# Cluster Headache and Indomethacin Responsive Headaches

Headache Academy

October 2025

Diana Wei

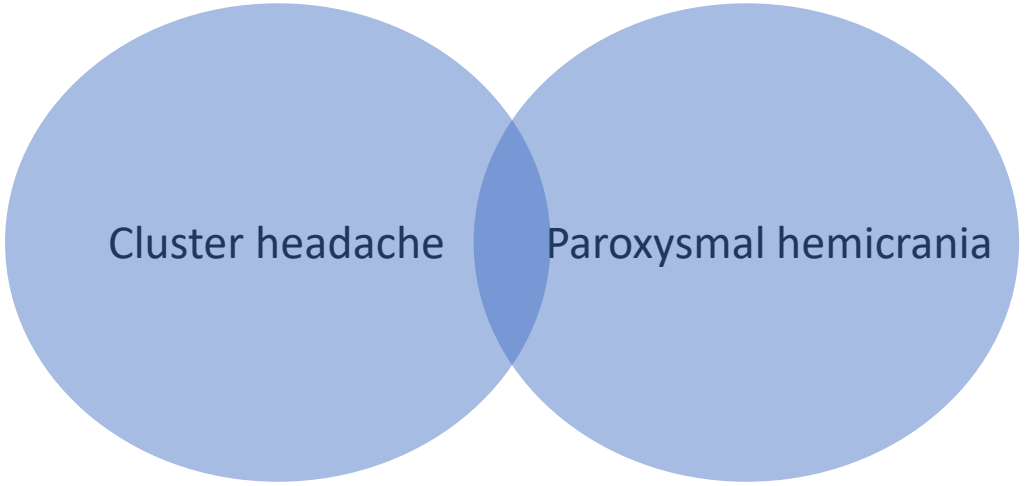
# What are TACs?

Cluster headache

Paroxysmal hemicrania

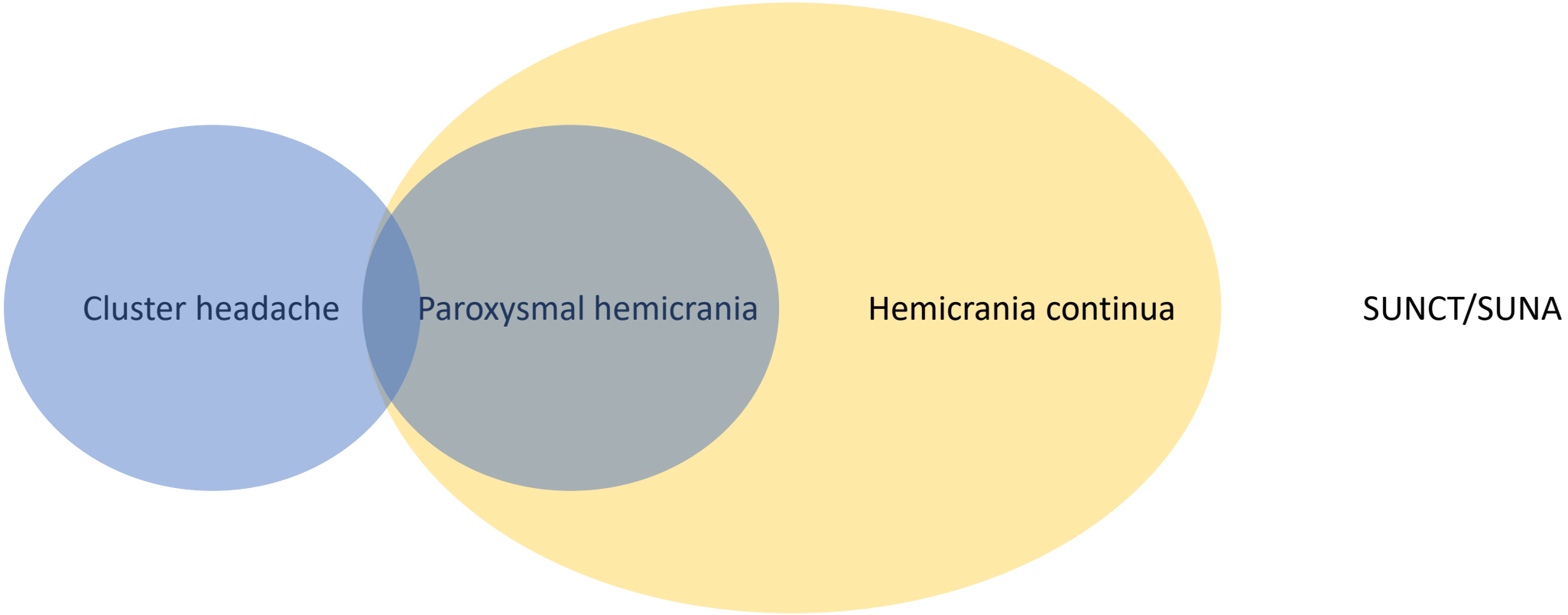
Hemicrania continua

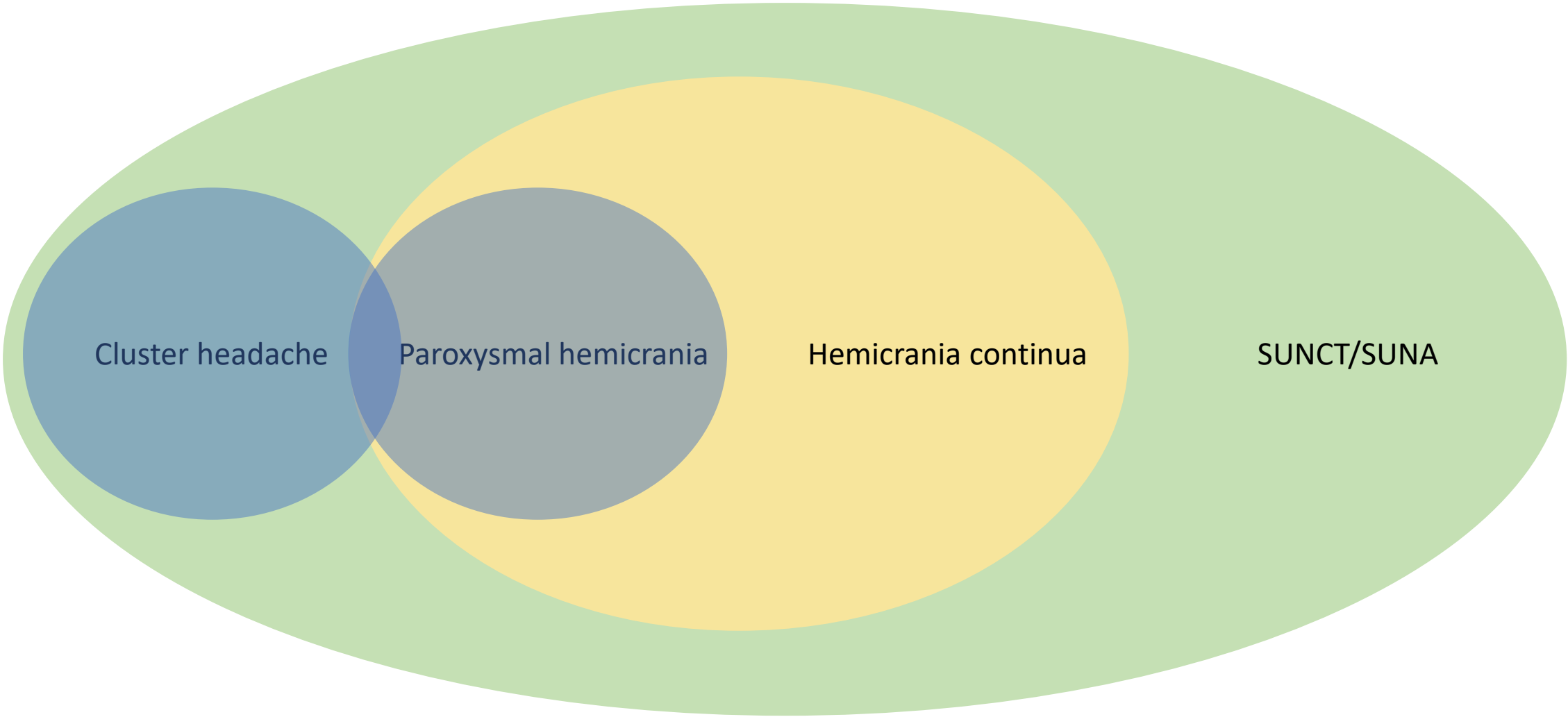
SUNCT/SUNA




Hemicrania continua

SUNCT/SUNA


Cluster headache
Paroxysmal hemicrania
Hemicrania continua
SUNCT/SUNA


Cluster headache
Paroxysmal hemicrania
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SUNCT/SUNA

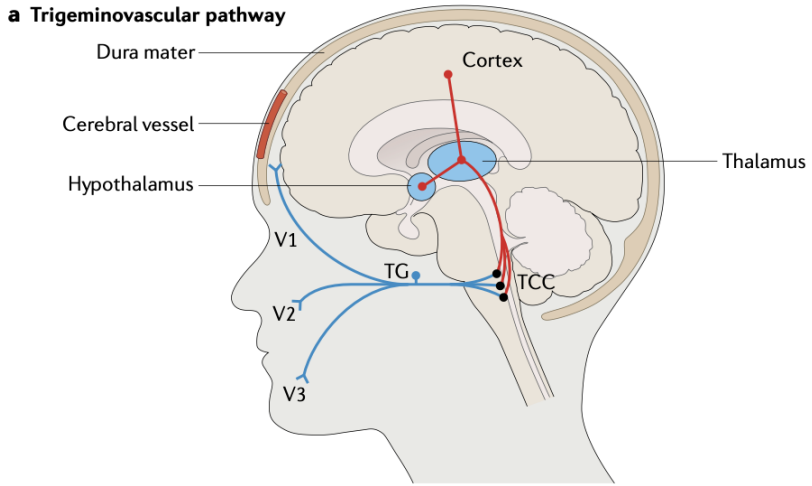
# Pathophysiology

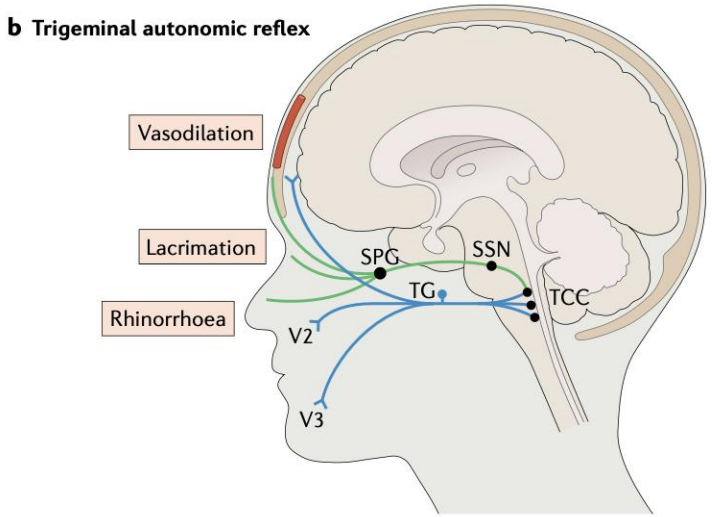
Key components:

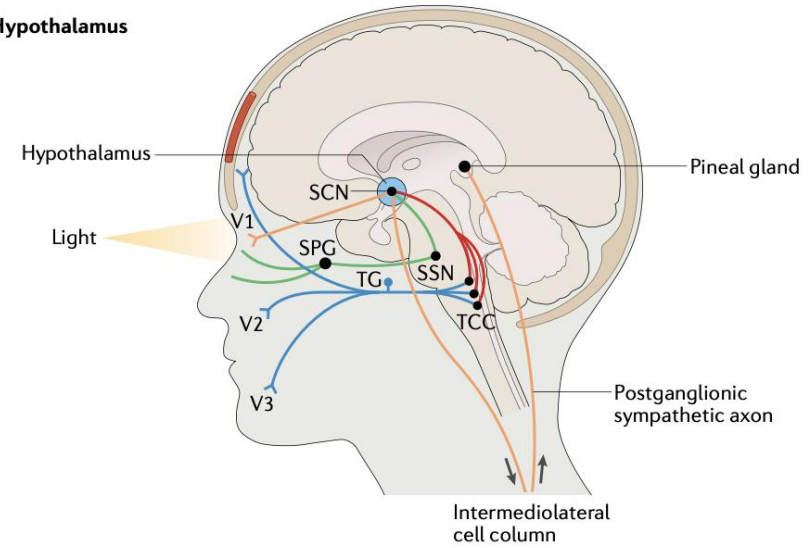
a) Trigeminovascular pathway

b) Trigeminal autonomic reflex

c) Hypothalamus




Neuropeptides involved

Calcitonin gene-related peptide (CGRP)

Pituitary adenylate cyclase-activating polypeptide (PACAP-38)

Nitric oxide synthase (NOS)

Vasoactive intestinal polypeptide (VIP)

PACAP-38, Neuropeptide Y,

Acetylcholine, NOS

PACAP-38

Glutamate

Wei, DY., Goadsby, PJ. (2021). Nat Rev Neurol 17(5): 308-324.

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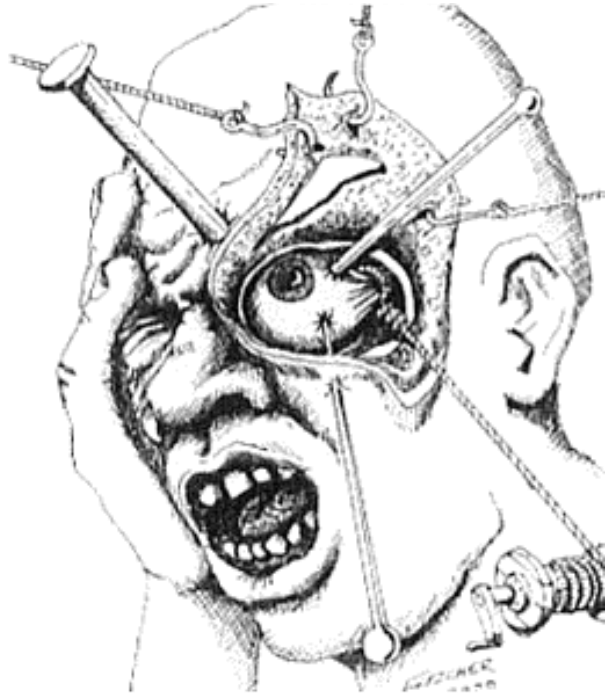
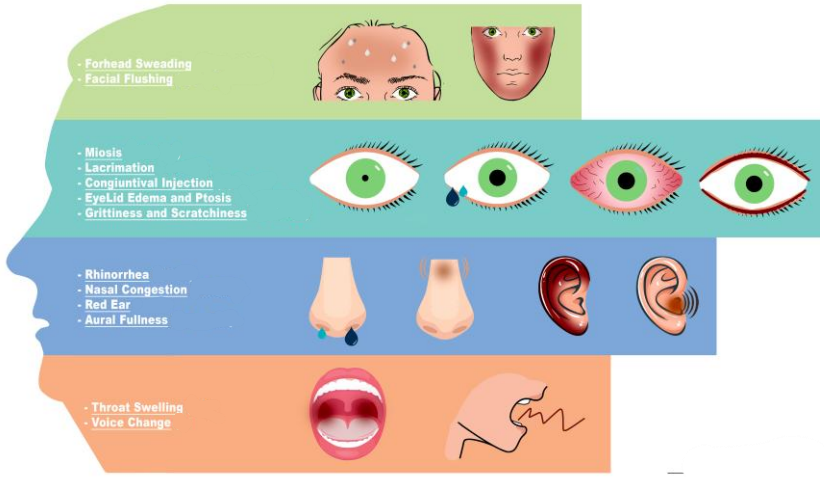
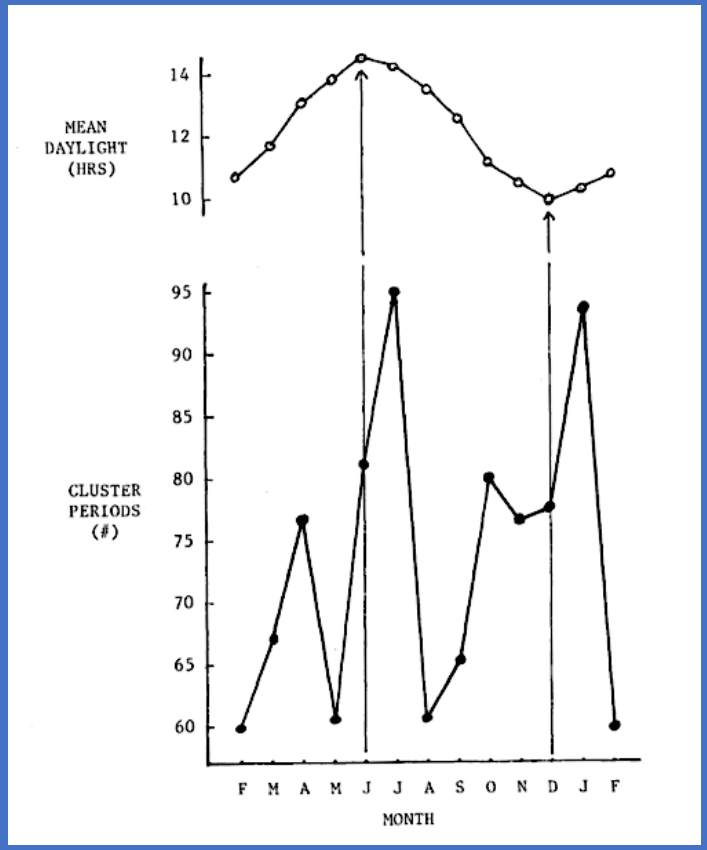


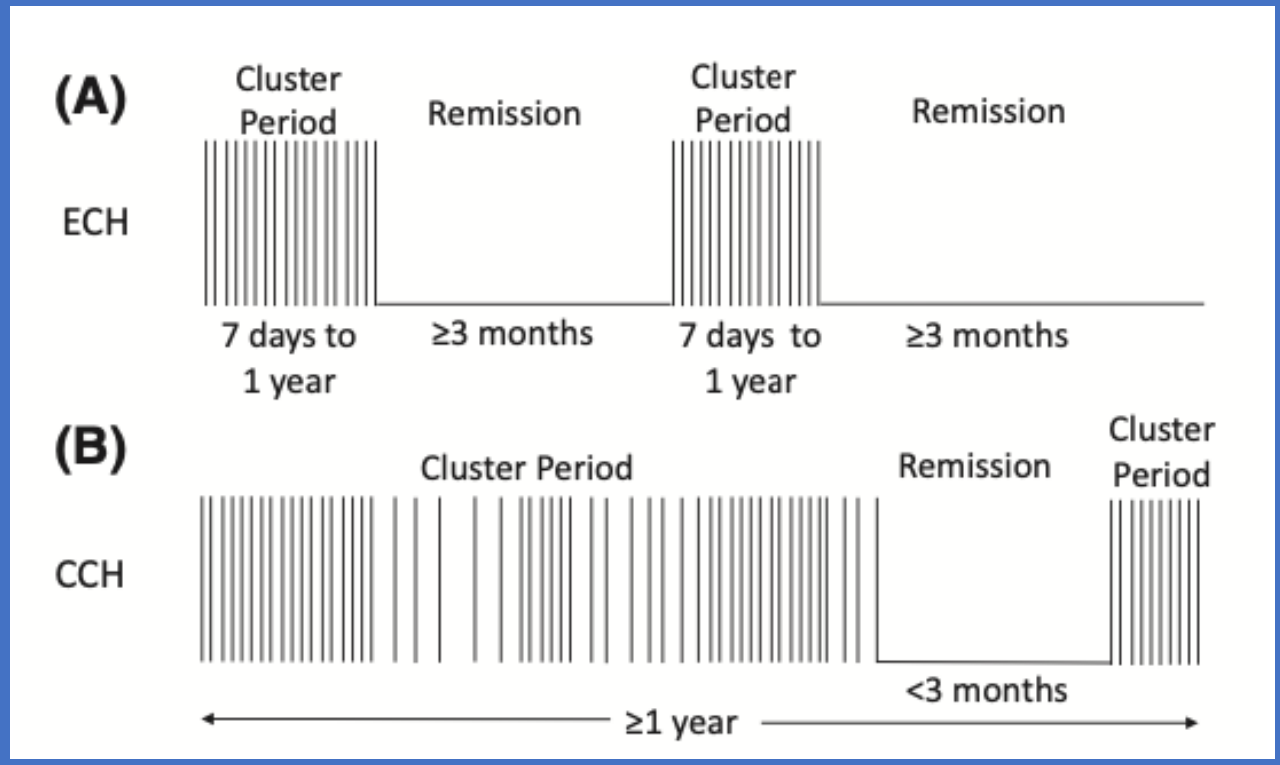
# Cluster headache




# Cluster headache vs Migraine




Kudrow, L. (1987). Cephalalgia 7:76-78




Dodick, D.W. et al. (2022). Headache 62:453-472

# Acute Treatment for CH

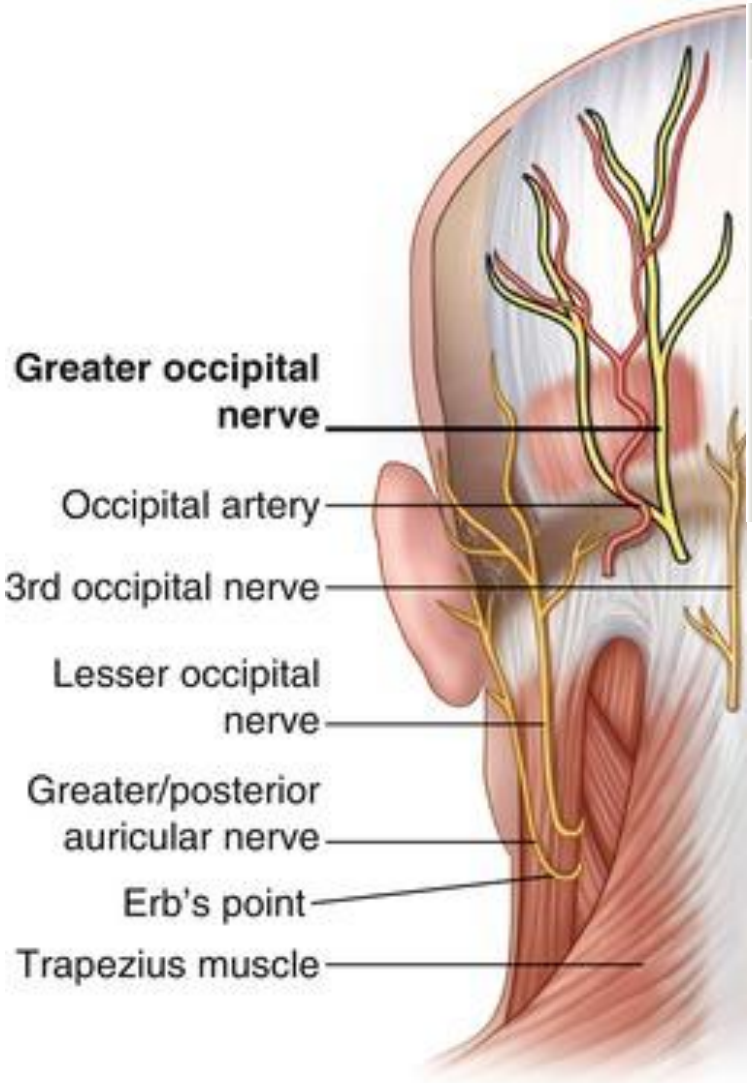
| *Acute treatment* | | |
|---|---|---|
| Subcutaneous sumatriptan (6 mg) | Multicentre randomized, placebo-controlled, double-blind, crossover study ($n = 49$)[95] | Useful for reducing severity or becoming pain-free within 15 min |
| High-flow oxygen via non-rebreather mask (12 l/min for 15 min) | Double-blind, randomized, placebo-controlled, two-period crossover study ($n = 109$)[96] | Useful for becoming pain-free within 15 min |
| Non-invasive vagus nerve stimulation (three 2-min stimulations) | Multicentre, randomized, double-blind, sham-controlled study in ECH ($n = 85$) and CCH ($n = 48$); 1-month, followed by 3-month open-label phase[97], 2-week multicentre, randomized, double-blind study comparing sham treatment with non-invasive vagus nerve stimulation in ECH ($n = 27$) and CCH ($n = 65$)[98] | Useful for pain relief within 15 min in ECH but not in CCH |
| Intranasal sumatriptan (20 mg) | Multicentre, randomized, placebo-controlled, double-blind, crossover study ($n = 118$)[99] | Useful for reducing attack severity or becoming pain-free within 30 min |
| Intranasal zolmitriptan (5 mg and 10 mg) | Multicentre, randomized, placebo-controlled, double-blind, three-period crossover study ($n = 52$)[101]<br>Randomized, placebo-controlled, double-blind, crossover study comparing 5 mg and 10 mg doses ($n = 69$)[100] | Useful for reducing attack severity or becoming pain-free within 30 min |

Wei, DY., Goadsby, PJ. (2021). Nat Rev Neurol 17(5): 308-324.

# Non-invasive vagal nerve stimulation (nVNS)

| Study | Treatment type | Response rate | | | Outcome measures |
|---|---|---|---|---|---|
| ACT1 | Acute in ECH | nVNS (n=38) | Sham (n=47) | P-value | |
| | | 34.2% | 10.6% | 0.008 | Pain intensity of 0 or 1 at 15 minutes |
| ACT2 | Acute in ECH | nVNS (n=101 attacks) | Sham (n=81 attacks) | P-value | |
| | | 48% | 6% | <0.01 | Proportion of all treated attacks achieving pain-free status within 15 minutes |
| PREVA | Adjunctive preventive in CCH | nVNS +SoC (n=45) | SoC alone (n=48) | P-value | |
| | | -5.9 | -2.1 | 0.02 | Change from baseline in mean number of attacks per week (weeks 3 and 4 of randomised phase v baseline) |


Silberstein, S. D. et al. Headache 2016;56, 1317–1332.
Goadsby, P. J. et al. Cephalalgia 2018;38, 959–969.
Gaul, C. et al. Cephalalgia 2016;36:534–546




| *Interim treatment* | |
|---|---|
| Oral prednisone (30 mg and 100 mg with tapering) | Double-blind, placebo-controlled crossover study of a single 30 mg dose ($n=19$)[121]<br>Multicentre, randomized, double-blind, placebo-controlled study of prednisone (100 mg for 5 days then tapered by 20 mg every 3 days) combined with verapamil for ECH ($n=109$)[124] |
| Ipsilateral greater occipital nerve injection of local anaesthetic or steroid | Double-blind, randomized, placebo-controlled study of betamethasone injection in the suboccipital region in ECH ($n=16$) and CCH ($n=7$)[128]<br>Prospective observational study of single occipital nerve block with 10 mg triamcinolone and bupivacaine in ECH ($n=61$) and CCH ($n=30$)[133] |

| *GON block* |
|---|
| Safe and well-tolerated |
| Can be used in pregnancy and teenagers |
| Can be repeated in 3 months if required |

# Interim Treatment for CH

Wei, DY., Goadsby, PJ. (2021). Nat Rev Neurol 17(5): 308-324.

# Preventive treatment

| *Preventive treatment* | | |
|---|---|---|
| Verapamil (360 mg/day) | Multicentre, randomized, double-blind, crossover study to compare verapamil with lithium in CCH ($n = 30$)[143]<br>Double-blind, placebo-controlled study of 120 mg verapamil three times daily in ECH ($n = 30$)[142] | Immediate-release formulation is more effective than modified release<br>Need close monitoring for cardiac arrhythmias during titration and on a stable dose (every 1–2 months for the first 6 months then every 6 months) |
| Lithium (800–900 mg/day) | Multicentre, randomized, double-blind, crossover study comparing verapamil with lithium in CCH ($n = 30$)[143]<br>Double-blind, placebo-controlled study of 800 mg slow-release lithium once daily ($n = 27$)[159] | Needs close monitoring for multiple adverse effects and therapeutic serum concentration |
| Topiramate (25–400 mg/day)<br>Min 100mg/day | Prospective, open-label study in ECH ($n = 12$) and CCH ($n = 14$)[182]<br>Prospective, open-label study in ECH ($n = 12$) and CCH ($n = 9$)[183]<br>Open-label study in ECH ($n = 10$)[180]<br>Case reports of use of 75–200 mg topiramate daily for ECH ($n = 2$) and CCH ($n = 3$)[181]<br>Retrospective study in ECH ($n = 9$) and CCH ($n = 3$)[246]<br>Open-label study over 20 days in ECH ($n = 23$) and CCH ($n = 10$)[184] | Evidence is limited to open-label studies<br>Poorly tolerated — patients often discontinue and report many adverse effects |
| Melatonin (10 mg) | Double-blind, placebo-controlled study of 10 mg melatonin for 14 days in CCH ($n = 2$) and ECH ($n = 18$)[169] | Immediate-release formulation is more effective than modified-release formulation; well tolerated |

Wei, DY., Goadsby, PJ. (2021). Nat Rev Neurol 17(5): 308-324.

# Verapamil

- First line preventive
- Regular ECGs [1]
- Side effects: constipation and pedal oedema
- Minimum daily dose 240mg
- Should only be used for the bout duration
- Restart onto effective dose next bout

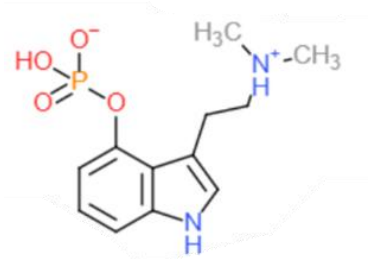
| | Morning | Midday | Evening |
|---|---|---|---|
| For 2 weeks take: | 80mg | 80mg | 80mg |
| *Arrange to have an ECG performed - if the ECG is normal then:* | | | |
| For 2 weeks take: | 80mg | 80mg | 160mg |
| *Arrange to have an ECG performed - if the ECG is normal then:* | | | |
| For 2 weeks take: | 80mg | 160mg | 160mg |
| *Arrange to have an ECG performed - if the ECG is normal then:* | | | |
| For 2 weeks take: | 160mg | 160mg | 160mg |
| *Arrange to have an ECG performed - if the ECG is normal then:* | | | |
| For 2 weeks take: | 160mg | 160mg | 240mg |
| *Arrange to have an ECG performed - if the ECG is normal then:* | | | |
| For 2 weeks take: | 160mg | 240mg | 240mg |
| *Arrange to have an ECG performed - if the ECG is normal then:* | | | |
| For 2 weeks take: | 240mg | 240mg | 240mg |
| *Arrange to have an ECG performed - if the ECG is normal then:* | | | |
| For 2 weeks take: | 240mg | 240mg | 320mg |
| *Arrange to have an ECG performed - if the ECG is normal then:* | | | |
| For 2 weeks take: | 240mg | 320mg | 320mg |
| *Arrange to have an ECG performed - if the ECG is normal then:* | | | |
| For 2 weeks take: | 320mg | 320mg | 320mg |

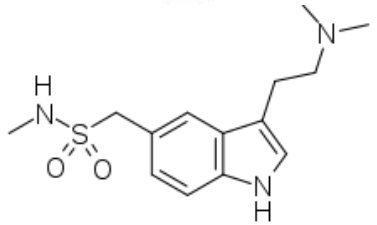
[1] Cohen AS, Matharu MS, Goadsby PJ. (2007). Neurology. 69(7):668-75

# Alternative treatments

Psilocybin

- Tryptamine structure
- Tried as an abortive



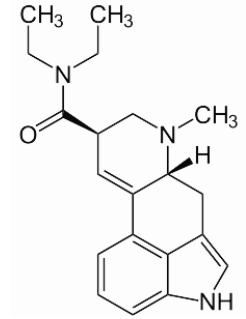


Sumatriptan

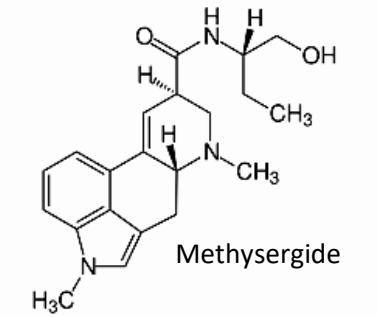
- Low-to-moderate doses of psilocybin (NCT04280055) in chronic cluster headache patients
  - Study terminated due to poor recruitment due to COVID 19 pandemic

Lysergic acid diethylamide (LSD)

- Ergoline structure
- Tried as a preventive



LSD



Methysergide

- BOL-148: non-hallucinogenic LSD analogue
  - 3 single doses within 10 days could break a bout or improve frequency and severity

Karst, M. et al. Cephalalgia 2010;30:1140-1144

Sewell, R. A. et al. Neurology 2006;66:1920-1922.
Schindler, E. A. et al. J Psychoactive Drugs 2015;47:372-381

# Case referred from neurologist for consideration of Botox

# 31 year old, right handed female

- First experienced headache age 8- migraines
- Aged 19 viral meningitis
- December 2018- developed right sided headache
  - Went to see ENT ?sinus problem
  - Went to dentist ?related to filling right upper tooth and had filling removed
- May 2019- developed 1 episode of hemiplegia of right arm with dysarthria, flashing lights. Arm symptoms lasted 1 day
- PMH: vitamin D deficiency
- SH: midwife, G1P1 menarche aged 12, non-smoker, drinks occasionally and no recreational drugs
- FH: mother and sister suffer from headaches

# Two headache types

**Generalised weekly headache**

- Generalised R>L lasting 1 day untreated
- 10/10 severity
- Associated: nausea & vomiting, right-sided photophobia, phonophobia, osmophobia, cranial allodynia, movement sensitivity, internal vertigo
- Aura: 2 episodes
- CAS: bilateral periorbital oedema and R>L nasal congestion and R rhinorrhoea

**Daily continuous headache since 2018**

- Right-sided around occipital region with sharper worsenings into her right cheek
- Severity: 4/10 in AM → 8/10 in PM
- Associated: nausea, right-sided photophobia, phonophobia, osmophobia, movement sensitivity
- No aura
- CAS: continuous R eye grittiness

# Past medications tried

Acute

- Sumatriptan 50mg- not helpful, no side effects
- Zolmitriptan nasal spray- was mentioned in referral letter but not tried
- Ibuprofen- not helpful
- Naproxen- not helpful
- Paracetamol- not always helpful
- Co-dydramol- not helpful just made her groggy
- Aspirin sometimes helpful

Preventive

- Amitriptyline 10mg- not helpful and stopped due to side effects of drowsiness
- Nortriptyline 10mg- not helpful and side effects
- Topiramate- lowest dose but stopped due to side effects and not helpful
- Propranolol- lowest dose, lightheaded and palpitations and sweaty, not helpful
- Gabapentin- lowest dose, cognitive symptoms and side effects
- Candesartan suggested but not tried yet

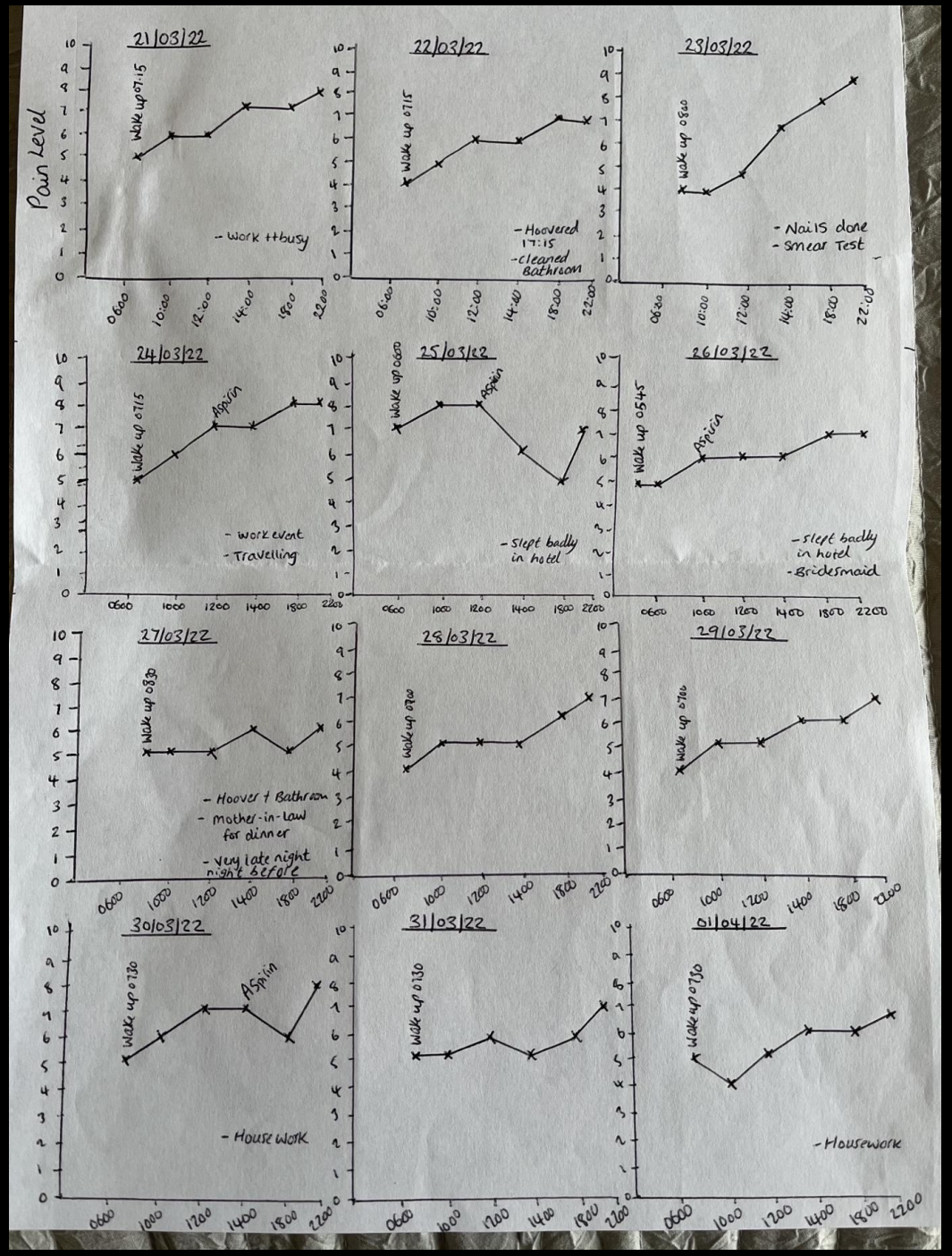
Blocks

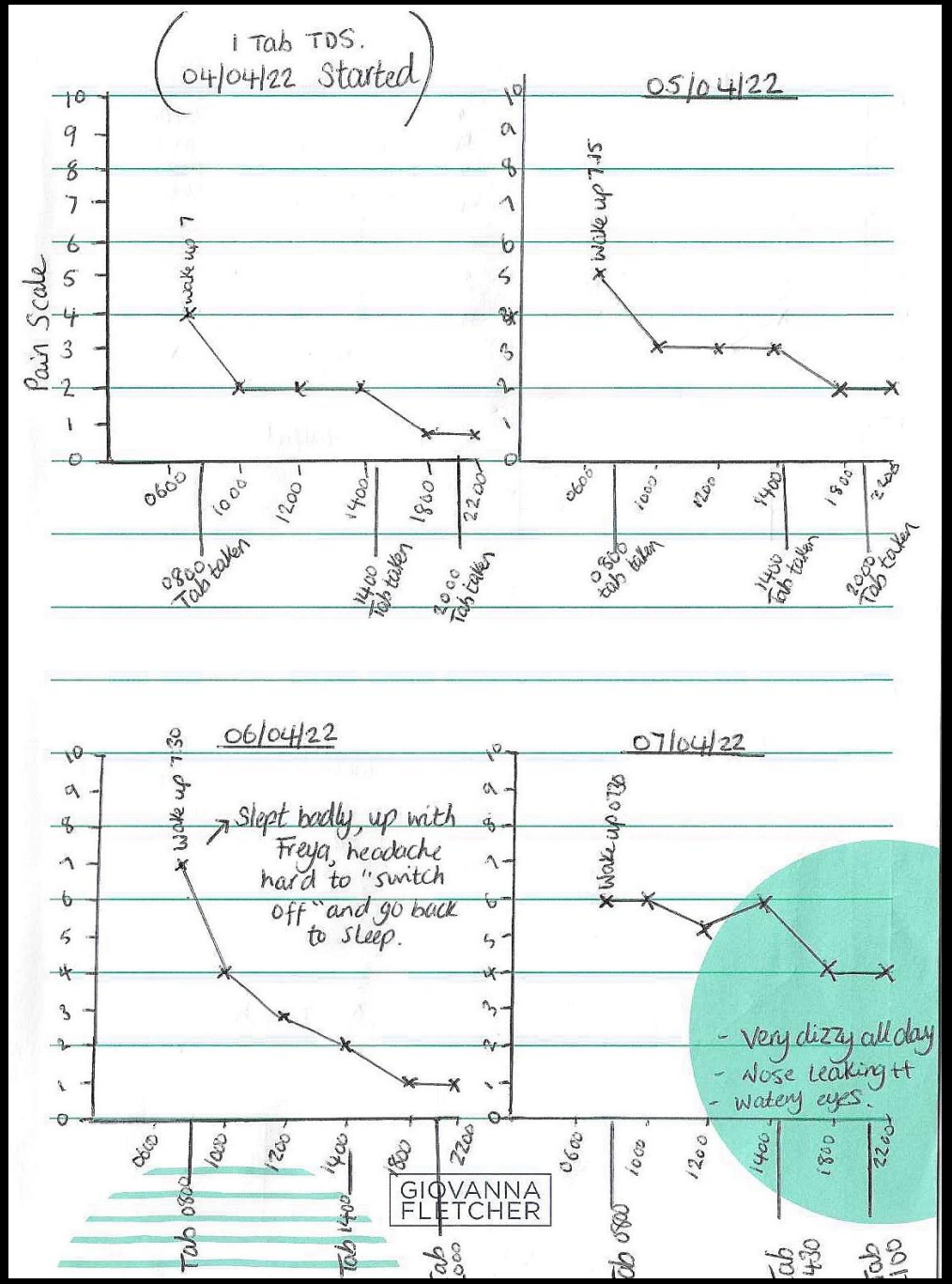
- Multiple occipital nerve and trapezii blocks- privately 9th Nov 2020 with 1 month relief with reduced severity
- Greater occipital nerve block 10th Feb 2021- not helpful

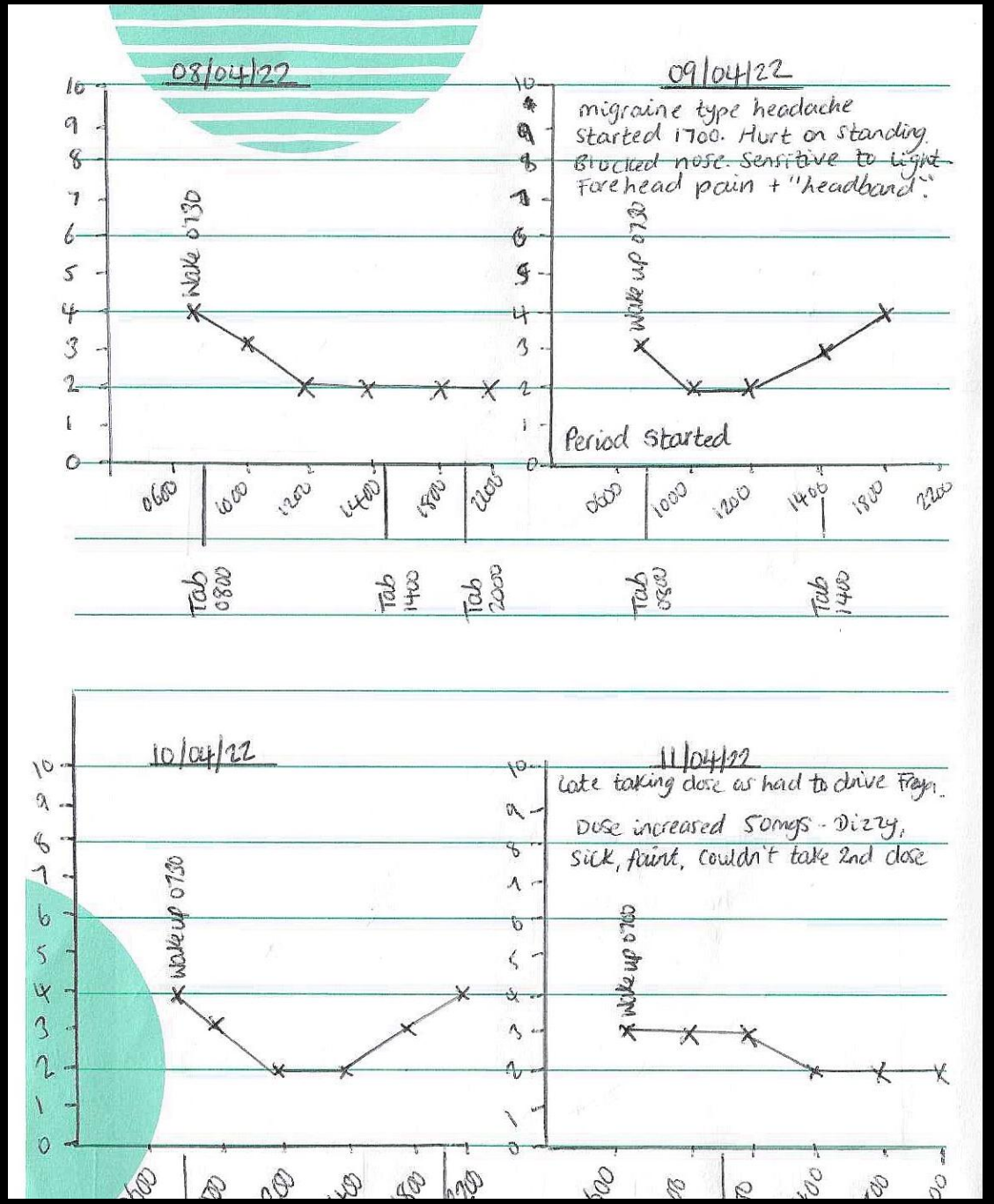
# Next step?

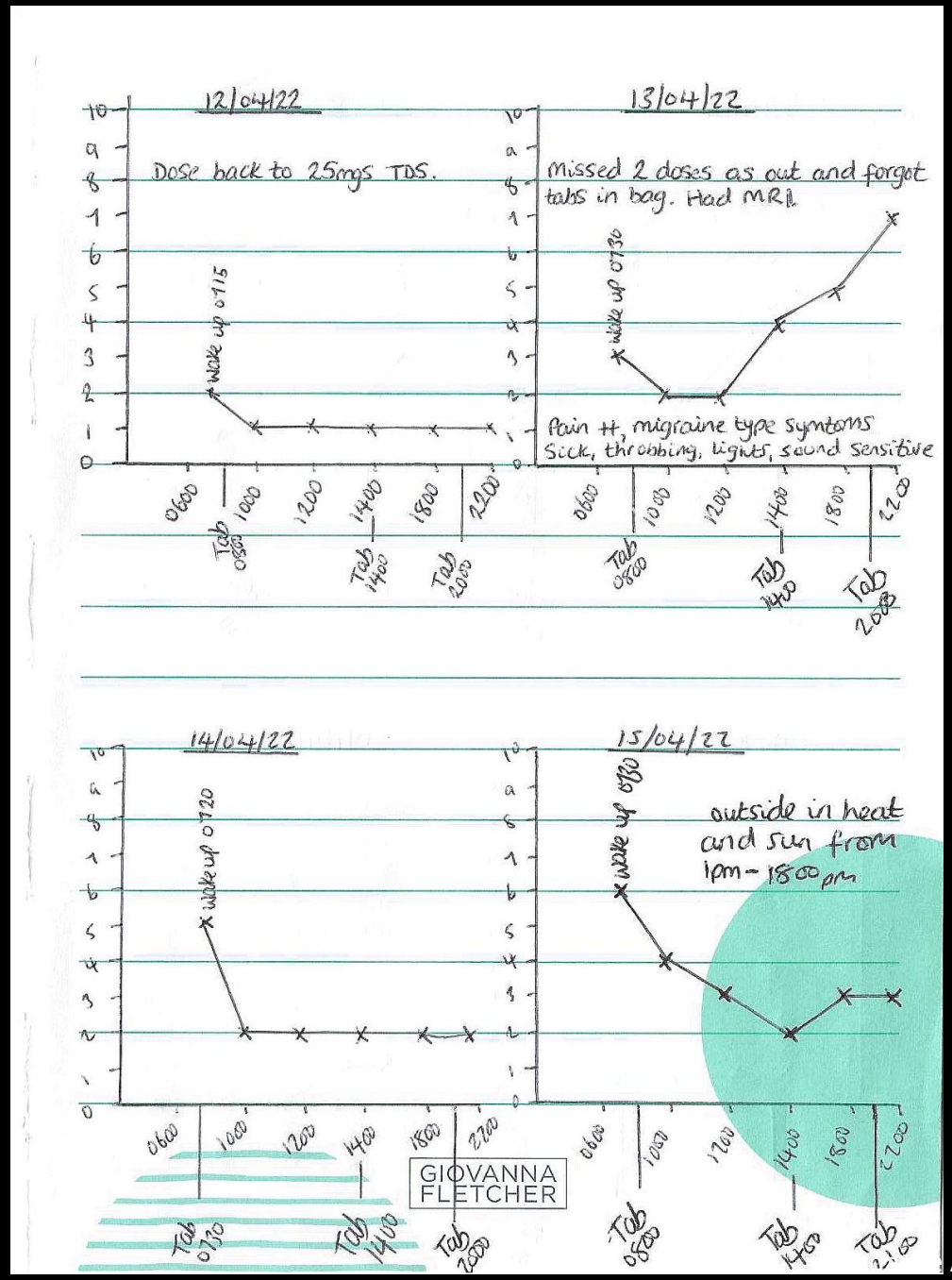
# Indomethacin

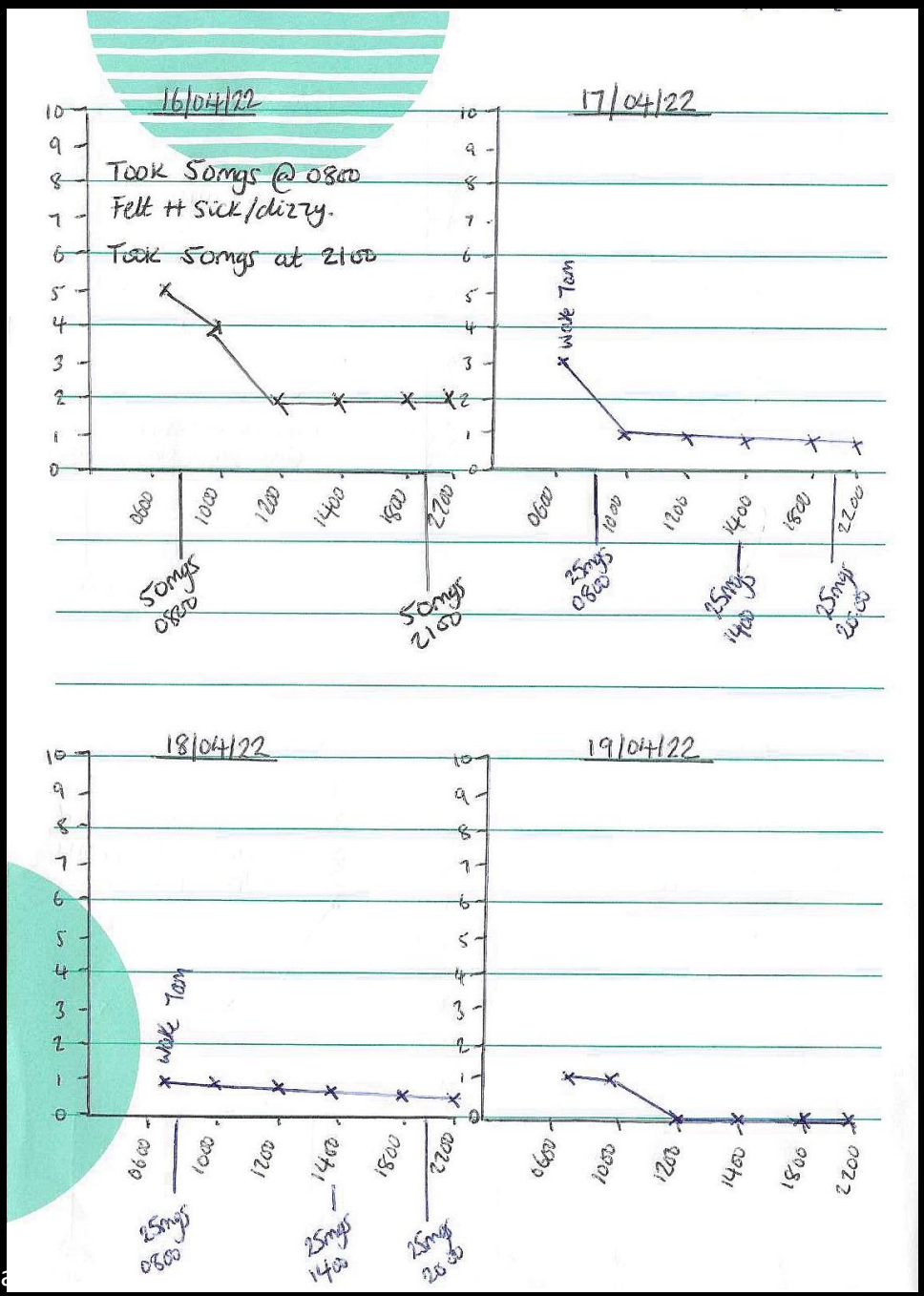

# Headache diary before indomethacin trial

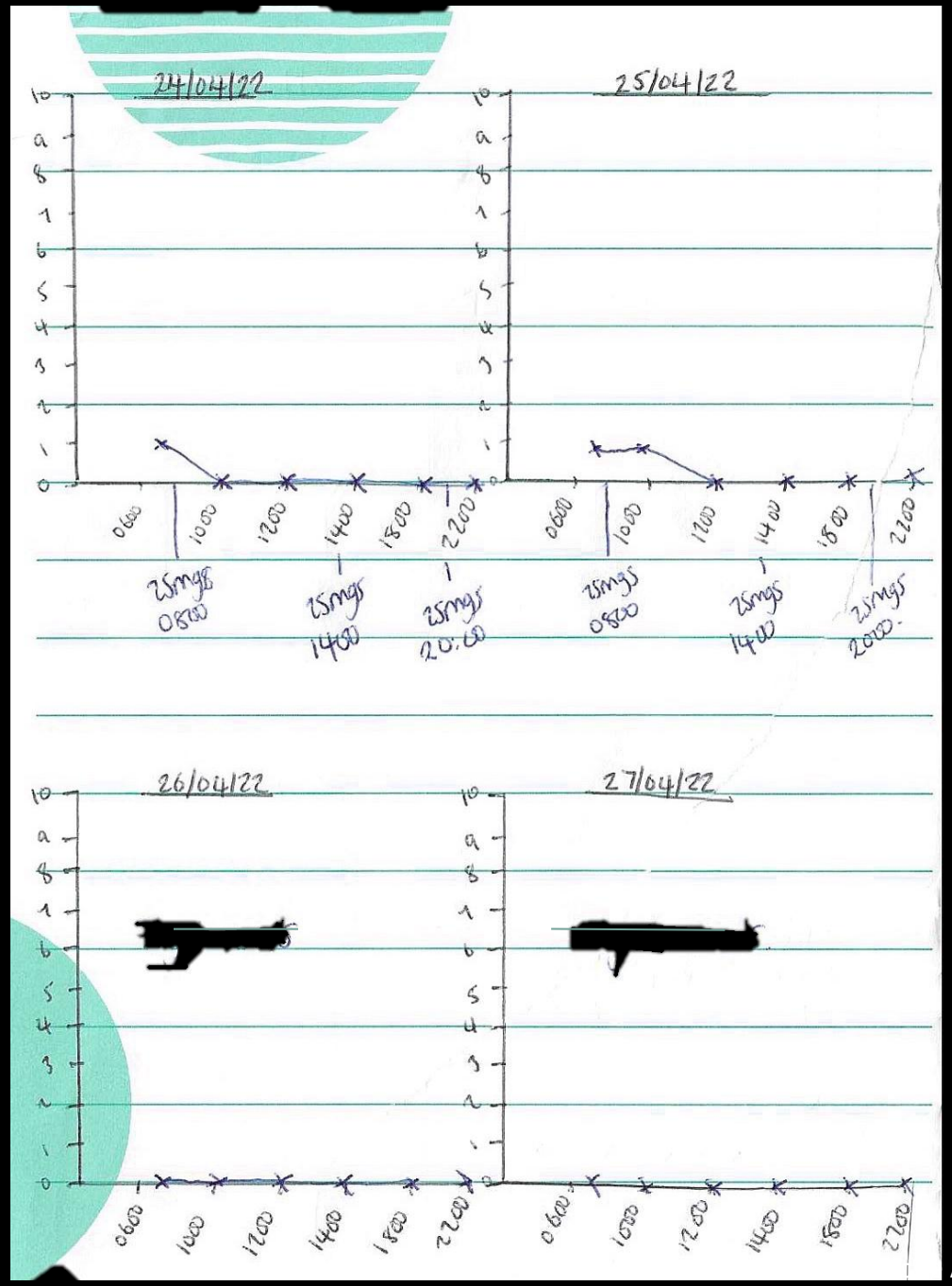


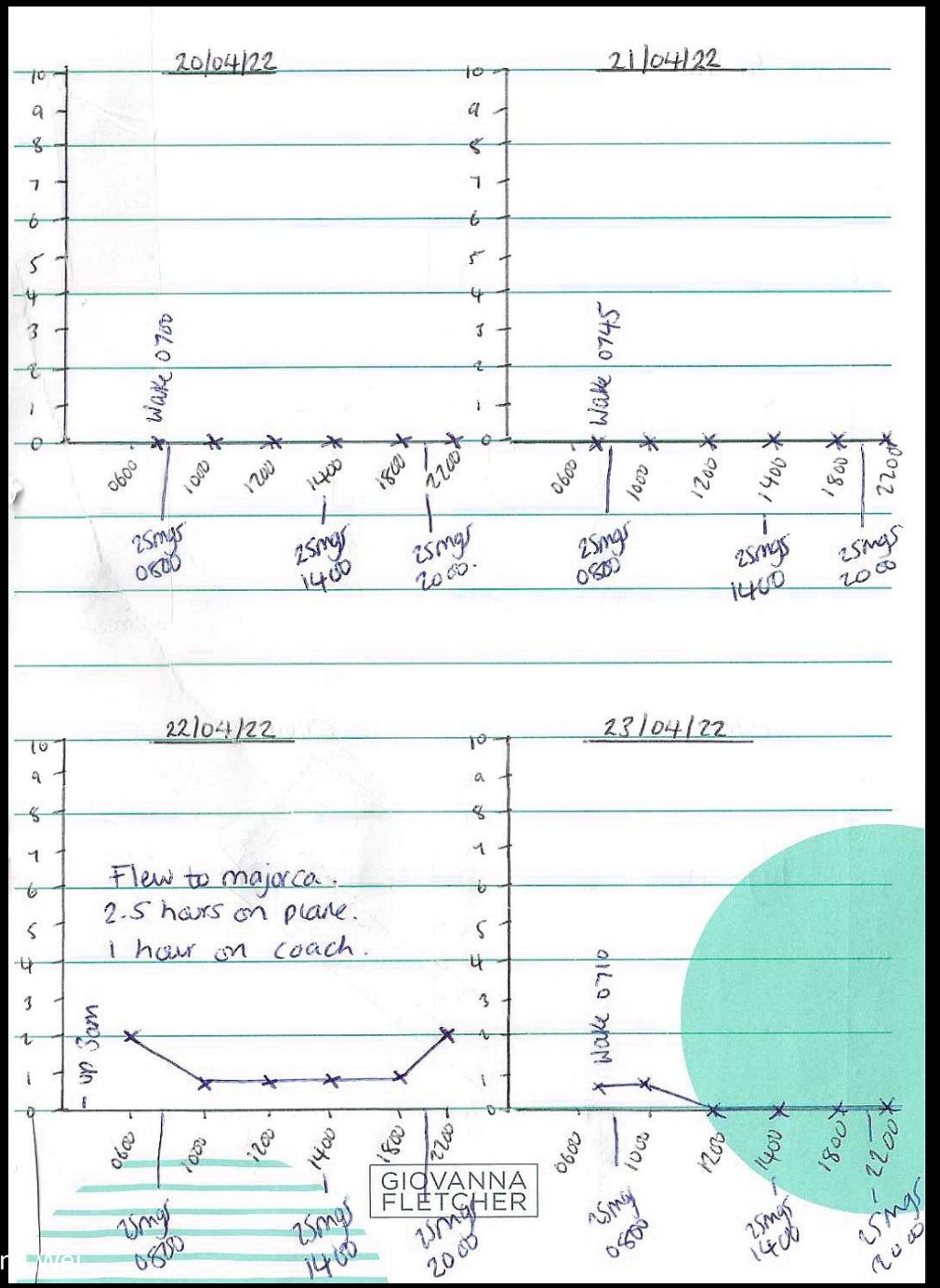

1 Tab TDS.
04/04/22 Started
05/04/22
Pain Scale
Wake up 7
Wake up 7.15
0800 Tab taken
1400 Tab taken
2000 Tab taken
06/04/22
Wake up 7.30
Slept badly, up with Freya, headache hard to "switch off" and go back to sleep.
07/04/22
Wake up 0730
- Very dizzy all day
- Nose leaking tt
- watery eyes.
GIOVANNA FLETCHER


08/04/22
Wake 0730
09/04/22
migraine type headache
Started 1700. Hurt on standing
Blocked nose. Sensitive to light
Forehead pain + "headband".
Wake up 0730
Period Started
Tab 0800
Tab 1400
Tab 2000
10/04/22
Wake up 0730
11/04/22
Late taking dose as had to drive Freya.
Dose increased 50mgs - Dizzy, sick, faint, couldn't take 2nd dose
Wake up 0700



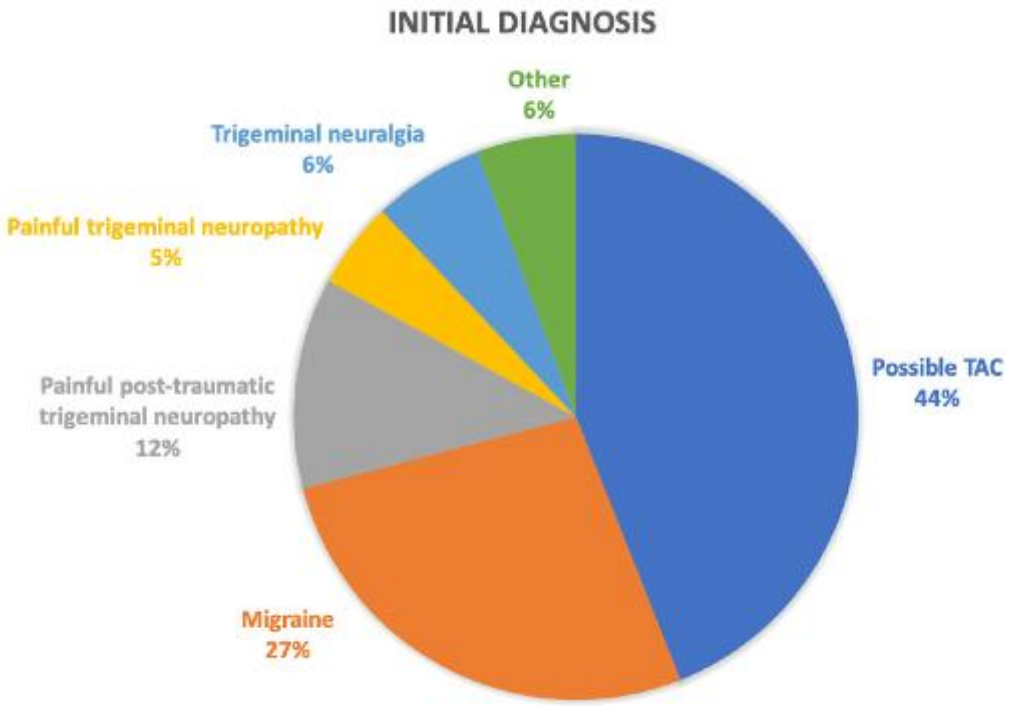





# Key points in the history

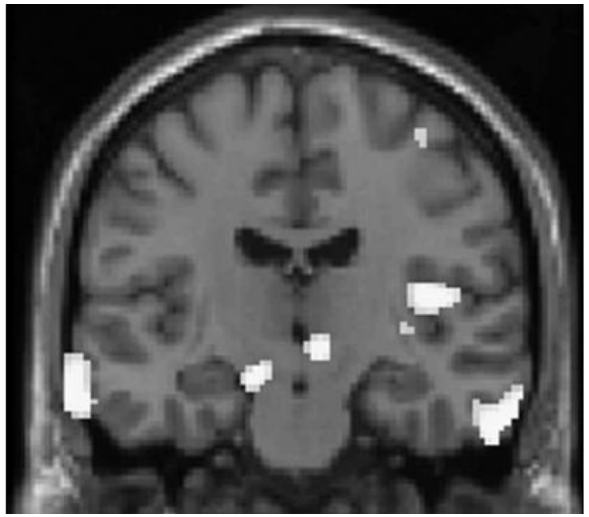
- Strictly unilateral continuous pain- different from her migraine
- Ipsilateral cranial autonomic symptoms
- Lateralising photophobia
- Response to aspirin
- Seen ENT and had dental procedures




Wei, DY, Moreno-Ajona, D, Renton, T, Goadsby PJ. J Headache Pain. 2019;20(1):69-74

# Hemicrania continua

- Unilateral continuous pain with ipsilateral cranial autonomic symptoms
- Baseline pain with worsenings, with no resolution
- Diagnostic test response to indomethacin
  - Oral dose of at least 150 mg daily up to 225 mg daily
  - “Indo test” by intramuscular injection is 100-200 mg, especially if active gastrointestinal ulcer
- Indomethacin mechanism of action:
  - inhibitory modulation of nitric oxide (NO)-induced vasodilation and trigeminal activity



HC

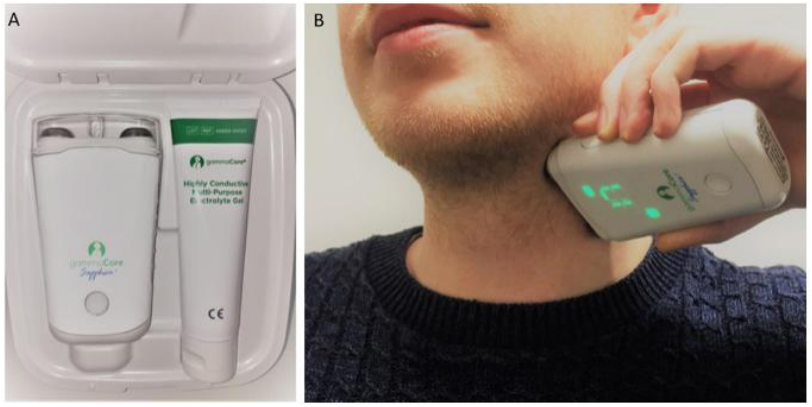
Matharu, M. S. and P. J. Goadsby. Current Pain and Headache Reports 2005;9(4): 281-288.

Wei, DY,. AIAN 2018;21(5):39-44
Villar-Martínez, et al. Headache 2021;61(5):700-14
Summ, O, et al.  Pain 2020;162(2):591-599

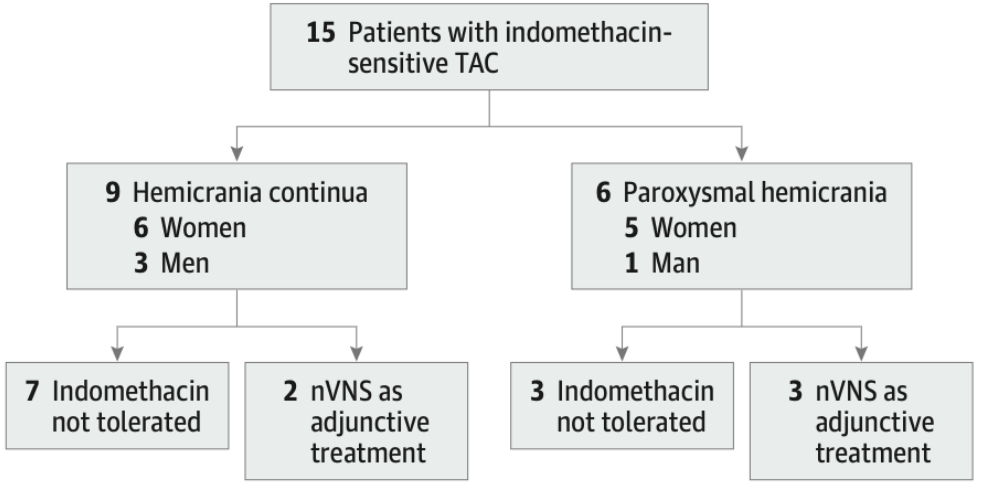
# Progress

- Unable to tolerate even 25mg BD indomethacin with regular PPI
- Took an indomethacin break for 1 ½ weeks and right sided HC returned
- Started trial of non-invasive vagal nerve stimulator Oct 2022






Wei, D, Khalil, M, Goadsby PJ. Pract Neurol 2019;19(6)521-528




| Sex/Age, y | Laterality | Treatment Response | Treatment Duration[a] |
|---|---|---|---|
| **Hemicrania Continua** | | | |
| Male, 49 | Left | Persistent pain reduced by 60% | 2 y and 8 mo |
| Man, 37 | Left | Persistent pain reduced by 40% | 2 y |
| Female, 55 | Left | Persistent pain reduced by 80% | 5 y |
| Female, 27 | Left | Persistent pain reduced by 50% or more, exacerbations reduced from 4 per wk to 2 per mo; acute treatment (1 dose) reduced severity and duration from 48-72 h to 12-24 h | 1 y |
| Female, 42 | Left | Persistent pain reduced by 15%, exacerbation duration reduced from days to 1 h | 6 mo |
| Female, 23 | Left | Persistent pain reduced by 30% | 2 y and 4 mo |
| Female, 53 | Right | Persistent pain reduced by 30%-50%, exacerbations reduced from 15 per mo to 1 every 2 mo; acute treatment (6-8 doses) reduced severity by 40% and duration from >24 h to <24 h | 5 mo |
| Female, 38 | Right | No response | 3 mo |
| Male, 61 | Left | No response | 6 mo |

Tso AR *et al*. JAMA Neurology 2017;**74**(10):1266-67

# Paroxysmal hemicrania (PH)

Acta neurol. scandinav. 54, 140–159, 1976

Department of Neurology and Institute for Surgical Research, Rikshospitalet,
Oslo, Norway.

## A NEW (?) CLINICAL HEADACHE ENTITY "CHRONIC PAROXYSMAL HEMICRANIA" 2.

OTTAR SJAASTAD and INGE DALE

The pain attacks can be abolished by continuous indomethacin medication. In spite of the ocular findings it has in common with cluster headache, this headache seems to differ from cluster headache.

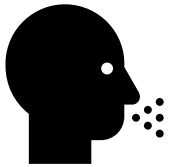
# Paroxysmal hemicrania (PH) attacks

- Severe pain in V1>V2
- Ipsilateral cranial autonomic symptoms
- Duration untreated 2-30 minutes
- More than 5 attacks/day up to 40 attacks/day
  - Average 11 attacks/day[1]

- Episodic PH: time of remission > 3 months
- Chronic PH: time of remission < 3 months

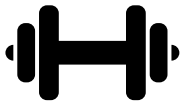
[1] Cittadini, E., et al. Brain 131(4): 1142-1155.

# Other indomethacin responsive headaches



Primary cough headache

Primary stabbing headache

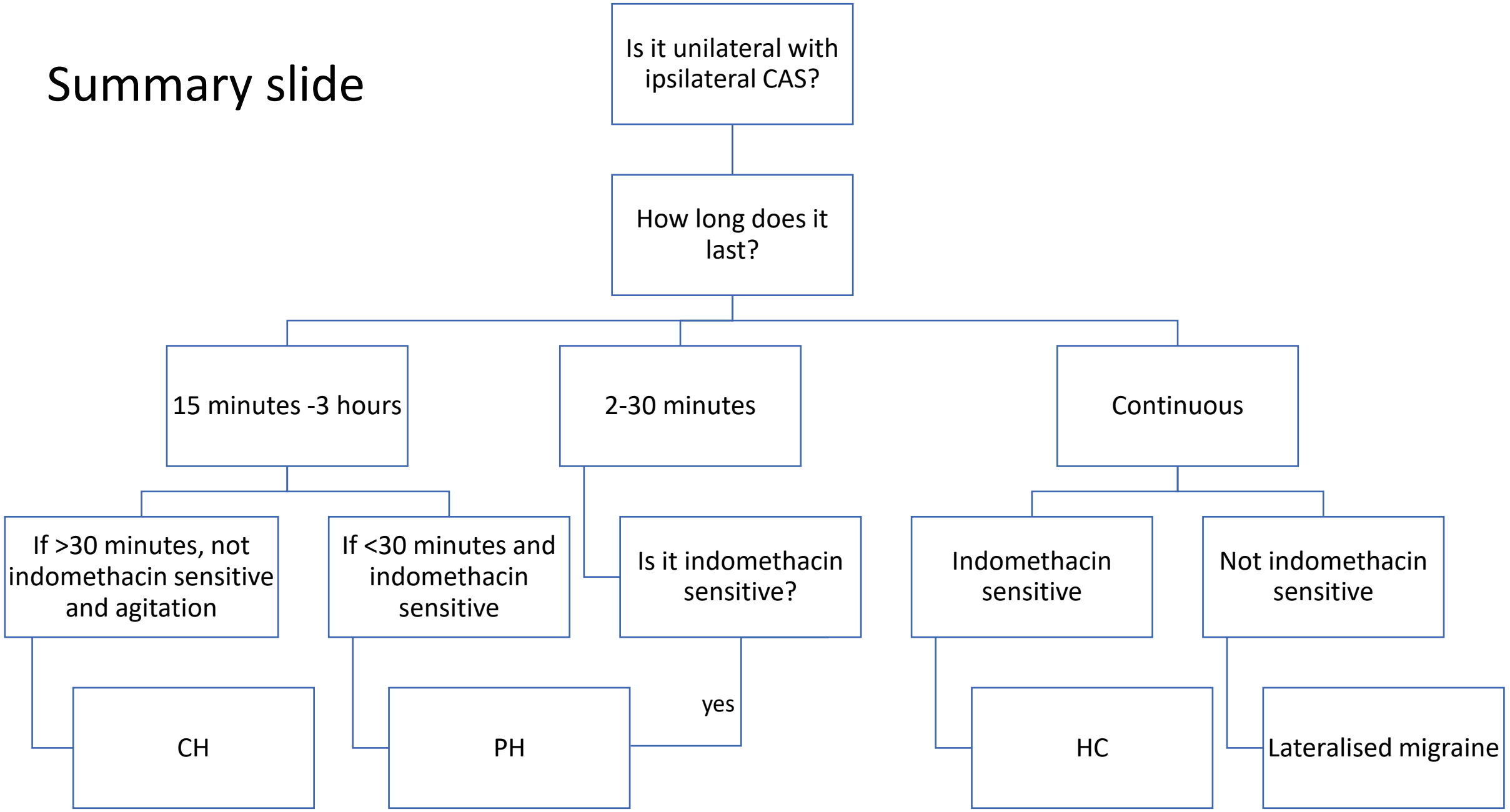


Primary exercise headache

Primary headache associated with sexual activity

| Features | SUNCT/SUNA | Paroxysmal Hemicrania | Cluster Headache | Hemicrania continua |
|---|---|---|---|---|
| Gender ratio (male to female) | 1.5:1 | 1:1 | 3:1 | 1:2 |
| Pain quality | Sharp/stab/throb | Sharp/stab/throb | Sharp/stab/throb | Baseline- dull pain. During worsenings can be throbbing or sharp |
| Pain severity | Severe | Very severe | Very severe | Baseline-mild to moderate.<br>Worsenings- moderate to severe |
| Distribution of maximal pain | V1>C2>V2>V3 | V1>C2>V2>V3 | V1>C2>V2>V3 | V1>C2>V2>V3 |
| Attacks per day | 1-100 | 1-40 | 1-8 | Daily in 50% |
| Attack duration | 1-10 minutes | 2-30 minutes | 15-180 minutes | 30 minutes to 3 days |
| Autonomic features | Prominent and ipsilateral to pain | Prominent and ipsilateral to pain | Prominent and ipsilateral to pain | Present during worsenings and can be bilateral |
| Restlessness during attack | 65% | 80% | 95% | 69% |
| Circadian periodicity | Absent | Absent | Present | Absent |
| Triggers | | | | |
| Alcohol | - | + | +++ | + |
| Nitroglycerin | - | + | +++ | - |
| Cutaneous | +++ | - | - | - |
| Associated migraine features | | | | |
| Nausea | | | | |
| Photophobia | 10% | 40% | 50% | 53% |
| Phonophobia | 25% | 65% | 56% | 74% |
| | 25% | 65% | 43% | 79% |
| Treatment response | | | | |
| Oxygen | No | No | Yes | No |
| Sumatriptan injection | No | Partial | Yes | Partial |
| Indomethacin | No | Yes | No | Yes |

# Summary slide



# Useful references:

EAN CH guidelines 2023 doi:10.1111/ene.15956

Continuum 2024
doi:org/10.1212/CON.0000000000001409

Practical neurology paper 2019: doi:
10.1136/practneurol-2018-002124

## Thank you

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KING'S HEALTH PARTNERS