Migraine Diagnosis, management and complications

Julie Edwards

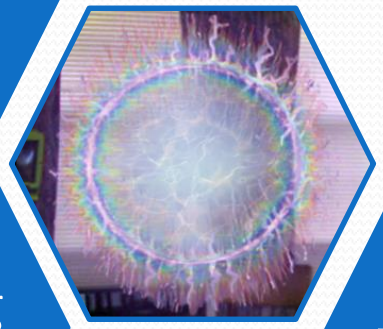
CNS for Headaches 2019

Migraine

Aura

Photo-phobia

Phono-phobia



Goes to bed

Osmo-phobia

Pounding

nausea

vomiting

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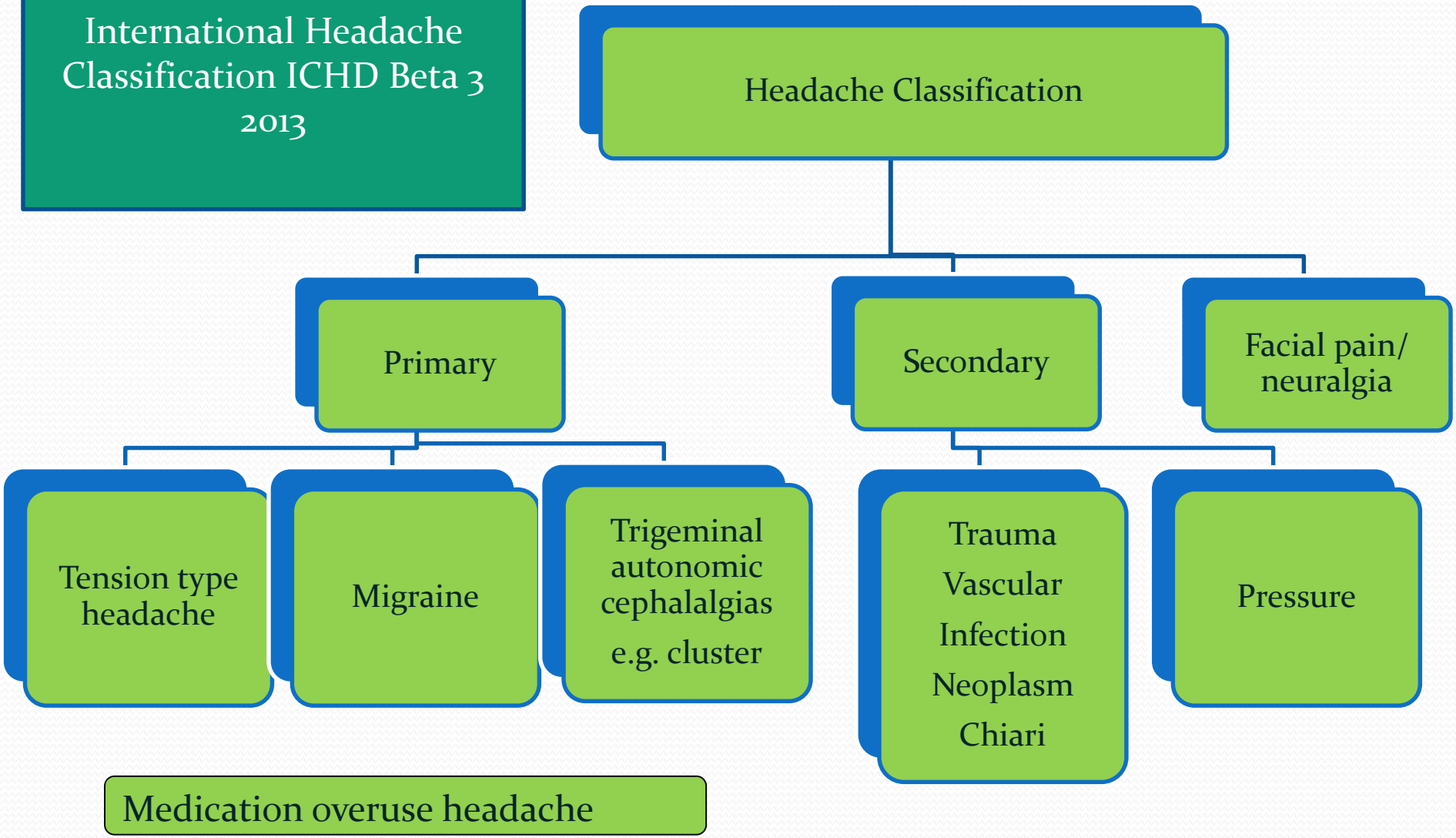
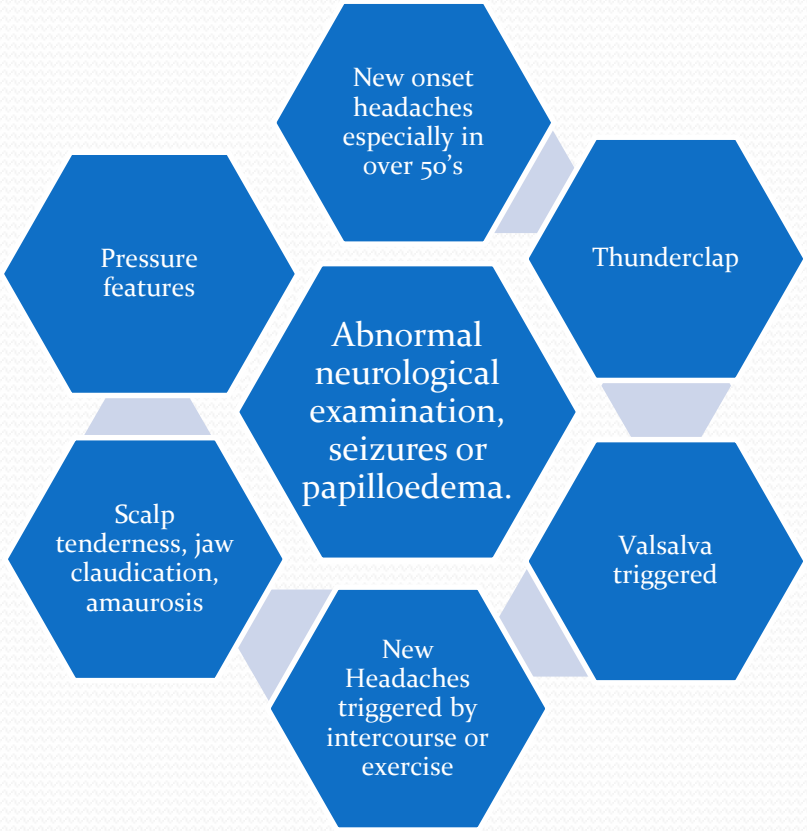
International Headache Classification ICHD Beta 3 2013



Patient worry about brain tumours

- The clues are in the history.
- Neurological examination is usually normal
- Always check Fundi
- Do not scan for reassurance alone (NICE guidance CG150)
- Exclude Red Flags
- Migraine is not curable like all chronic pain but most can be managed.

Red flags



Three levels of risk of brain tumour and suggested management. Kernick 2008.

Red flags — underlying tumour is likely to be greater than 1%. These warrant urgent investigation.

Orange flags — underlying tumour is likely to be between 0.1 and 1%. These need careful monitoring and a low threshold for investigation.

Yellow flags — underlying tumour is likely to be less than 0.1% but above the population rate of 0.01%. These require appropriate management but the need for follow-up is not excluded.

Red Flags

- Papilloedema
  - New onset Cluster Headache
  - alterations in consciousness
- New Epileptic Seizure
  - Headache with a history of cancer
  - Headache with abnormal examination

Orange Flags

- Unclear diagnostic pattern in 8 weeks
- Headaches associated with vomiting
- Headaches that wake from sleep
- Headaches triggered by Valsalva manoeuvre
- Significant change in pattern
- New headache in the over 50's

Yellow Flags

Diagnosis of tension type headache

Weakness or motor loss

Personality change

Diagnosis of migraine

Memory Loss

"RED FLAG" Mnemonic

"S N O O P S"

SYSTEMIC SYMPTOMS (e.g. fever,weight loss)

NEUROLOGIC SYMPTOMS/SIGNS

ONSET (SUDDEN)

OLD AGE (50 YEARS)

PRIOR HISTORY (New Headache)

SECONDARY ILLNESSES (HIV, CANCER)

Scanning.

- Why Not Just Scan everyone, that way we don't miss anything ?
- Cost
- Lack of resources.
- Reinforces negative thoughts in otherwise healthy individuals.
- This does not treat the underlying headache and does not meet patient needs.
- Can have negative effects on getting mortgage, insurance etc.

Co-incidental Findings.

In a study of 2000 healthy volunteers imaged with MRI (Vernooji et al 2007)

145 (7.2%) had asymptomatic brain infarcts

1.8% had cerebral aneurysms

1.6% had a benign primary tumor

0.9% Meningioma, 0.3% pituitary adenoma, 0.2% vestibular schwannoma and 1 possible glioma

Incedentalomas on MRI scan

	% prevalence
Neoplasia	0.7
Memingioma	0.29
Pituitary adenoma	0.15
Low grade glioma	0.05
Acoustic neuroma	0.03
Lipoma	0.04
Epidermoid	0.03
Vascular	0.56
Aneurysm	0.35
Cavernous malform	0.16
AV malformation	0.05
Inflammatory	0.09
Demyelination – definite	0.06
Demyelination -possible	0.03
Cyst	0.54
Arachnoid	0.5
Colloid	0.04
Chiari 1	0.24
Hydrocephalus	0.10
Extra-axial collection	0.04

- Incidental findings in 2.7% of "healthy" scanned for research / routine medicals
  - White matter hyperintensities, silent brain infarcts, brain microbleeds, and anatomical variants were not included
- Higher on 3T scans Vs 1.5T MRI scanner

Morris Z et al 2009 BMJ

Why Treat Migraine?

Migraine - its common 1 in 7

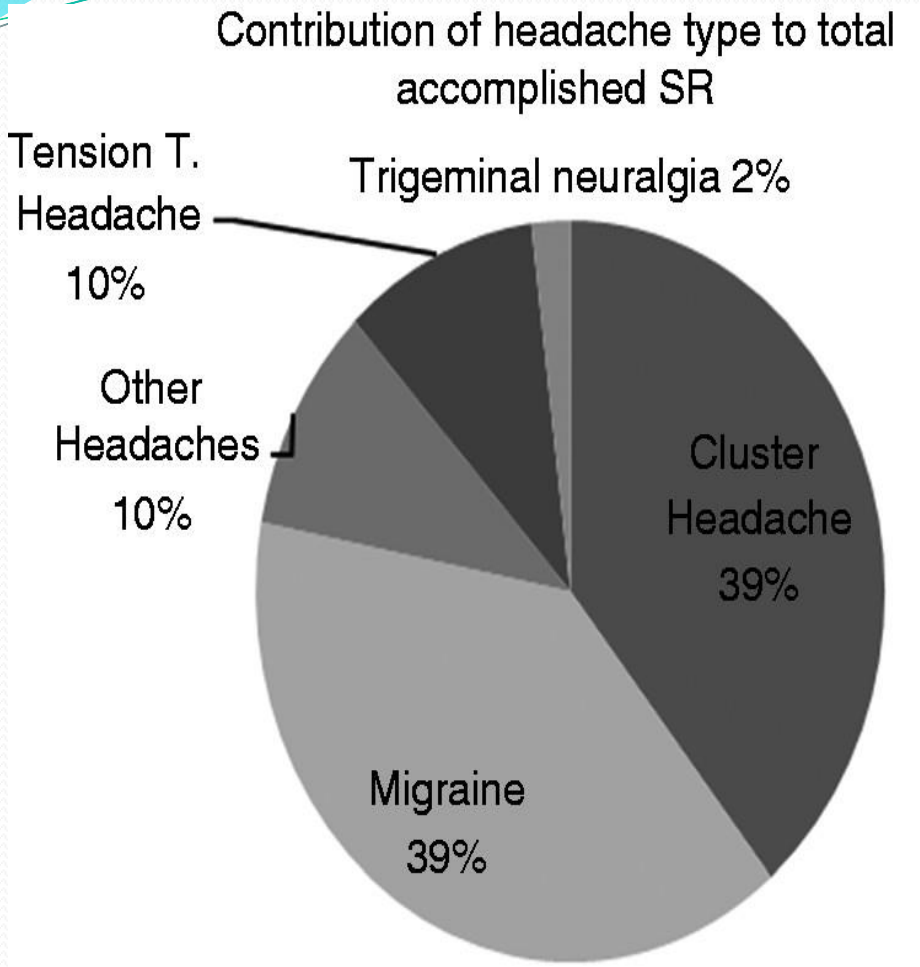
- **Most patients with headache have migraine**
- A positive diagnosis is usually correct (98%)
- Those identified as a non-migrainous primary headache……
  - 82% actually have migraine BUT:
- A quarter of patients with migraine will have their diagnosis missed

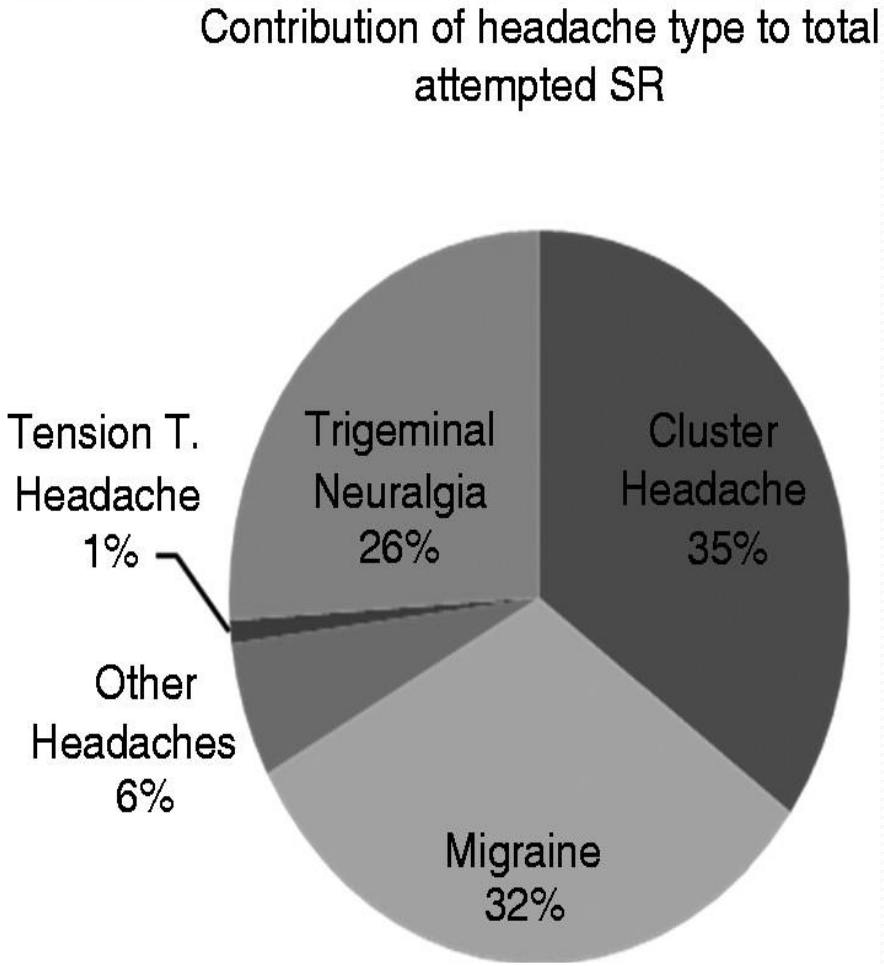
Landmark study 2004

Migraine – its costly and disabling

- Global burden of disease study
  - Migraine number 3, number 1 for the working age group.
- Common – Migraine effects 15% of population
- Global prevalence of 47%

- Disabling
  - Missed work / school
  - Impaired activities of daily living
  - Costing 6.6 to 8.8 billion per year in UK, in treatment, lost sick days and lost productivity.





- Trejo-Gabriel-Galan JM, Aicua-Rapun I, Cubo-Delgado E. (2017). Suicide in primary headache in 48 countries: a physician survey based study. Cephalalgia Jan 17.

Migraine diagnosis

Migraine without aura

A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
   - unilateral location
   - pulsating quality
   - moderate or severe pain intensity
   - aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
   - nausea and/or vomiting
   - photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

ICHD = International Classification of Headache Disorders

1. Headache Classification Committee; Olesen J, et al. The International Classification of Headache Disorders: 3rd Edition Celphalalgia 2013.

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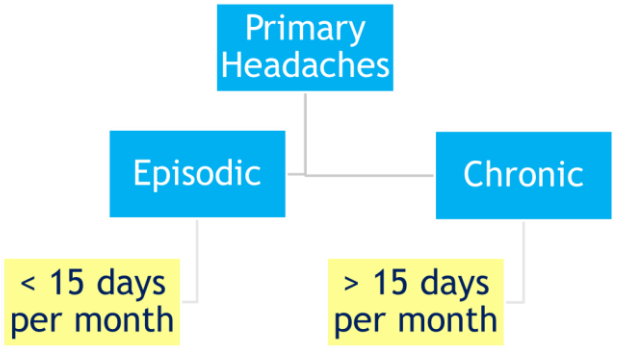
Aura

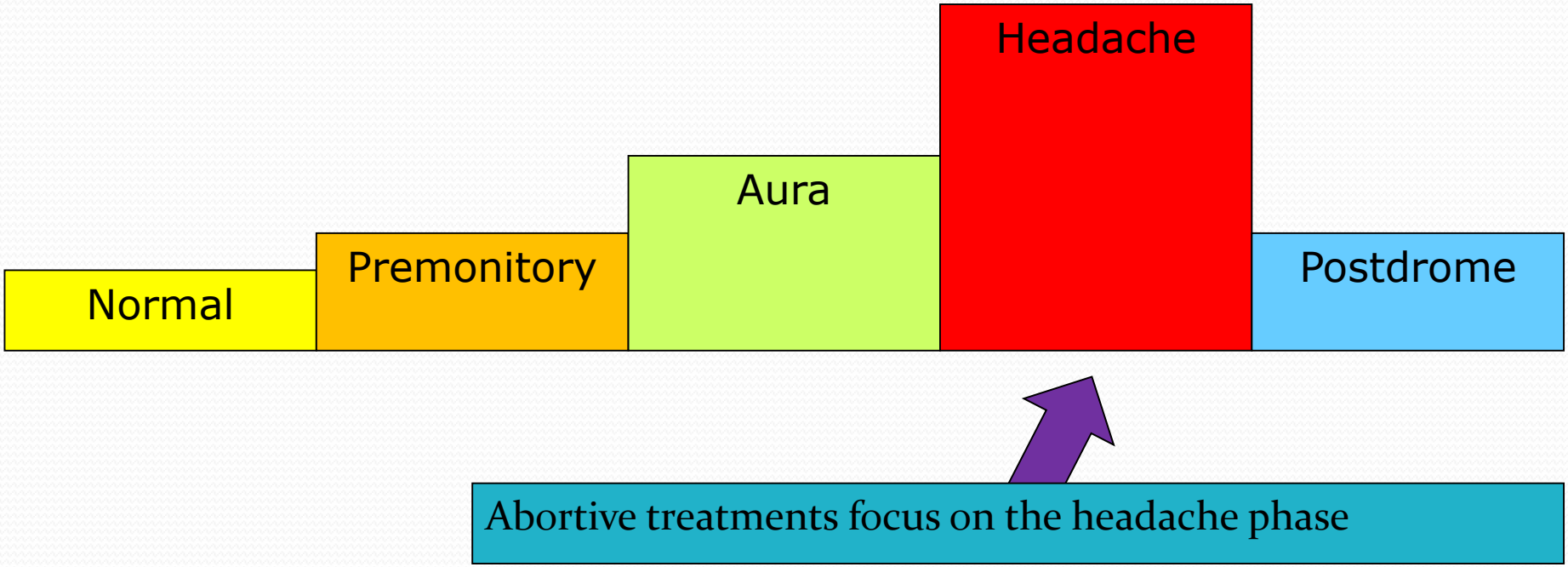
- Visual
- Sensory/ Motor
- Speech

Migraine

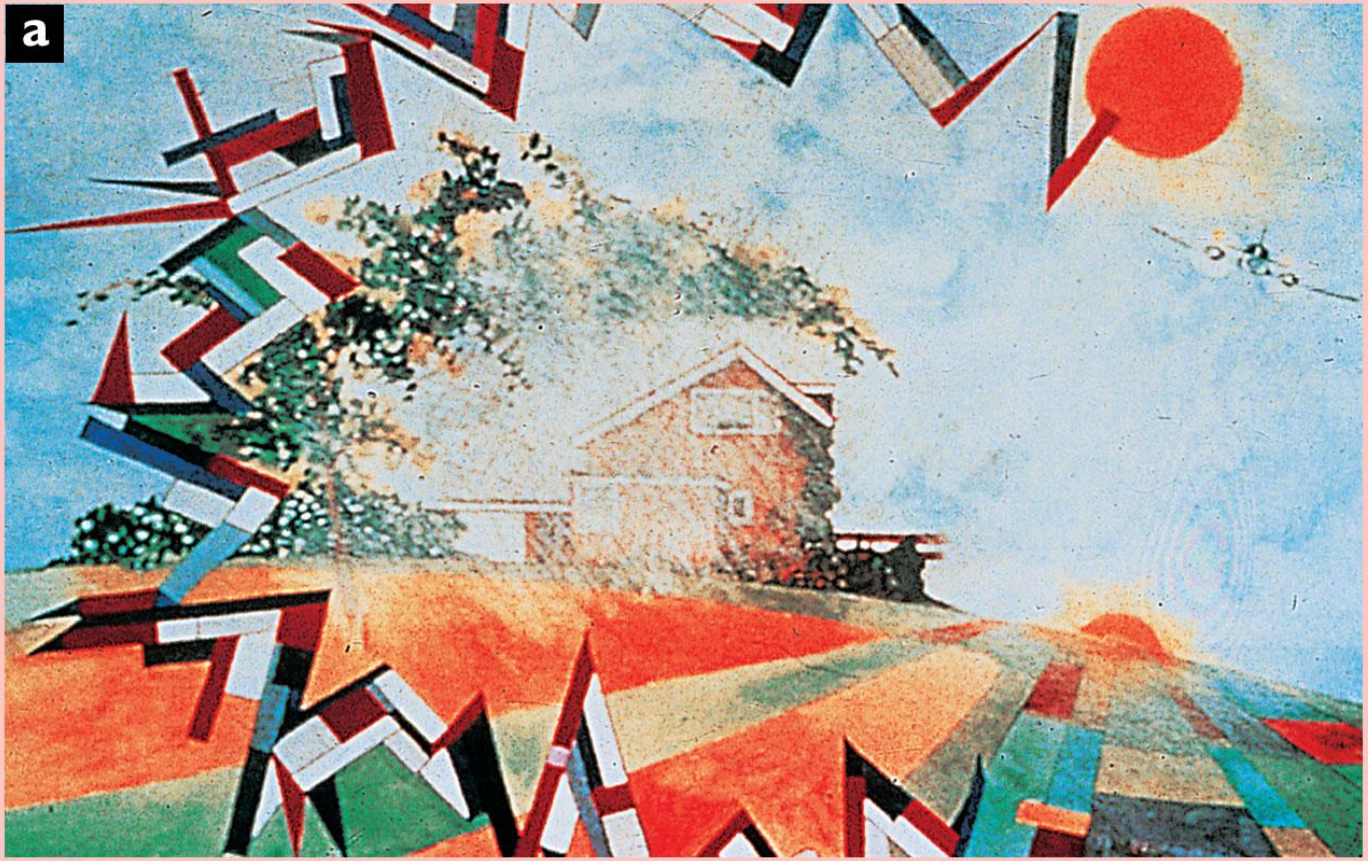
- Moderate or Severe pain
- Duration 4 - 72 hours
- Frequency: any
- Location: unilateral or bilateral
- Throbbing
- Nausea +/- vomiting
- Aggravated by routine physical activity
- Photo + phonophobia



Migraine Stages

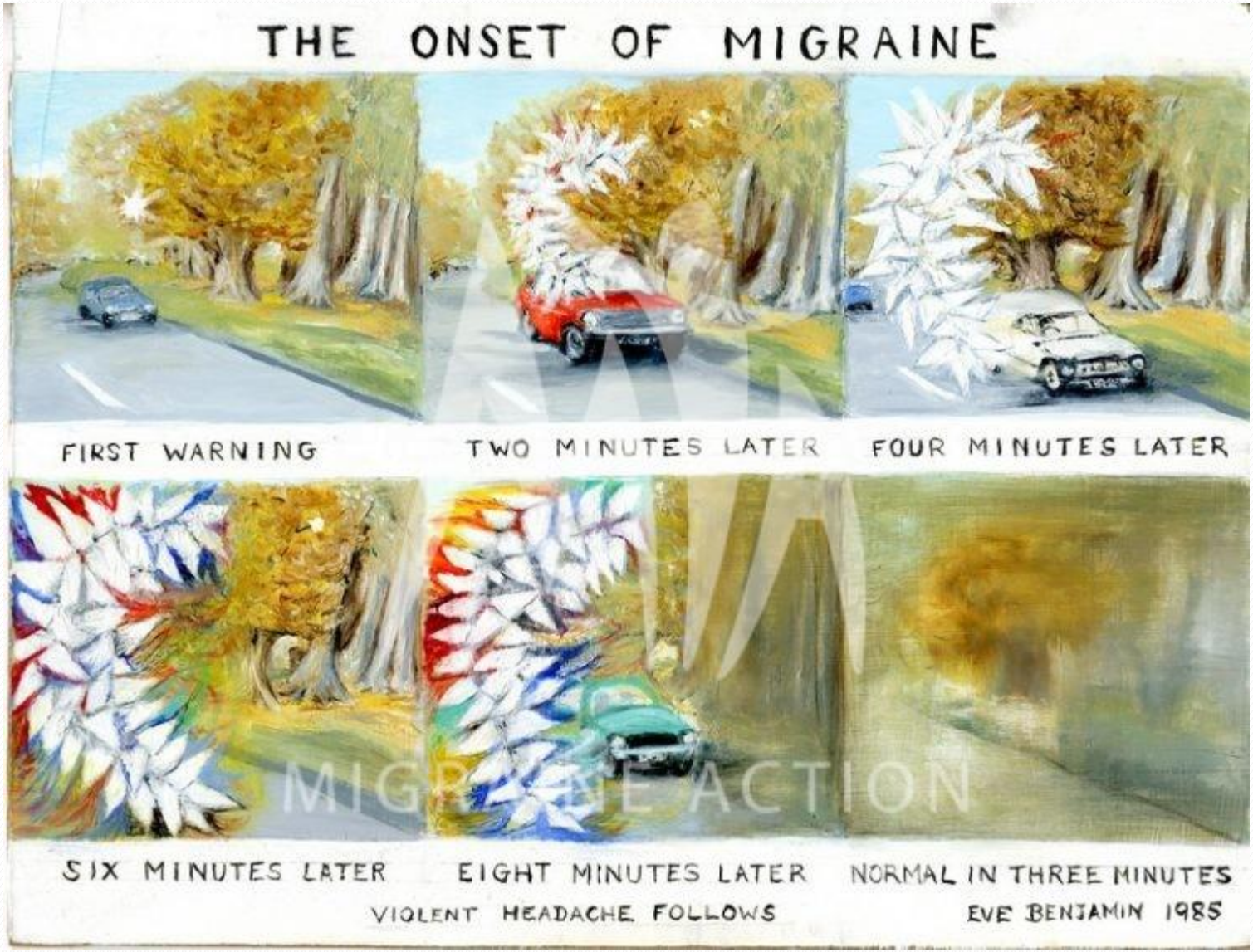


Visual aura - distorted vision

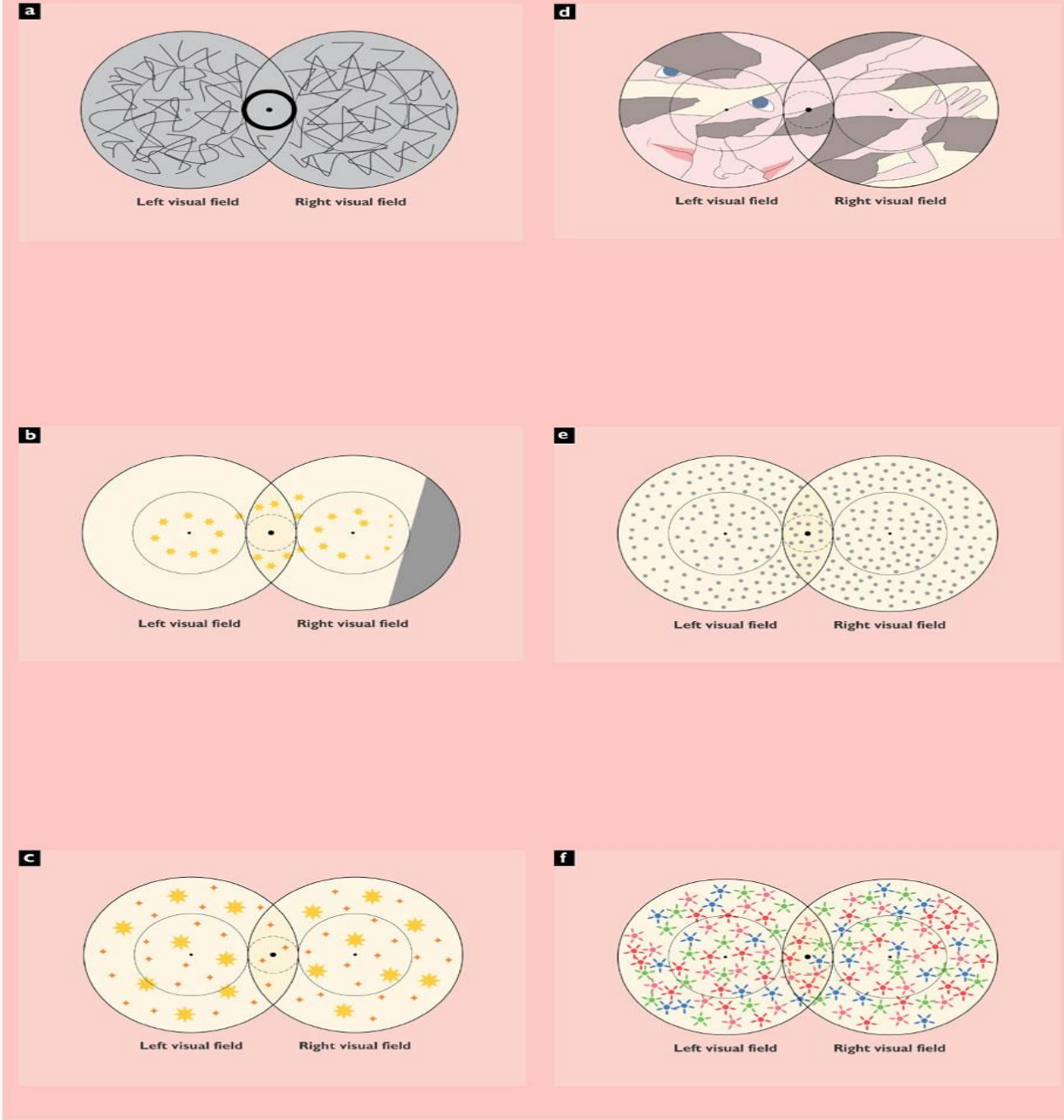


Migraine Aura

Visual aura



Variety of visual aura



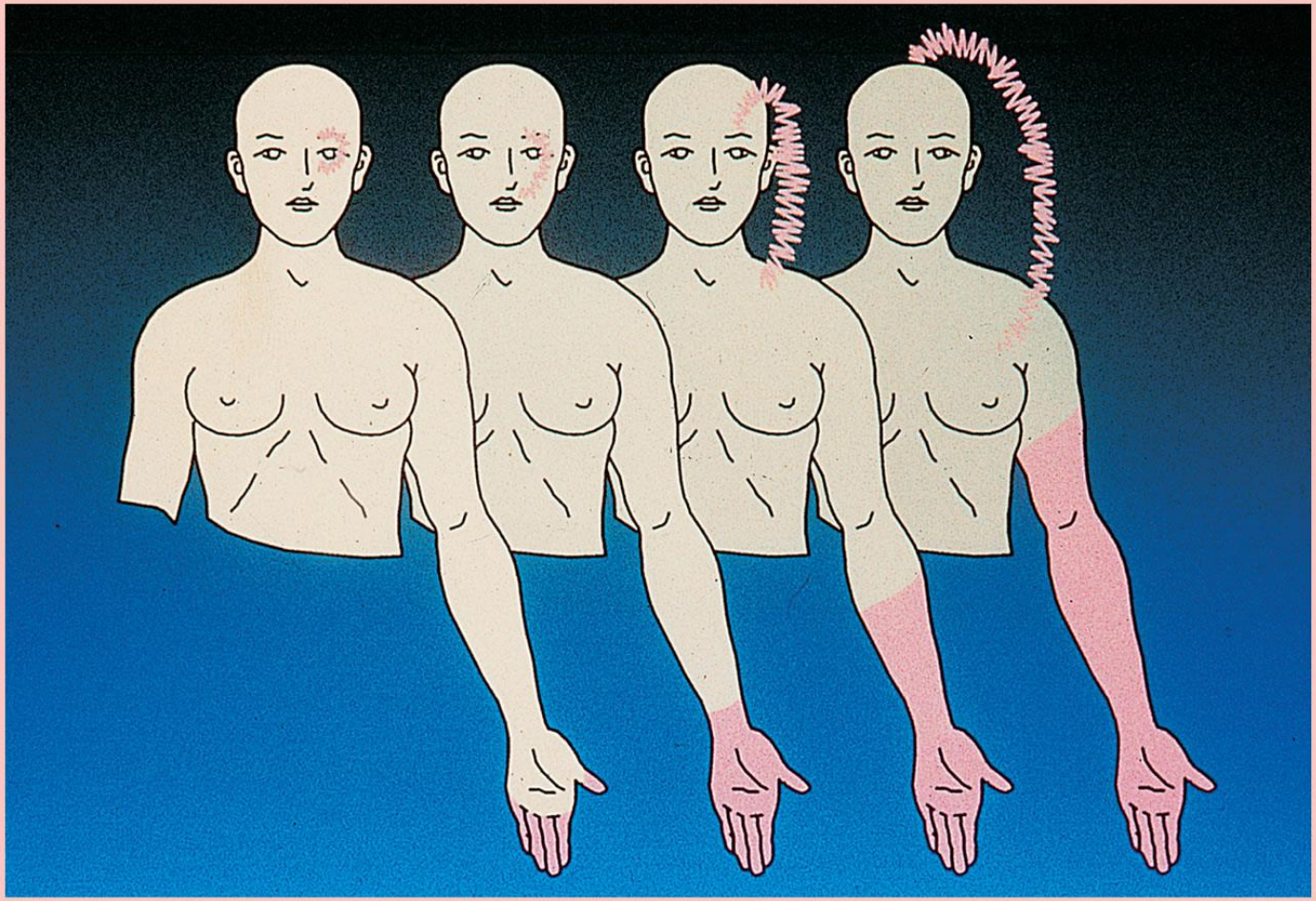
Limb aura

Evolving area of sensory disturbance

- Arm or leg
- Hemifacial

Progressive loss of power

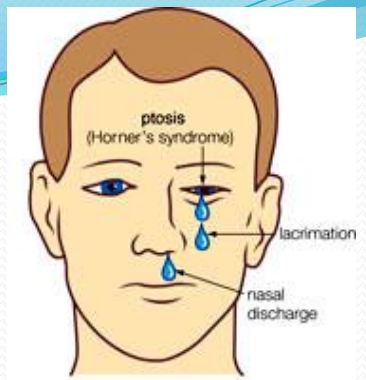
- Arm or leg
- Face
- Hemiplegia

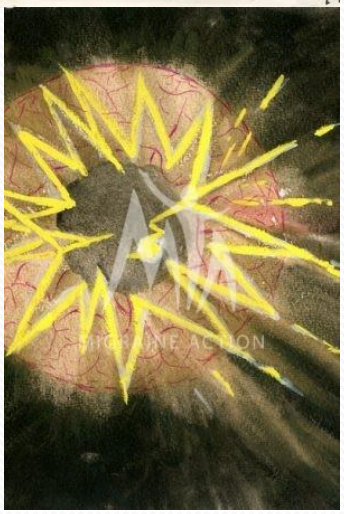


Autonomic features seen in migraine but less prominent than a TAC..

Autonomic features can occur in migraine

Feature	Cluster headache	Migraine
Gender M:F	2.5:7.1	1:3
laterality	unilateral	Uni or bilat
Duration	15min -3 hrs	4 hrs – 3 days
Onset	rapid	Gradual
Frequency	1 alt days – 8xday	Variable
Circadian periodicity	yes	No
Autonomic	++	+
Migrainous features	+	++
Alcohol trigger	30min-2 hrs	6-24 hrs
movement	restless	still





Aura

- Viana et.al (2016) in a study of 54 patients experiencing 162 auras, in which the same patient could have multiple aura features in the same attack,

- 229 auras reported in total.
- aura being longer than one hour in 14% (n=158)
- of those with visual aura, 21% (n=52)
- of those with sensory aura 17% (n=18)

- It is normally reported aura will proceed the headache
- headache before the aura in 9%,
- commenced simultaneously with the aura in 14%,
- during the aura in 26%.
- Simultaneously with the end of the aura in 15%
- Headache in 36% at the end of the aura.

Clinical scenario

- 32 year old lady comes to clinic
- Worried about changing headaches
- Headaches on and off for many years (+10years)
  - Last 2 years - headaches once a week
- Now headaches twice a week
  - More than usual and more severe but still 4-5 days per week pain free.
  - Last all day
  - Feels sick and often vomits
  - Throbbing pain in her right eye, back of her head and neck
  - Goes to bed to avoid light and noise
  - Washed out the day before and after

Migraine Management Overview

- Aim for effective control of symptoms
  - A cure can be unrealistic
- Under-treatment is not cost-effective
  - Results in unnecessary pain and disability
  - Repeat consultations are expensive

1: Acute treatment

2: Preventative treatment

Acute migraine management

The NICE guidelines (CG150)

- Combination therapy:

Triptan + NSAID/ paracetmol + Antiemetic

- Alternatively (per patient request):
  a single agent (triptan, NSAID or paracetamol) ± antiemetic

Opiate-based, mixed analgesics and ergot's should be avoided.

Acute migraine management

Non-specific Treatments

Non-steroidal anti-inflammatory drug (NSAID)

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

Or

- **Paracetamol 1g**

Antiemetics

For nausea and/or as a prokinetics such as;

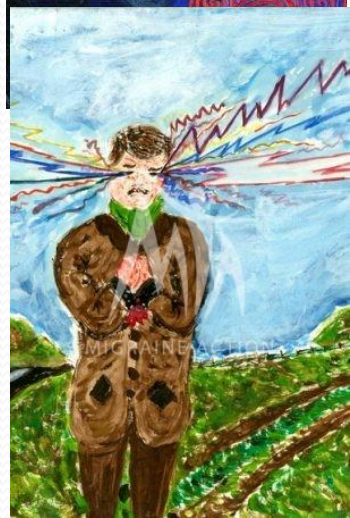
- Domperidone 10mg up to TDS (or 60mg suppository)
- Metoclopramide 10mg
- Prochlorperazine 3-6mg as buccal preparation

If oral medication non tolerated offer non-oral preparation

Which triptan?

Pharmacokinetics of Triptans

Triptan	Peak level	Half-life
Almotriptan	1.5-2 hours	3.5 hours
Eletriptan	1.5-2 hours	4 hours
Frovatriptan	2-4 hours	26 hours
Naratriptan	2-3 hours	6 hours
Rizatriptan	1-1.5 hours	2 hours
Sumatriptan	2-3 hours	2 hours
Sumatriptan SC	12 minutes	1.9 hours
Sumatriptan IN	1-1.5 hours	2 hours
Zolmitriptan	1-1.5 hours	2.5 hours
Zolmitriptan IN	15 minutes	3 hours



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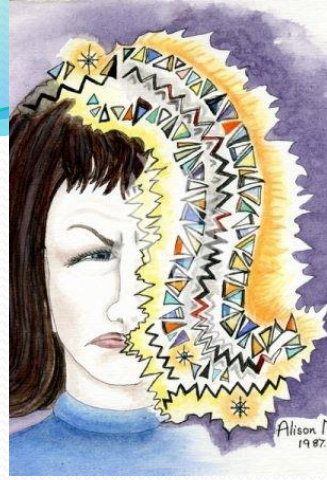
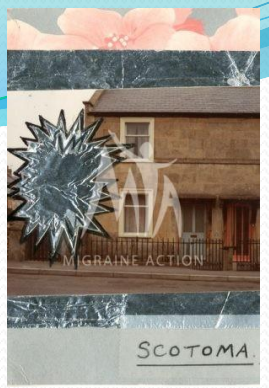


For oral therapies Start here and try up to 100mg

Which triptan?

Pharmacokinetics of Triptans



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Other rapidly acting oral therapies

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Longer half life

Which triptan?

Pharmacokinetics of Triptans

Triptan	Peak level	Half-life	Usual dose (Max daily dose)	Cost (per tablet)
Almotriptan	1.5-2 hours	3.5 hours	12.5mg (25mg)	3.0 GBP (12.5mg)
Eletriptan	1.5-2 hours	4 hours	40mg (80mg)	3.8 GBP (40mg)
Frovatriptan	2-4 hours	26 hours	2.5mg (5mg)	2.8 GBP (2.5mg)
Naratriptan	2-3 hours	6 hours	2.5mg (5mg)	3.8 GBP (2.5mg)
Rizatriptan	1-1.5 hours	2 hours	10mg (20mg) –same for melt	4.5 GBP (5mg)
Sumatriptan	2-3 hours	2 hours	50-100mg (300mg)	0.3 GBP (50mg)
Sumatriptan SC	12 minutes	1.9 hours	6mg (12mg)	21.2 GBP (per injection)
Sumatriptan IN	1-1.5 hours	2 hours	10-20mg (40mg)	5.9 GBP (per dose)
Zolmitriptan	1-1.5 hours	2.5 hours	2.5-5mg (10mg)	3.8 GBP (2.5mg)
Zolmitriptan IN	15 minutes	3 hours	5mg into one nostril, once (10mg)	11.0 GBP (per spray)

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£

Clinical Scenario

- 57 year old male
- Migraine episodically since early 20's, visual aura in thirties but none since.
- Increased in frequency from late forties and has been daily since 52 years old.
- MI at 54 requiring stenting.
- Not previously presented to his GP about the headaches since the MI.

Triptan Safety - Cardiovascular

- Triptans are $5HT_{1B/1D}$ receptor agonists
  - vasoconstrictive effects on blood vessels.
- **Contraindicated in coronary artery disease, cerebrovascular disease, peripheral vascular disease, and uncontrolled hypertension.**
- In clinical trials, cardiovascular complications were fewer than one per million exposed
  - Systematic review of cardiovascular safety data there was no strong cardiovascular safety issue identified.
- **Triptan sensations**, such as burning or tingling in the chest or limbs, are **relatively common (7%),** but patients can be reassured that this is not associated with cardiac ischaemia.

Roberto Cephalalgia 2015
Dodick D. Headache 2004

Triptan Safety + anti depressants

- 2006 United States Food and Drug Administration issued a warning about **serotonin syndrome** in patients taking triptans + SSRI's or SNRI's (29 cases)
- However, American Headache Society critically examined these 29 cases and found that only 10 cases met Sternbach criteria for diagnosing serotonin syndrome
- Conclusion
  - **Triptans do not need to be restricted in patients on SSRIs or SNRIs.**

Evans Headache 20120
Pringsheim. BMJ 2014

Triptan Safety

- Drug interactions
  - Concomitant use of ergotamine within 24 hours of triptan use is contraindicated
  - Concomitant use of monoamine oxidase inhibitors within two weeks is contraindicated

Treatment options

- DO not use triptan's in patients who have had a heart attack, stroke or who have uncontrolled cardiovascular risk factors
- Use simple analgesics with an anti-emetic to help with gastric absorption
- Exclude and manage medication overuse headache
- Use prophylaxis early in presentation as pain management options limited.
- Sodium Valproate is worthy of consideration in male patients but not women of child bearing age.

Which preventative?

Migraine preventatives

- **NICE guidelines**

1st line

- Beta Blocker
- Topiramate

2nd line

- Amitriptyline / dothiepin
- BOTOX
- ~~Gabapentin~~
- Acupuncture

NEXT

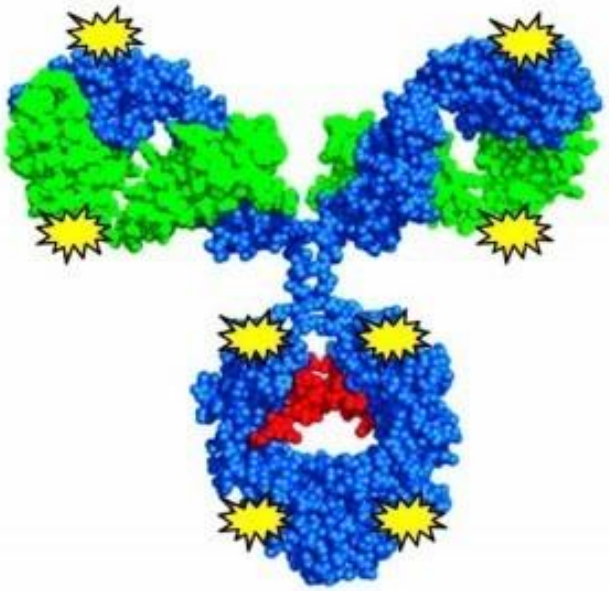
- Valproate
- Pregabalin
- Pizotifen
- Candesartan

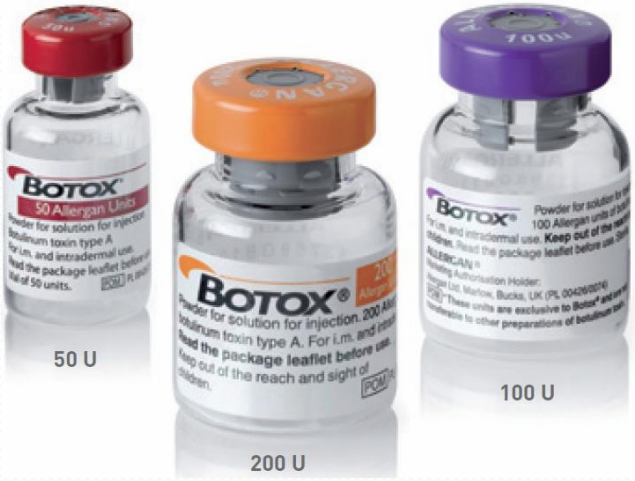
Preventive Treatments of Migraine

Preventive	Start dose	Increments	Target dose
Propranolol	10-20mg bd	10 mg bd every 1-2 weeks	80mgs bd
Amitriptyline	10mg od	10mg every 1-2 weeks	50-75mg nocte
Dosulepin	25mg od	25mg every 2 weeks	50-75mg nocte
Pizotifen	0.5 mg od	0.5mg every 1-2 weeks	3mg nocte
Topiramate	25mg od	25-50mg every 1-2 weeks	100mg/day
Valproate	200mg od	200mg every 2 weeks	1.0g daily
Candesartan	4mg od	4mg every 1 week	8mg bd

Start Low – build slow
Need a 3 month trial

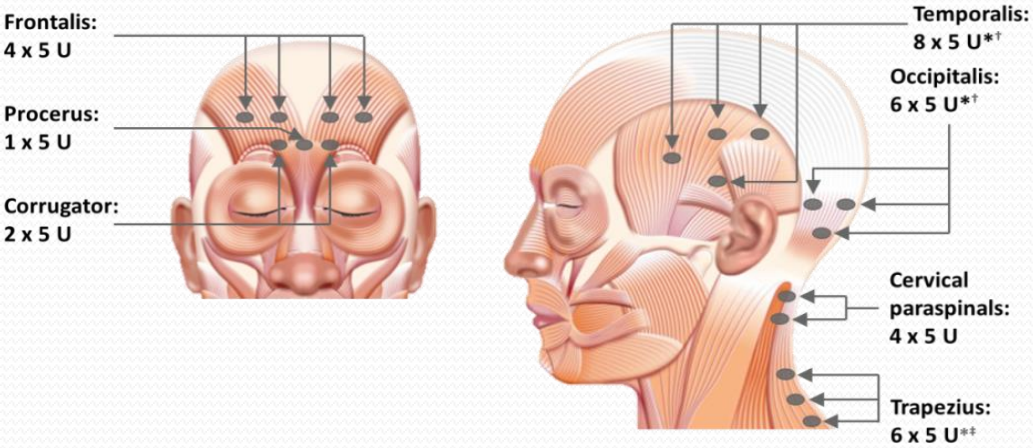
Where does the future lie?





NICE BOTOX

- Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine
- Chronic migraine is defined as headaches on at least 15 days per month of which at least 8 days are with migraine:[1]
  - That has not responded to at least **three prior** pharmacological prophylaxis therapies
  - Whose condition is appropriately **managed for medication overuse**

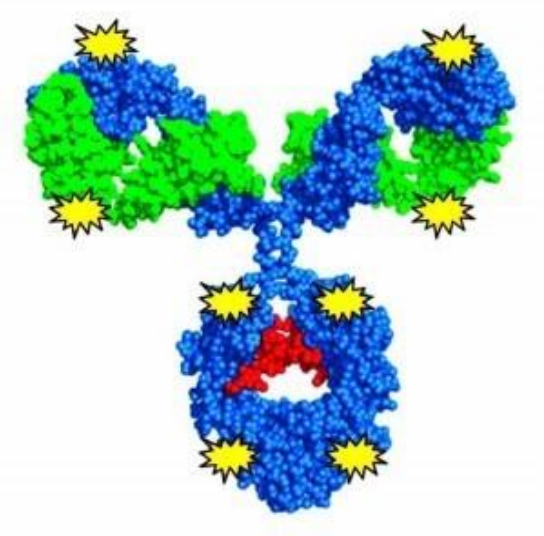


NICE: National Institute for Health and Clinical Excellence.

1. NICE technology appraisal guidance 260. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. June 2012

Erenumab

- First launched CRGP Monoclonal antibody specifically for migraine
- Licenced in US and Europe 2018
- Nice rejected in Sept 2019 but approved in Scotland.
- Once per month injection to prevent migraine.

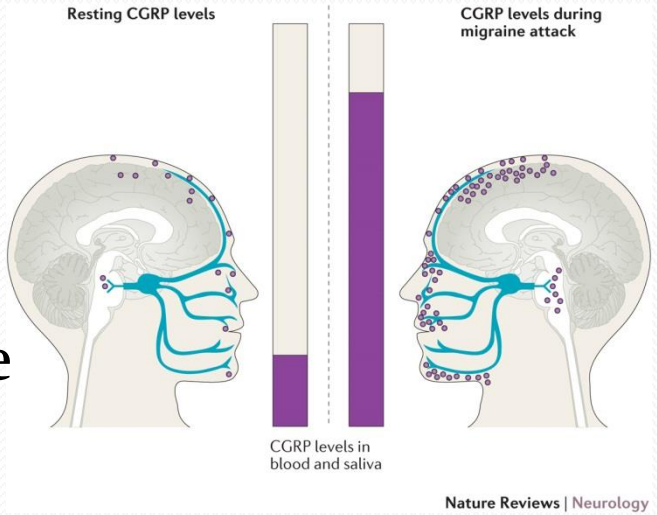


FUTURE CRGP therapy

- Calcitonin Gene-Related Peptide is widely present in peripheral and central neurons, including trigeminal neurons
- CGRP is a potent vasodilator
- Administration of CGRP to patients with migraine will trigger migrainous headache

- CGRP levels are elevated during a migraine attack
- Triptans block the release of CGRP

- Could CGRP antagonists abort an acute migraine?



Headachemasterclass.com

Schuster, N et al *Nat. Rev. Neurol 2016*

	Placebo N=281	Erenumab 70mgs N=188	Difference or odds ratio (95% CI)	P value	Erenumab 140mgs. N=187	Difference or odds ratio (95% CI)	P value
Primary end point							
Monthly migraine days	-4.2 (0.4)	-6.6 (0.4)	-2.5 (-3.5 to -1.4)	<0.0001	-6.6 (0.4)	-2.5 (-3.5 to -1.4)	<000.1
Secondary end points							
50% responder rates	66(23%)	75 (40%)	2.2±(1.5 to 3.3)	0.0001	77(41%)	2.3± (1.6 to 3.5)	<0.0001
Monthly acute migraine-specific drug treatment days	-1.6 (0.2)	-3.5 (0.3)	-1.9 (-2.6 to 1.1)	<0.0001	-4.1 (0.3)	-2.6 (-3.3 to -1.8)	<0.0001
Cumulative monthly headache hours	-55.2 (5.7)	-64.8 (6.9)	-9.5 (-27.0 to 7.9)	0.2833	-74.5 (6.9)	-19.3 (-36.7 to -1.9)	0.0296

Other Prophylactics

- Botulinum Toxin only licensed for Chronic migraine.
- Flunarizine not licensed in UK.
- Duloxetine 60-120mgs
- Feverfew- private
- Riboflavin-private
- Magnesium- private
- Co Enzyme Q10- private
- Lisinopril 20-40 mgs.
- Gammacore- private for migraine
- Cefaly- private
- Occipital or vagal nerve implanted stimulation
- Deep brain stimulation

Principles of treatment on medication

- Use migraine specific pain killers
- Use the correct dose
- Pain killers only 2 x a week
- Build up prevention tablets slowly
- Aim to try the prevention tablets for >3months

Clinical Scenario

- A 24 year old female currently 10 weeks pregnant with her first child has been sent to clinic by her GP, who is unsure what treatments can be considered.
- Migraine with aura since 16 years old. Visual aura lasts 45 minutes with evolution of the fortification spectrum followed by a sever headache for 48 hours. She has profuse vomiting and is restricted to bed.
- Migraine remains unchanged during pregnancy apart form increased frequency to 2-3 per week. Aura still the same but vomiting is worse. Struggling to keep fluids down and has required sever al admissions to hospital for dehydration.

Management of Acute Migraine Pregnancy

BEWARE TERATOGENICITY

- NSAIDs can be used in early pregnancy but are absolutely contraindicated in the third trimester
- Aspirin is a particular concern, due to the possibility of developing Reye's Syndrome in the neonate.
- Of the abortives, paracetamol is probably the safest.

Triptans in pregnancy?

- Only use if benefit > risk
- Sumatriptan pregnancy register (626 pregnancies)
  - First trimester birth defects was 4.2% vs 3-5% in the general population
- Rizatriptan pregnancy registry
  - No evidence of risk, but insufficient no. of reports

- The current NICE CG150 Headache guidelines: **"Triptans can and should be considered for pregnant patients"**
  - If disabling attacks
  - Other therapies unhelpful
  - Counselled about potential risks

Triptans and breastfeeding?

- Triptans are generally considered to be compatible with breast feeding
- Less than 10% of the drug dose is found in breast milk
- However, there are no large studies in this area.
- If patient is concerned, express and discard the breast milk for 24 hours after using a triptan.
- Use frozen expressed milk from the freezer.

Hutchison S. Headache 2013

Analgesics

Drug	1st Trimester	2nd Trimester	3rd Trimester	Lactation
Paracetamol	✓	✓	✓	✓
Codeine	(✓)	(✓)	(✓)	✓
Aspirin	(✓)	(✓)	**Avoid**	Avoid
Doclofenac	(✓)	(✓)	**Avoid**	✓
Ibuprufen	(✓)	(✓)	**Avoid**	✓
Naproxen	(✓)	(✓)	**Avoid**	✓

CI = contraindicated ID= insufficient data ?(✓) = limited data, but probably safe

(✓)=data suggest unlikely to cause harm ✓ = no evidence of harm

MacGregor 2007

Antiemetics

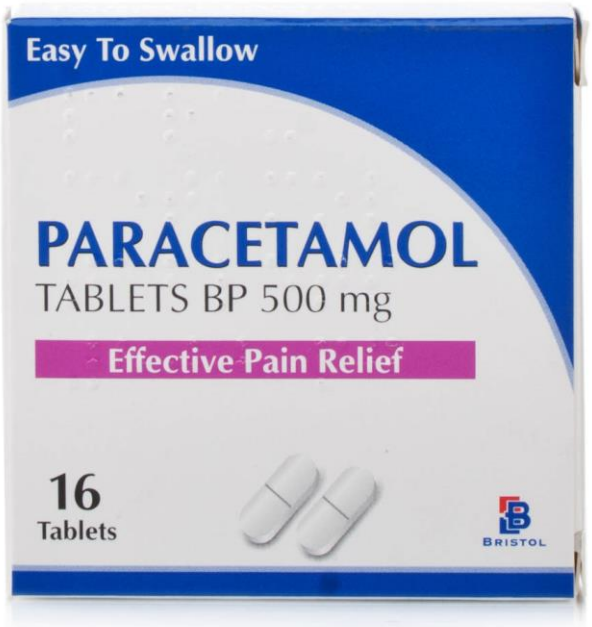
Drug	1st trimester	2nd trimester	3rd trimester	lactation
Buclizine	(✓)	(✓)	(✓)	✓
Cyclizine	(✓)	(✓)	(✓)	✓
Domperidone	(✓)	(✓)	(✓)	✓
Doxylamine	(✓)	(✓)	(✓)	(✓)
Metoclopramide	(✓)	(✓)	(✓)	(✓)
Prochorperazine	(✓)	(✓)	(✓)	✓

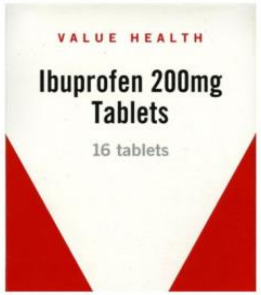
MacGregor 2007

How would I treat

- Discuss the treatment options.
- Offer a triptan such as Sumatriptan
- Add an anti-emetic to avoid dehydration and aid gastric absorption.
- Offer a Greater Occipital Nerve Block.
- Discuss low dose Amitriptyline or Propranolol and associated risks.
- Liaise with obstetrician and Gp as required

Medication overuse Headache





Medication Overuse Headache

- Headache present more than 15 days per month
- Regularly overusing analgesics during the time the headache worsened or developed.
- Simple analgesics ….15 days per month for 3 months
- Opiates, Triptans and codeine based drugs….10 days per month for 3 months
- Is all that is required to produce a daily headache and worsen migraine
- This is regardless of what the condition the painkillers are taken for. If the patient is also susceptible to headaches then this is a potential risk.
- Prevention is better than cure.

Drugs associated with medication overuse in chronic daily headache

- Overuse of barbiturates and opiates, but not triptans, has been associated with increased risk of progression from episodic migraine to chronic migraine.[2]

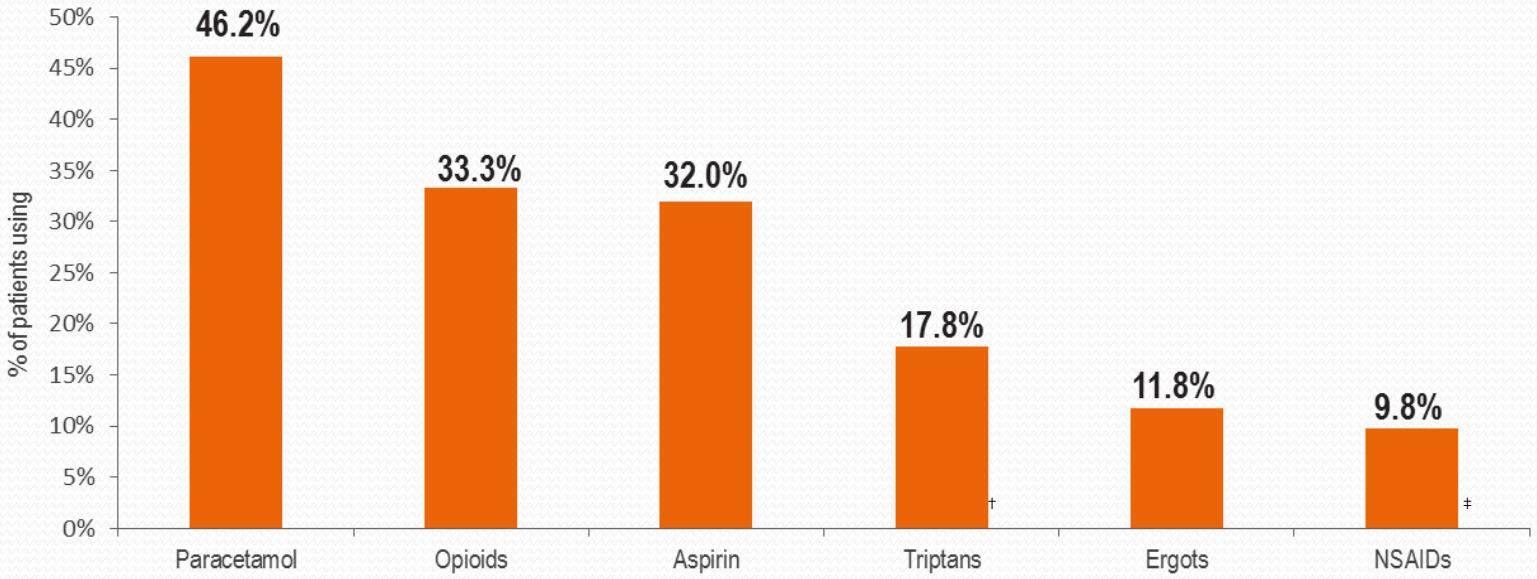


Figure adapted from Bigal ME, et al. 2004

*Medication overuse defined as 1. Simple analgesic use (>1000 mg ASA/acetaminophen) >5 days/week; 2. Combination analgesics use (caffeine) >3 tablets a day for >3 days a week; 3. Opiate use >1 tablet a day for >2 days a week; 4. Ergotamine tartrate use: 1 mg PO or 0.5 mg PR for >2 days a week. For triptans, we empirically considered overuse >1 tablet per day for >5 days per week. †Combined results for sumatriptan, zolatriptan, rizatriptan and naratriptan. ‡excluding aspirin

NSAID = non-steroidal anti-inflammatory drug;.

1. Bigal ME et al. *Cephalalgia* 2004;24:483–90
2. Bigal ME, et al

Where to look for help

- NICE CG150
- BASH Guidelines (British Association for the Study of Headaches) 2019
- Charities, Migraine Trust, OUCH UK, TN Association, IIH UK.

- Remember that most treatments in headache are unlicensed, many are similar to chronic pain treatment.