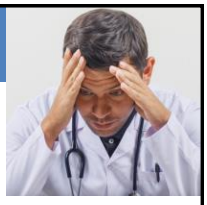
Primary Headache Syndromes (Generally present as chronic and episodic)		Secondary Headache (Generally present as an abrupt single episode and/or new onset in older age)		
Common	**Uncommon**	**Mass-occupying lesions**	**Other CNS pathology**	**Disorders primarily external to the CNS**

Tension-type headache
 	
Migraine headache
• Migraine without aura (a.k.a. "common migraine")
• Migraine with aura
  ▪ Typical aura (a.k.a. "classic migraine")
  ▪ Retinal migraine
  ▪ Hemiplegic migraine
  ▪ Basilar-type migraine (i.e. with brainstem aura)
	Trigeminal autonomic cephalagias
	• Cluster headache
	• Paroxysmal hemicrania
	• Short-lasting unilateral neuralgiform headache attacks (SUNCT)
	
	Primary thunderclap headache
	
	Trigeminal neuralgia*
		Hemorrhage
		• Epidural (EDH)
		• Subdural (SDH)
		• Subarachnoid (SAH)
		• Intraparenchymal (IPH)
		• Intraventricular (IVH)
		
		Tumor
		• Primary brain
		• Metastatic to brain
		
		Brain abscess
			Meningitis/Encephalitis
			
			Venous sinus thrombosis
			
			Arterial dissection
			
			Reversible cerebral vasoconstriction syndromes (RCVS)
			
			Idiopathic intracranial hypertension (a.k.a. pseudotumor cerebri)
			
			Post lumbar puncture headache
			
			Post head trauma
			
			Ischemic stroke/TIA
				Systemic infection (e.g. severe URIs, sinusitis, etc…)
				
				Hypertensive emergency
				
				Acute narrow-angle glaucoma
				
				Vasculitis (e.g. temporal arteritis)
				
				Obstructive sleep apnea
				
				Preeclampsia / eclampsia
				
				Carbon monoxide poisoning
				
				Substance use (e.g. alcohol) or withdrawal (e.g. caffeine)
				
				Medication side effect
				• Nitrates
				• Analgesic overuse

* Headache experts usually classify trigeminal neuralgia as a "painful cranial neuropathy" rather than a true primary headache syndrome

46

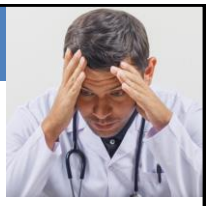
First Attempt at Pain-relief Failed… Options?



- **Repeat 1st line agent(s)**

47

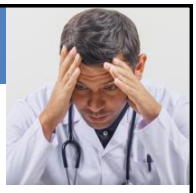
First Attempt at Pain-relief Failed… Options?



- **Repeat 1st line agent(s)**
- **Ergots (DHE)**
- **Valproic acid: 800-1000mgIV**
- **Mg++ 1-2 gm IV 15-20min**
- **IV Ketamine**
- **Propofol**
- **IV caffeine**
- **Timolol eye drops**

48

First Attempt at Pain-relief Failed… Options?



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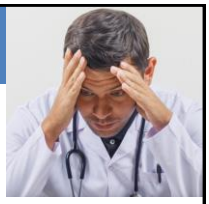
- **Ergots (DHE)**
- **Valproic acid: 800-1000mgIV**
- **Mg++ 1-2 gm IV 15-20min**
- **IV Ketamine**
- **Propofol**
- **IV caffeine**
- **Timolol eye drops**

- **Head-to-head trial[1]**
  1mg SQ = 6mg Sumatriptan
- Dose: 1mg IV over 2min, or SQ
  May repeat in 8 hrs
- Avoid in pregnancy, breastfeeding, uncontrolled hypertension, CV or PAD, recent triptan use.

[1]Winner P, et al. *Arch Neurol.* 1996;53(2):180-184

49

First Attempt at Pain-relief Failed… Options?



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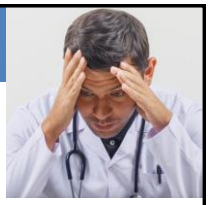
- **Ergots (DHE)**
- **Valproic acid: 800-1000mgIV**
- **Mg++ 1-2 gm IV 15-20min**
- **IV Ketamine**
- **Propofol**
- **IV caffeine**
- **Timolol eye drops**

- Is used for prevention
- How it works--- unknown
- **2 Meta-analysis suggest that Valproic acid is NOT as effective as Dopamine antagonists at 24 hours**

Wang F, et al. Acta Neurol Scand. 2020;142:521-530.
Viau JA, et al. Can J Neurol Sci. 2022;49:688-695.

50

First Attempt at Pain-relief Failed… Options?



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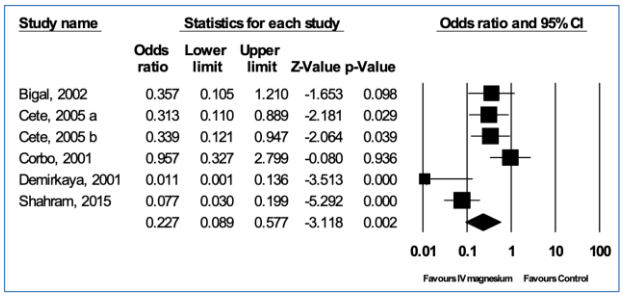
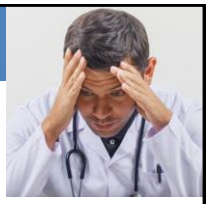
- Propofol
- IV caffeine
- Timolol eye drops



Chiu WY, et al. Pain Physician 2016; 19:E97-E112

51

First attempt at pain-relief failed… options?



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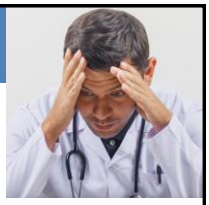
- Ergots (DHE)
- Valproic acid: 800-1000mgIV
- Mg++ 1-2 gm IV 15-20min
- **IV Ketamine**
- **Propofol**
- IV caffeine
- Timolol eye drops

"Controversial, experimental" (Annals EM review)
With mixed, limited results…

Cortel-LeBlanc MA et al. Ann Emerg Med. 2023;82:732-751

52

First Attempt at Pain-relief Failed… Options?



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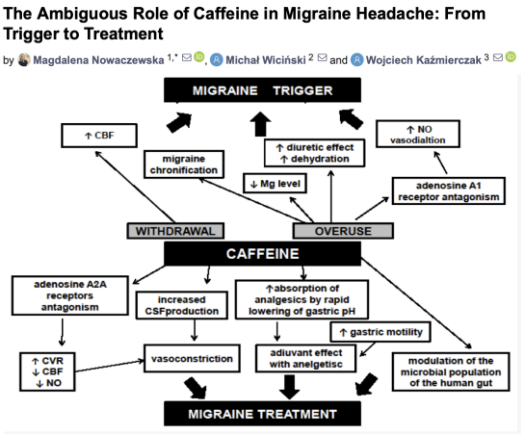
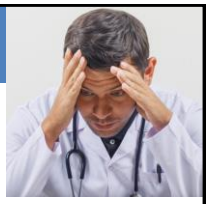
- Ergots (DHE)
- Valproic acid: 800-1000mgIV
- Mg++ 1-2 gm IV 15-20min
- IV Ketamine
- Propofol
- **IV caffeine**
- Timolol eye drops



Nutrients **2020**, *12*(8), 2259

53

First Attempt at Pain-relief Failed… Options?



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- Ergots (DHE)
- Valproic acid: 800-1000mgIV
- Mg++ 1-2 gm IV 15-20min
- IV Ketamine
- Propofol
- **IV caffeine**
- Timolol eye drops

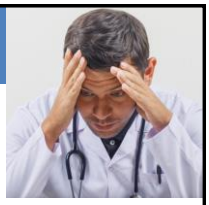
Only one prospective trial…

	Caffeine 60mgIV (n=35)	Mg++ 2gm IV (n=35)
Baseline pain	9.0	8.0
@1hr	5.0	2.0
@2hr	4.0	0.0

Baratloo A et al. Korean J Pain 2017 July; Vol. 30, No. 3: 176-182

54

Caffeine Combinations



- **Acetaminophen + Aspirin + Caffeine: OTC**

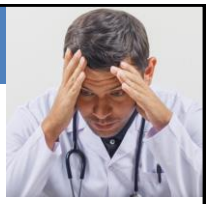
Excedrin Extra Strength, Vanquish, Bayer Migraine Formula, Excedrin Migraine, Excedrin Menstrual Complete, Goody's Extra Strength Fast Pain Relief Powders, Goody's Extra Strength, Goody's Extra Strength Headache Powders, Goody's Migraine Relief, Anacin Advanced Headache, Arthriten, Pamprin Max

- **Ergotamine + Caffeine: Cafergot**

2 tab, then 1 tab q 30 minutes prn
Each tablet contains 1 mg ergotamine and 100 mg caffeine.
Do not use more than 6 tab qd or 10 tab in a week

55

First Attempt at Pain-relief Failed… Options?



- **Repeat 1st line agent(s)**

- Ergots (DHE)
- Valproic acid: 800-1000mgIV
- Mg++ 1-2 gm IV 15-20min
- IV Ketamine
- Propofol
- IV caffeine
- **Timolol 0.5% eye drops**

Methods: blinded, RCT

	Timolol 1 drop both eyes repeat in 10min (n=20)	placebo (n=23)
Baseline pain	6.01	5.93
@ 20 min	5.03	5.00

Kurian A, et al. JAMA Ophthalmol. 2020;138(11):1160-1166.

56

How Do Beta-blockers Prevent (Treat?) Migraine HA?

Theories….

- **Restrict blood flow in the brain.** Beta-blockers reduce blood vessel dilation, which is known to contribute to migraine.
- **Reduce nervous system electrical activity.** Beta-blockers make the nervous system less excitable. They also suppress waves of electric currents that are thought to be a factor in migraine aura.
- **Maintain brain serotonin levels.** Fluctuations in serotonin levels are associated with migraine. Beta-blockers stabilize serotonin levels.
- **Increase activity in the hypothalamus.** The hypothalamus also plays a role in migraine activity. Beta-blockers may affect activity in this region of the brain.
- **Decrease overall stress.** Stress is a common migraine trigger. Beta-blockers may help reduce migraine frequency by reducing anxiety.

57

First Attempt at Pain-relief Failed… Options?

- **Repeat 1st line agent(s)** 👍👍
- **Ergots (DHE)**
- **Valproic acid: 800-1000mgIV**
- **Mg++ 1-2 gm IV 15-20min** 👍
- **IV Ketamine**
- **Propofol**
- **IV caffeine**
- **Timolol 0.5% eye drops** 👍

Bob's suggestions….

58

Annals of Emergency Medicine Recommendations (2023)

Bob's Recommendations

- **Repeat 1st line agent(s)**
- **Ergots (DHE)**
- **Valproic acid: 800-1000mgIV**
- **Mg++ 1-2 gm IV 15-20min**
- **IV Ketamine**
- **Propofol**
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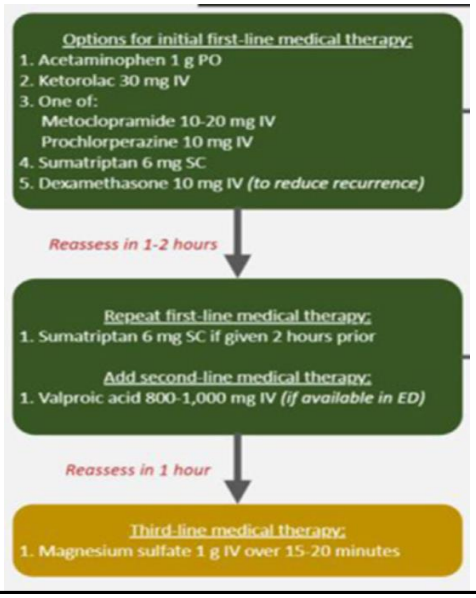


59

Question: No IV Access. What Now?

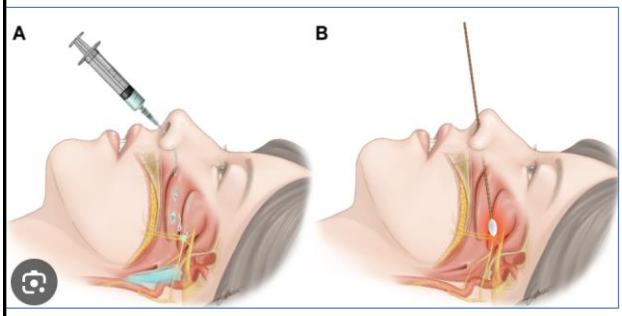
- An analgesic (ketorolac 15-30mg **IM**)
- Dopamine antagonist
  - prochlorperazine (Compazine) 10 mg **IM**
  - metoclopramide (Reglan) 10 -20 mg **IM**
- Diphenhydramine (Benadryl 12.5-25 mg **IM**)
- Steroid (Dexamethasone 10-24 mg **IM**)

Alternative: Sumatriptan 6mg SQ

- Haloperidol 2.5-5mg **IM**
- Droperidol 2.5mg **IM**
- Timoptic eye drops

60

What About…
Sphenopalatine Ganglion Nerve Block?



ED data limited

(+) study: JAMA, 1996, 53 patients
55% ➔ 50% reduction in pain
(vs. 21% placebo)

(-) study: Ann Emerg Med 2015, 93 pts
49% vs 41%
No statistical difference

61

What About…Oxygen?

brain sciences MDPI

Opinion

Oxygen Therapy in Headache Disorders: A Systematic Review

Tiziana Ciarambino [1], Gennaro Sansone [2], Giovanni Menna [2], Ombretta Para [3], Giuseppe Signoriello [2], Laura Leoncini [4] and Mauro Giordano [2,*]

Brain Sci. 2021 Mar; 11(3): 379

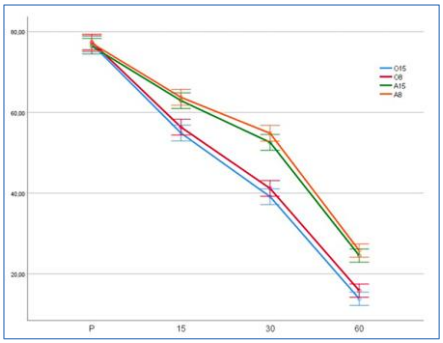
- 6 studies, 3 RCT's –
- Significant heterogeneity

- No evidence high-flow is beneficial

High or mid-flow oxygen therapy for primary headache disorders: A randomized controlled study

İlker Kaçer, MD [a,1,*], Ahmet Çağlar, Assoc Prof MD [b,2]

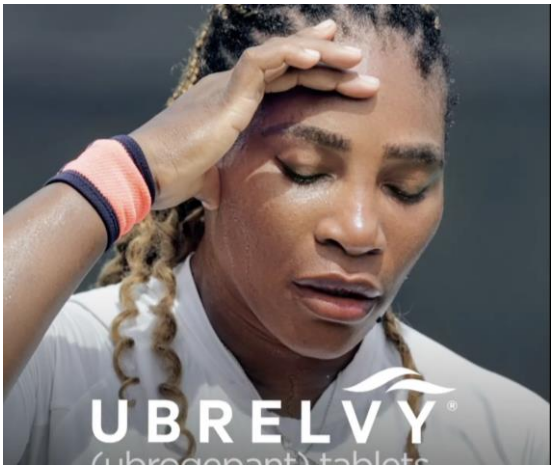
Am J Emerg Med 2023; 68: 138-43



2/3 of pts still need rescue analgesia compared to 76-81% placebo @ 30min

62

"I want the Serena Williams/Lady Gaga drug for migraine"



63

Gepants

- Ubrogepant *(Ubrelvy)* 50-100mg
  - may repeat in 2 hrs
- Zavegepant (Zavzpret) 10mg
  - intranasal qd
- Rimegepant *(Nurtec) ODT* 75mg qd
- Atogepant *(Qulipta)* (preventive med only)
- Erenumab *(Aimovig)* (preventive med only)

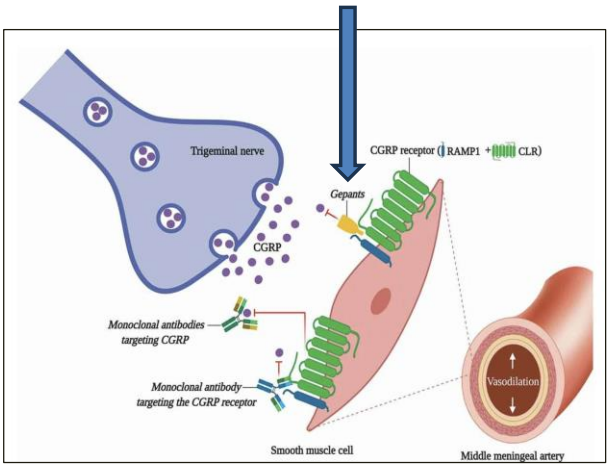
Ditans

- Lasmiditan *(Reyvow)* 200mg

64

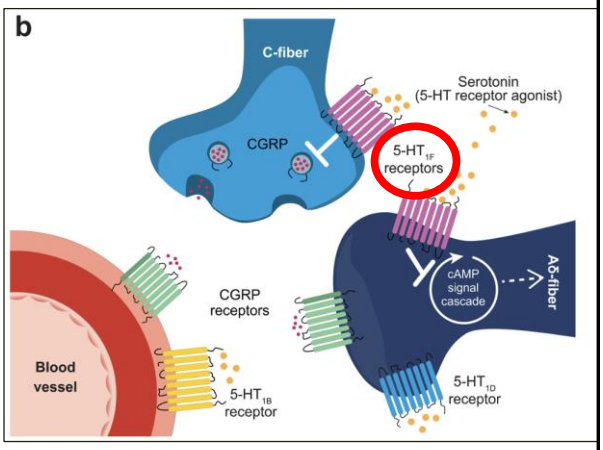
Gepants

- CGRP receptor antagonists



Ditans

- $5HT_{1F}$ receptor agonists



65

Gepants

- CGRP receptor antagonists

Ditans

- $5HT_{1F}$ receptor agonists

- Pro – can use with CVD/Peripheral Vasc Dis/Uncontrolled HTN *(advantage over triptans)*

66

Gepants

- CGRP receptor antagonists

Ditans

- $5HT_{1F}$ receptor agonists

- Pro – can use with CVD/Peripheral Vasc Dis/Uncontrolled HTN *(advantage over triptans)*

HEADACHE CURRENTS

Headache Currents

The Risks or Lack Thereof of Migraine Treatments in Vascular Disease

Hans-Christoph Diener, MD, PhD

March 2020

67

Gepants

- CGRP receptor antagonists

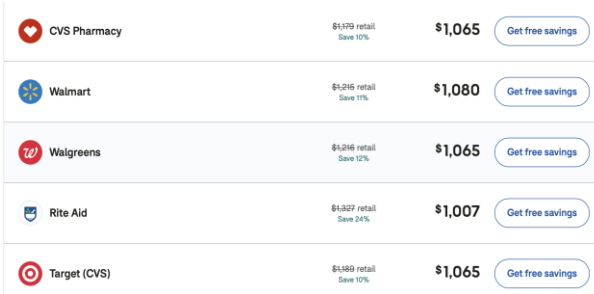
Ditans

- $5HT_{1F}$ receptor agonists

- Pro – can use with CVD/Peripheral Vasc Dis/Uncontrolled HTN

- Con – oral formulation, $$$$$

Reyvow approx. $83/tablet



Ubrelvy 10 tabs

$ per GoodRx.com
Accessed 2/28/24

68

Gepants

- CGRP receptor antagonists

Ditans

- $5HT_{1F}$ receptor agonists

- Pro – can use with CVD/Peripheral Vasc Dis/Uncontrolled HTN

- Con – oral formulation, $$$$$
- Slower onset of action
- No ED/UC studies, no head-to-head studies with other Rx

69

Summary

Migraine "Cocktail" 👍

triptans 👍

2nd line agents ...if needed

gepants

Not for ER/UC use at this time

ditans

70

Thank You for Your Time and Attention!

Questions???

71

Supplemental Studies

72

Question: "Cocktail" (3-4 Drugs) vs. "One-at-a-time"
"Stratified Care" "Stepped Care"

Stratified Care vs Step Care Strategies for Migraine
The Disability in Strategies of Care (DISC) Study: A Randomized Trial

- RCT of outpatient patients with migraine
- "Stratified care" – provide 2 or 3 meds at one time
  (based on severity of symptoms)

➔Outperformed "Stepped care"

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

73

Question: "Cocktail" (3-4 Drugs) vs. "One-at-a-time"
"Stratified Care" "Stepped Care"

Stratified care (n=279)

- ASA 800-1000mg po
- Metoclopramide 10mg po
- zolmitriptan, 2.5 mg po

=➔ 52%

Stepped care (n=271)

- ASA 800-1000mg po
- Metoclopramide 10mg po

if no improvement after 2hrs

- zolmitriptan, 2.5 mg po

=➔ 40%

A straw man comparison?

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

74

Question: "Cocktail" (3-4 Drugs) vs. "One-at-a-time"

"Stratified Care" "Stepped Care"

Sumatriptan-Naproxen for Acute Treatment of Migraine

A Randomized Trial

Brandes JL, et al. JAMA. 2007;297:1443-54

	Sumatriptan 85mg + Naproxen 500mg N = 726	Sumatriptan 85mg N = 723	Naproxen 500mg N = 720	Placebo N= 742
Headache relief@ 2hrs				
Study 1	**237 (65%)**	**200 (55%)**	**157(44%)**	**102 (28%)**
Study 2	**207 (57%)**	**182 (50%)**	**158 (43%)**	**109 (29%)**

Cochrane: 12 studies: sumatriptan 85 mg plus naproxen 500 mg tablet, One study sumatriptan 50 mg plus naproxen 500 mg as separate tablets Combination better than individual meds *Cochrane Library 2016*

75