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Acute Migraine management:
Evidence based approaches

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Disclaimer

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Funding for attending medical conferences & a visiting Professorship
Hospitality in and out of hospital premises

Migraine management
General principles

- **Validate** the impact the condition has on the individual and family

- **Manage expectations**- patients may have unrealistic or indeed low expectations of what can be achieved. Explain that migraine can not be cured but can be effectively managed in most cases

Rothrock et al; *Headache*; 2006; 46(7); 726-731

- **Reassurance**-patients often worry about an underlying serious disorder. Explaining the nature of the condition to the patient can often be of therapeutic value Laughley et al; *Cephalalgia*; 1999; 19; 328-329

- **Empower** the patient to promote self management

Kidelan-Calvo et al*; Pain Me*d; 2014; 15; 1619-1638

Principles of acute management of migraine

- Manage identifiable triggers
- Treat co-morbid mood and anxiety
- Appropriate use of pain relief medication
- To avoid medication overuse restrict acute relief medication to no more than 2 days a week on a regular basis
- Consider use of a headache diary and introduction of preventive treatment for disabling headaches occurring more than 4-5 days a month

Principles of acute management of migraine

- Effective treatment end point is a significant response at 2 hours, because the natural history for most attacks is to improve spontaneously in 4 hours

- All acute treatments to be taken as soon as patient knows that this is a migraine

- If there is an aura then acute treatment to be taken at the start of the headache phase

Edmeads; *Eur Neurol*; 2005; 53 Suppl 1: 22-82005

Management of acute migraine

Simple analgesics / anti-inflammatories

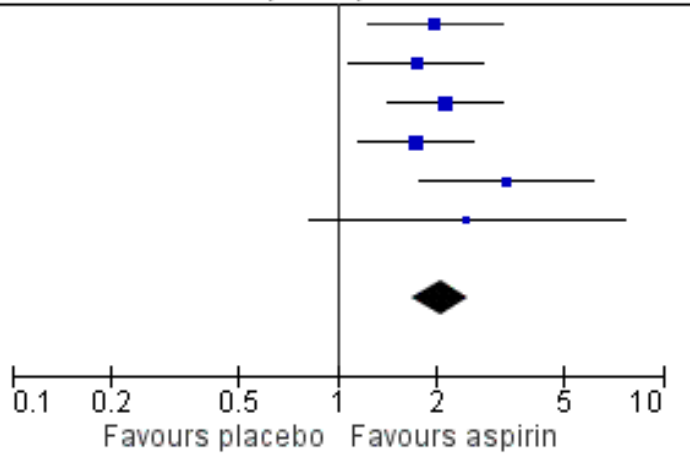
Drug	Dose	Max daily dose
Paracetamol	1000 mg	4 gm
Aspirin	600 – 1000 mg	3 gm
Ibuprofen	400 – 600 mg	2.4 gm
Naproxen	500-825 mg	1000 mg
Diclofenac	50 – 100 mg	150 mg
Tolfenemic Acid	200 mg	400 mg

Aspirin for acute migraine headaches

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Boureau 1994	44	198	22	198	18.9%	2.00 [1.25, 3.21]
Diener 2004a	37	146	22	152	18.6%	1.75 [1.09, 2.82]
Diener 2004b	60	221	28	222	24.1%	2.15 [1.43, 3.24]
Lange 2000	49	169	29	174	24.6%	1.74 [1.16, 2.61]
Lipton 2005	40	201	12	200	10.4%	3.32 [1.79, 6.13]
MacGregor 2002 (1)	10	73	4	73	3.4%	2.50 [0.82, 7.61]
Total (95% CI)		**1008**		**1019**	**100.0%**	**2.08 [1.70, 2.55]**
Total events	240		117			

Heterogeneity: $Chi^2 = 3.61$, $df = 5$ ($P = 0.61$); $I^2 = 0\%$

Test for overall effect: $Z = 7.10$ ($P < 0.00001$)



Footnotes

(1) aspirin 900 mg

Cochrane Database of Systematic Reviews
30 APR 2013 DOI: 10.1002/14651858.CD008041.pub3

Management of acute migraine

Anti-emetics

- Anti-emetics are important if vomiting a feature.

Drug	Dose	frequency
Prochlorperazine	3-6 mg buccal	4-6 hourly
Domperidone	10 mg	8 hourly
Metoclopramide	10 mg	8 hourly

- Other options can be;
  soluble aspirin
  diclofenac suppositories

- **Adding an anti-emetic to an acute treatment improves efficacy unrelated to nausea and / or vomiting**

Management of acute migraine

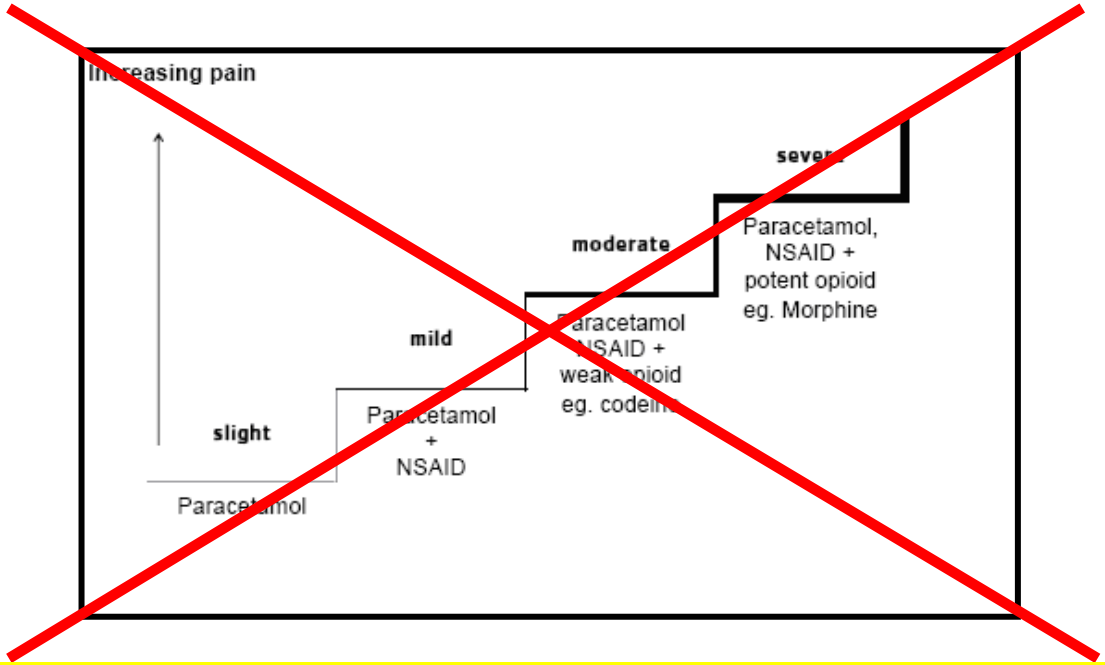
Simple analgesics / anti-inflammatories - ***problems***

- Not effective
  - dose? timing? route? combination?
- Contraindications
  - asthma, upper GI problems, renal impairment
- Side effects
  - gastro-intestinal, renal

Management of acute migraine

~~Opioids~~

- ….are **NOT** a treatment for headache
- the WHO analgesic ladder should **NOT** be applied to headache management

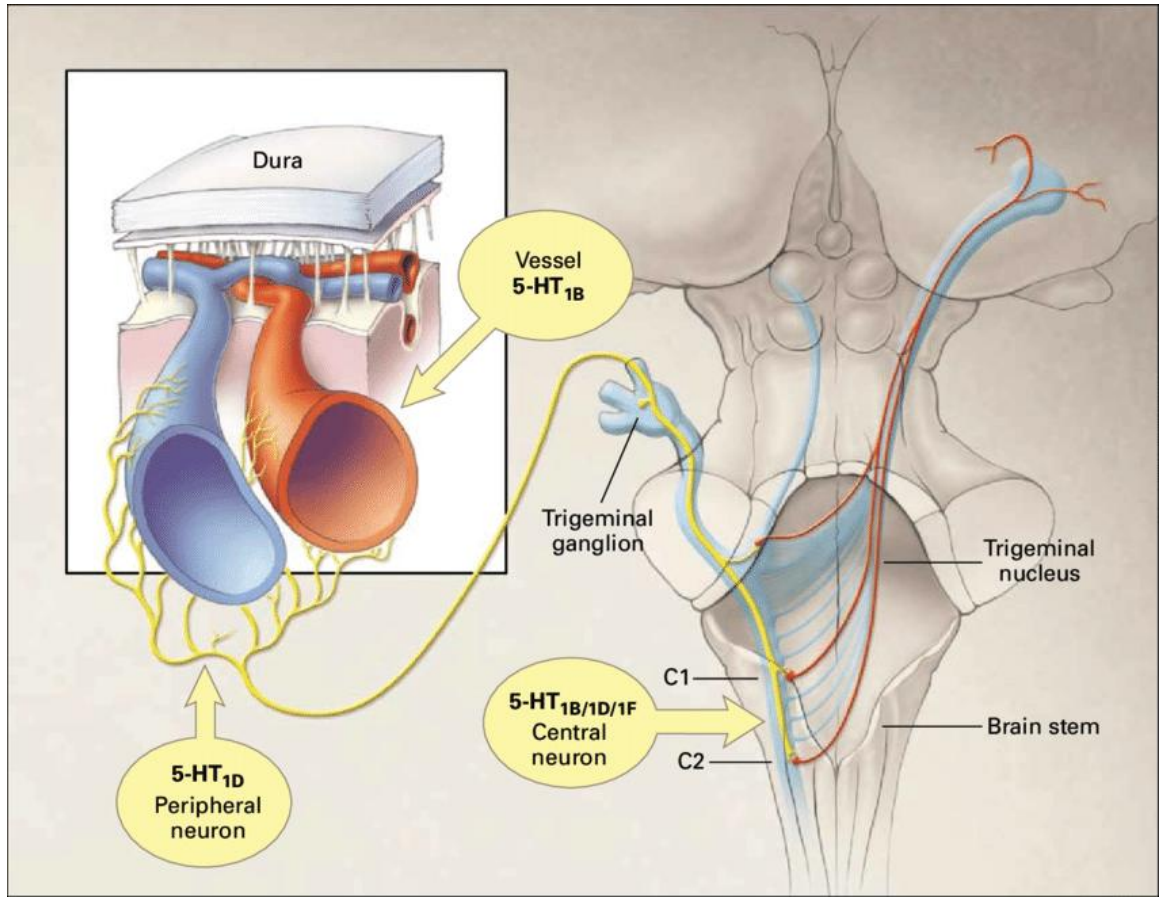


Opioids are not recommended for the treatment of acute headache because of the significant risk of medication overuse and the most protracted withdrawl

Limmroth et al; *Neurology*; 2002 Oct 8; 59(7); 1011-4

Management of acute migraine

Triptans



Mechanism of action

5HT1B & 1D receptor agnosits

Vasoconstriction of dilated meningeal blood vessels

Inhibition of the release of vasoactive neuropeptides from perivascular trigeminal sensory neurons

Reduction of pain signal transmission in the trigeminal dorsal horn

Goadsby et al; *NEJM*; Feb 2002; 346(4); 257-70

Management of acute migraine

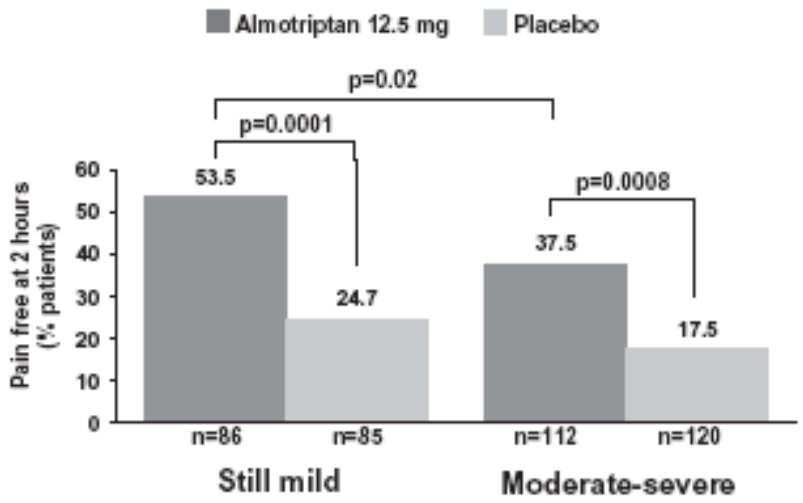
Triptans

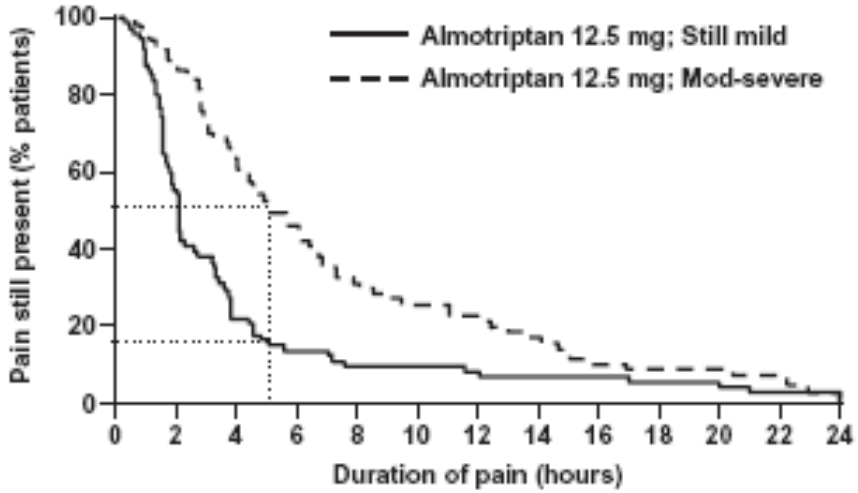
Drug	Formulation	Dose
Almotriptan	Oral	12.5/25 mg
Eletriptan	Oral	40/80 mg
Frovatriptan	Oral	2.5/5 mg
Naratriptan	Oral	2.5/5 mg
Rizatriptan	Oral	5/10 mg
	Buccal	10 mg
Sumatriptan	Oral	50/100 mg
	Buccal	50 mg
	Nasal	10/20 mg
	Subcutaneous	6 mg
Zolmitriptan	Oral	2.5/5 mg
	Buccal	2.5/5 mg
	Nasal	2.5/5 mg

Management of acute migraine

Triptans – ‘act when mild’

- Triptans are most effective when taken early in the headache phase of the attack





Goadsby et al; *Cephalalgia* 2008; Sep; 28 Suppl 2:36-41

- Triptans are ineffective at treating the headache if taken during the aura phase

Bates et al; *Cephalalgia;* 1994 Oct; 14(5); 330-8

Management of acute migraine

Triptan selection

- Daytime migraine of moderate-severe intensity
  Oral Sumatriptan 100 mg, Eletriptan 20 – 40 mg or Rizatriptan 5 – 10 mg

- Rapidly evolving pain (including migraine on awakening) and prominent GI symptoms
  sc sumatriptan 6 mg or intranasal sumatriptan 20 mg or zolmitriptan 5 mg

- If side effects with 1 triptan try another
  Oral Frovatriptan 2.5 – 5 mg, Naratriptan 2.5 – 5 mg, Almotriptan 12.5 – 25 mg

- Headaches of long duration, frequent headache recurrence, menstrual migraine;
  Oral Frovatriptan 2.5 – 5 mg, Naratriptan 2.5 – 5 mg

Triptan concerns

- Triptans are contraindicated in patients with uncontrolled hypertension and in symptomatic cardiovascular and cerebrovascular disease

- No association between triptan prescription and stroke (HR 1.13; 95% CI 0.78 to 1.65) or myocardial infarct (HR 0.93; 95% CI 0.60, 1.43) reported

  Neurology February 24, 2004 vol. 62 no. 4 563-568

- An OR of 0.86 (95% CI 0.52 to 1.43) reported for a serious cardiovascular event

  Roberto et al; *Cephalalgia* 2015; 35(2);118-31

- Triptans safe to use in 'hemiplegic migraine Artto V et al. *Eur J Neurol*;2007 Sep;14(9):1053-6

- Serotonin syndrome and triptans Evans et al; *Headache*; 2010; 50(6); 1089-99

Management of acute migraine

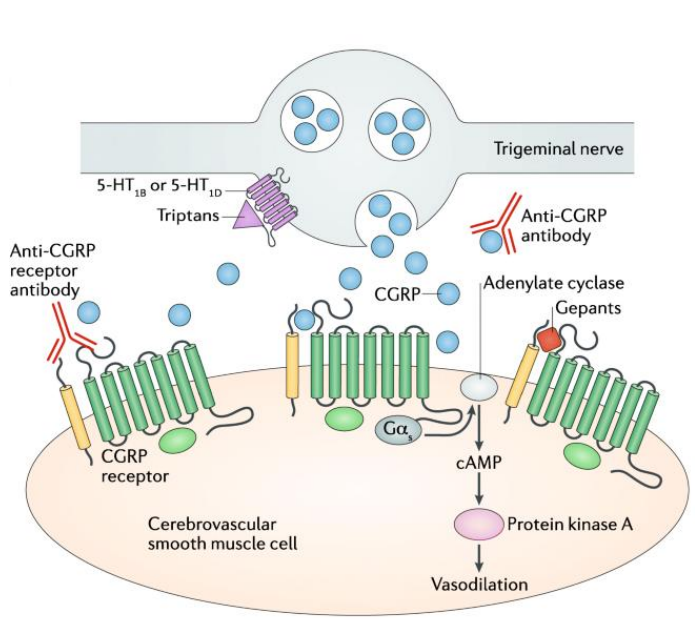
Triptans- ***problems***

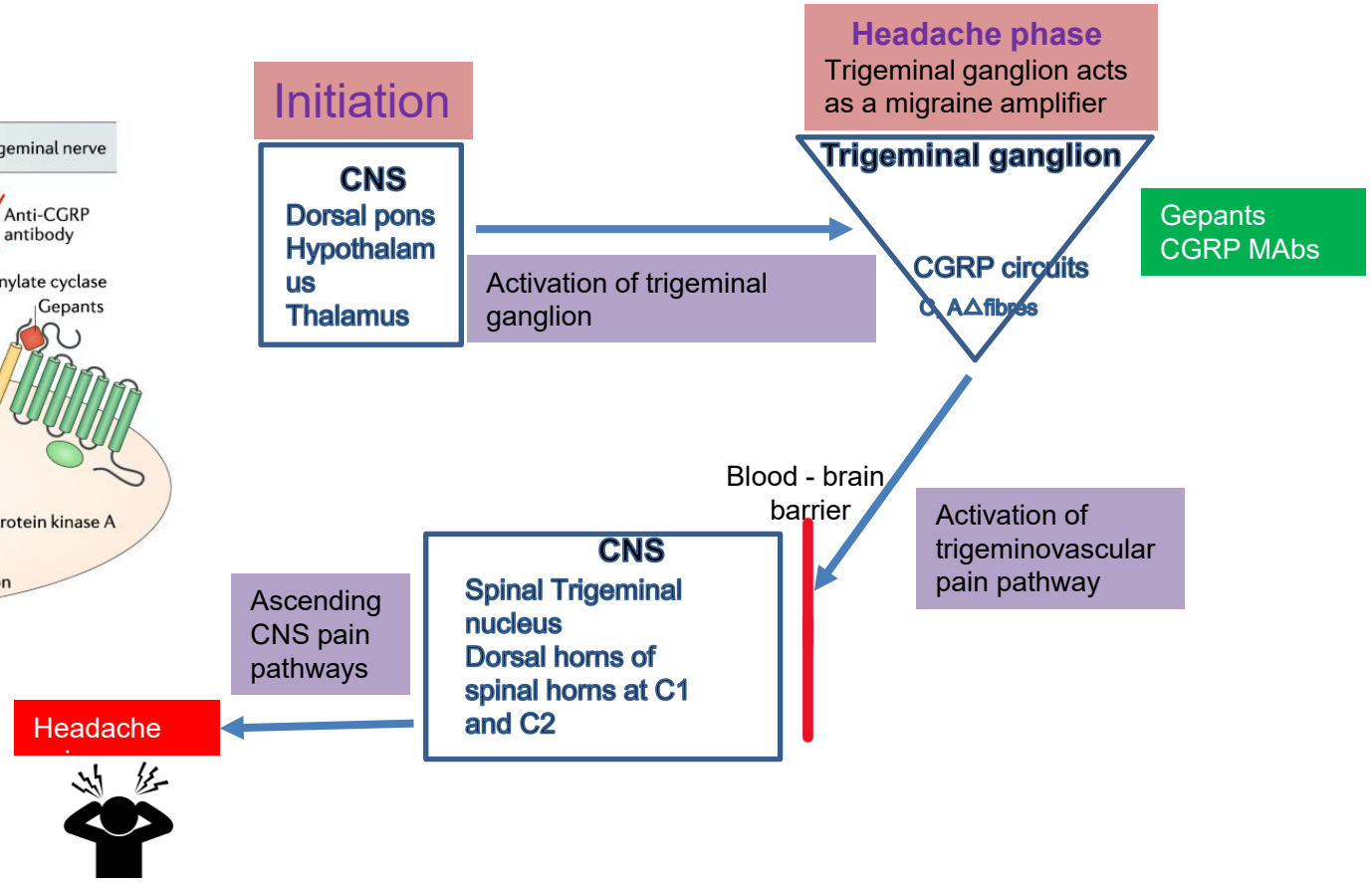
- Not effective
  - dose? route? combination?
  - Triptans ineffective in 30% Dahlof; *Cephalalgia*; 2006; 26(2); 98-106
  - timing? - 'act when mild'
    - less likely to be effective when migraine established

- Contraindications
  - Uncontrolled hypertension, symptomatic vascular disease

- Side effects
  - nausea, gastro-intestinal, sedation, chest tightness

Sites and mode of action of CGRP targeted therapies





Modified from Edvinsson L et al; Nat Rev Neurol; 2018; 14; 338 - 350

Small molecule CGRP antagonists

Drug name	Trade name (US)	Trade name (EU)	Trade name (UK)	Licensed Dose
Ubrogepant	Ubrelvy	NA	NA	
Rimegepant	Nurtec	Vydura	Vydura	75 mg oral dispersable
Atogepant	Quilepta	Aquipta	Aquipta	10 mg 60 mg
Zavegepant	Zavzpret	NA	NA	

Rimegepant - regulatory

- Rimegepant approved by NICE in October 2023 -

  *Rimegepant is recommended as an option for the **acute treatment of migraine** with or without aura in adults, only if for previous migraines:*

  - at least 2 triptans were tried and they did not work well enough or

  - triptans were contraindicated or not tolerated, and nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol were tried but did not work well enough.

- Rimegepant is the only medication approved for the acute AND the preventive treatment of migraine

Rimegepant for acute migraine – Phase 3 trials

	Pain free at 2 hours (%)	MBS free at 2 hours (%)	P value	Adverse events (%)	Adverse events – Rx arm (%)
Study 301 – 1162 patients with 2-8 migraine attacks per month					
Rimegepant 75 mg (n=543)	19.2	36.6	0.0298	12.6	Nausea 0.9% Dizziness 0.7%
Placebo (n=541)	14.2	27.7	0.0016	10.7	
Study 302 – 1186 patients with 2 – 8 migraine attacks per month					
Rimegepant 75 mg (n=537)	19.6	37.6	<0.001	17.1	Nausea 1.8% UTI 1.5%
Placebo (n=535)	12.0	25.2	<0.001	14,2	
Study 303 – 1466 patients with 2-8 migraine days a month					
Rimegepant 75 mg ODT (n=669)	21.2	59.1	<0.0001	13	Nausea 2% UTI 1% Dizziness 1%
Placebo (n=682)	10.9	43.3	0.0009	11	

Lipton RB et al; Headache 2018; 58(8); 1336-37, Lipton RB et al NEJM 2019; 381;142-9, Croop R et al; Lancet 2019; 394; 10200; 737-45

Rimegepant for acute migraine

- Rimegepant used as an oral acute treatment in patients receiving CGRP monoclonal antibodies is well tolerated with no safety issues identified.

Berman et al; Headache; 2020 Sep; 60(8); 1734-1742

- Concomitant administration of oral Rimegepant and subcutaneous sumatriptan is safe and well tolerated with no pharmacokinetic interaction

Croop et al; Cephalalgia Reports; 2021; 4; 1-10

- Rimegepant may be less likely to result in MOH with repeated use

McGinley JS et al; Neurology; 2020; 94(15S); 1793

- In patients with >6 migraine days per month prn acute treatment of Migraine over 52 weeks confers reduction in migraine frequency

Croop et al; Lancet; 2021; 397; 51-60, ema.Europe.eu

CGRP antagonists safety profile

- Ubrogepant & Atogepant are devoid of vasoconstrictive properties in human coronary arteries Rubio-Beltran E et al; Cephalalgia; 2020; 4; 357-366
- 11% of participants in ACHIEVE I & II trials were categorized as having moderate-high cardiovascular risk factors. The safety and efficacy of Ubrogepant did not differ by the presence of major cardiovascular risk factors. Hutchinson et al; Cephalalgia; 2021; 41(9); 979-990
- No hepatotoxicity attributable to the drug detected in any of the trials with Ubrogepant, Rimegepant or Atogepant
- CGRP antagonists can rarely be associated with hypersensitivity reactions including dyspnoea and rash
- Relatively contraindicated in severe renal or hepatic impairment, pregnancy or breast feeding

Main side effects are nausea, indigestion, fatigue, upper respiratory tract infections, urinary tract infections, constipation, nasopharyngitis and dry mouth, worsening of Raynaud's phenomenon

Acute migraine treatment comparison – Numbers needed to treat (NNT)

Pain freedom at 2 hours

Therapy	NNT
Simple analgesics	
Aspirin 900 mg or 1,000 mg[21]	8.1
Diclofenac potassium 50 mg[25]	8.9
Ibuprofen 400 mg[23]	7.2
Ibuprofen 200 mg[23]	9.7
Naproxen 500 mg or 825 mg[24]	11
Paracetamol 1,000 mg[27]	12
Oral triptans	
Sumatriptan 50 mg[33]	6.1
Sumatriptan 100 mg[33]	4.7
Zolmitriptan 5 mg[31]	4.8
Zolmitriptan 2.5 mg[31]	5.0
Nasal sprays	
Sumatriptan 20 mg[33]	4.7
Zolmitriptan 5 mg[31]	3.0
Subcutaneous injection	
Sumatriptan 6 mg[33]	2.3

Simple analgesics – **7.2 to 12**

Oral triptans – **4.7 to 6**

Nasal triptans – **3 to 4.7**

SC sumatriptan – **2.3**

Rimegepant 75mg – **9.7***
Ubrogepant 100mg - **10.6** +

*Croop R et al; Lancet 2019; 394; 10200; 737-45

+ Dodick DW et al; NEJM; 2019 Dec 5; 381(23); 2230-41

www.sign.ac.uk -pharmacological management of migraine Feb 2018

Strategies in acute management of migraine

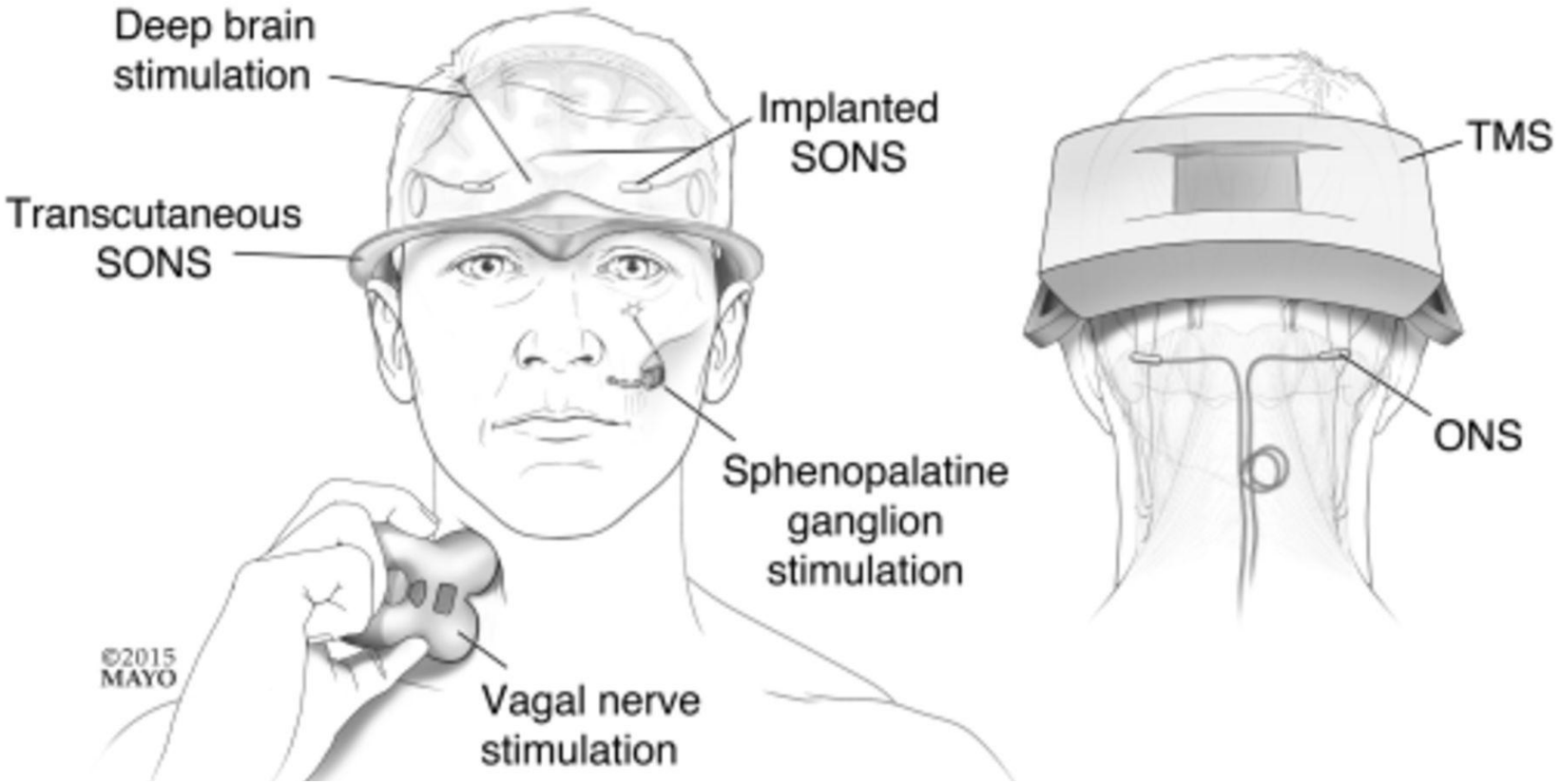
- **<u>Stepped approach</u>**

- Start with simple analgesics and if ineffective step up to a triptan.
- If two triptans ineffective, if triptans contraindicated or give side effects then consider a small molecule CGRP antagonist

- **<u>Stratified approach</u>** - target treatment based on attack severity

- In clinical practice the stepped approach is almost always preferred.

Neuromodulation



Treating acute migraine during pregnancy

- Routine and regular use of any treatment for acute migraine during pregnancy should be avoided
- Paracetamol 1000 mg can be used safely
- Sumatriptan can be considered if above fail

www.sign.ac.uk - pharmacological management of migraine Feb 2018

- Triptans, sumatriptan in particular, are not associated with an increased risk of major congenital malformations or prematurity.

Marchenko et al; *Headache*; 2015; 55(4);490-501

- No definite increased risk of spontaneous abortion.

Spielman et al; *Cephalalgia* 2017 Jan 1. Epub

Management of acute migraine

10 steps to success !

- Make the diagnosis
- Use the right drugs
- Use effective doses
- Treat early when the pain is mild
- Treat associated symptoms
- Use appropriate route of delivery
- Observe contraindications
- Use prior experience to select drugs
- Combine medications if necessary
- Avoid medication overuse headache