Headache 2013

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Headache

a Symptom

Many causes:-

Some structural

Some perhaps pharmacological

Some psychological
The *History* is paramount

Clinical examination is *usually* normal

Investigations can only exclude specific causes
TEN QUESTIONS FOR HEADACHE PATIENTS

Age, Occupation, etc. General past history.

1. How old when headache began?
2. In attacks?
3. Frequency?
4. Duration?
5. Location?
6. Throbbing? Worse on exercise?
7. Nausea or Vomiting?
8. Any focal symptoms related to attacks?
9. What acute treatments tried
10. What long term treatments tried?
   Pill or other hormones?
Lipton’s Self-administered Screener
(Best discriminators of 9 questions)

- Has your headache ever limited you from working, studying, or doing what you needed to do?
- Do you feel nauseated?
- Does light bother you when you have a headache?

Lipton et al Neurology 61 375 2003
Most patients complaining of headache have no structural explanation or physical signs

Almost always migrainous!
Prevalence of headache in the previous year


<table>
<thead>
<tr>
<th>Age group</th>
<th>Migraine</th>
<th>Tension-type headache</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>n</td>
<td>387</td>
<td>353</td>
</tr>
<tr>
<td>25-34</td>
<td>5%</td>
<td>18%</td>
</tr>
<tr>
<td>35-44</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td>45-54</td>
<td>6%</td>
<td>12%</td>
</tr>
<tr>
<td>55-64</td>
<td>7%</td>
<td>19%</td>
</tr>
<tr>
<td>All ages</td>
<td>6%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Recent US figures similar Lipton Neurology 2007 68 343.
MAJOR CAUSES OF HEADACHE

- Migraine
- Tension Headache
- Cluster Headache (Migrainous Neuralgia)
- Cervical Spondylosis
- Temporal arteritis
- Sinusitis
- Trigeminal Neuralgia
- Atypical facial pain
- Raised intracranial pressure - tumour, abscess, benign intracranial hypertension
- Subarachnoid haemorrhage
- Meningitis
- Paget's disease
- Closed angle glaucoma
- Severe hypertension
- CO$_2$ retention – obstructive sleep apnoea
- Orbital disease, uveitis, RBN, eye strain
Patterns of headache

**Acute single headache**
- Febrile illness, sinusitis
- First attack of migraine
- Following a head injury
- Subarachnoid haemorrhage, meningitis

**Recurrent headaches**
- Migraine
- Cluster headache
- Episodic tension headache
- Trigeminal or post-herpetic neuralgia

**Triggered headache**
- Coughing, straining, exertion
- Coitus
- Food and drink

**Dull headache, increasing in severity**
- Usually benign
- Overuse of medication (e.g. codeine)
- Contraceptive pill, hormone replacement therapy
- Neck disease
- Temporal arteritis
- Benign intracranial hypertension
- Cerebral tumour

**Dull headache, unchanged over months**
- Chronic tension headache
- Depressive, atypical facial pain
Exclude treatable structural disease

- First or worst headache, especially if of sudden onset
- Headaches of increasing frequency or severity
- Increased frequency of vomiting and headache on waking
- Headache triggered by coughing, straining or postural changes
- Persistent physical symptoms or signs after attacks, neurological or endocrine
- Meningism, confusion, impairment of consciousness or seizures
Subarachnoid haemorrhage

Sudden generalised headache
- ‘blow to the head’.

Most are caused by a ruptured aneurysm, a few from arteriovenous malformations, and some are unexplained.
Subarachnoid haemorrhage

~50% are instantly fatal.
Vasospasm may stop the leak;
these patients are at risk of a further bleed,
especially in the first month.

Early neurosurgical assessment will confirm the bleed
and establish the cause.

Aneurysms can be clipped, or filled with platinum coils.
Causes of Sudden Headache; <5 min

- Sub-arachnoid haemorrhage 10% in the Community 60% in Hospital
- Intracranial venous sinus thrombosis
- Dissection of intracranial vessels
- Meningitis
- Cerebral contusion (same CT changes)
- Coital and exertional headache
- Cough headache
- Exploding head syndrome
- ‘Crash Migraine’ - rare form of common disease (1/10,000)
- Non-Specific

Van Gijn RSM 2002
Raised intracranial pressure

Most focal lesions cause other symptoms or signs before the patient develops headache due to raised intracranial pressure:

- Seizures
- Focal brain dysfunction -
  - hemiparesis
  - visual field defect
  - sensory symptoms or signs
  - dysphasia
  - personality change

- Papilloedema

It is very rare for these patients to present with headache alone, though all will develop it as the pathology advances.
Presenting symptoms of single intracerebral tumours
Scottish audit of 324 patients with gliomas

Headache 23.5%
Headache alone, with no other symptoms or signs 1.9%
Seizures 21.3%
Confusion 4.5%
Personality change, visual, language, weakness, numbness, unsteadiness 26.1%

81% had physical signs - hemiparesis, confusion, visual, dysphasia.

Grant JNNP 2004 75 Suppl 2 18-23
Aranjuez and Orihuela, Spain
1876 consecutive new patients age > 15 with headache for > 4 weeks
Variably CT (1432) or MRI (580)
22 Abnormal scans (1.2%); 5 had abnormal signs (0.9% in those without). Most of these were not typical migraine
- Pituitary adenoma 3*
- Large arachnoid cyst 2*
- Meningioma 2*
- Hydrocephalus 2**
One each of:- Arnold Chiari Malformation, Stroke, Cavernoma, AVM*, Low grade astrocytoma, Brain stem glioma, colloid cyst*, Posterior fossa papilloma*
* Only these operated; how many were relevant?
Sempere et al Cephalalgia 2005 25 30-35
Scanning is not without risk!

- Radiation
- Allergies to contrast media
- Expense
- Misleading results:
  - Wrong part scanned
  - Other investigations more appropriate
  - False reassurance
  - Irrelevant abnormalities (cysts, tiny lumps, calcification, non-specific ischaemia etc)
  - Insurance consequences, e.g. of a small aneurysm
## Incidental Brain MRI findings

<table>
<thead>
<tr>
<th></th>
<th>German Air Force recruits</th>
<th>Population of Rotterdam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>2536</td>
<td>2000</td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td>20.5 (17-36)</td>
<td>63.3 (46-97)</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>All</td>
<td>47.6%</td>
</tr>
<tr>
<td><strong>Contrast</strong></td>
<td>When indicated</td>
<td>No</td>
</tr>
<tr>
<td><strong>Asymptomatic infarcts</strong></td>
<td>Nil</td>
<td>145 (7.2%)</td>
</tr>
<tr>
<td><strong>Aneurysms</strong></td>
<td>Nil</td>
<td>35 (1.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All but one &lt;7mm</td>
</tr>
<tr>
<td><strong>Meningiomas</strong></td>
<td>Nil</td>
<td>18 (0.9%)</td>
</tr>
<tr>
<td><strong>Pit. macroadenoma</strong></td>
<td>4 (0.16%)</td>
<td>6 (0.3%)</td>
</tr>
<tr>
<td><strong>Glioma</strong></td>
<td>1 (&lt;0.1%)</td>
<td>1 (&lt;0.1%)</td>
</tr>
<tr>
<td><strong>Metastasis</strong></td>
<td>Nil</td>
<td>1 (&lt;0.1%)</td>
</tr>
<tr>
<td><strong>Subdural</strong></td>
<td>Nil</td>
<td>1 (&lt;0.1%)</td>
</tr>
<tr>
<td><strong>Arachnoid cyst</strong></td>
<td>43 (1.7%)</td>
<td>22 (1.1%)</td>
</tr>
</tbody>
</table>
Red Flags

- Headache in patients with cancer or HIV disease
- Sudden onset of symptoms
- Onset after age 50
- Accelerating pattern
- Fever, stiff neck, rash
- Focal neurological symptoms or signs

Detsky  JAMA 2006  296 1274
Trigeminal Neuralgia

Short lived pain in the distribution of a sensory nerve. Often triggered by innocuous stimuli. Usually lower divisions of the nerve (11% include V1) Majority of patients have a vascular or other anomaly at the point of entry of the nerve to the pons. 2% have neuralgia as a symptom of M.S.

Prophylactic treatment

Carbamazepine, Gabapentin, Phenytoin, Baclofen, Clonazepam.

Surgery to the Gasserian ganglion or to the causative lesion.
Cervical Spondylosis

Commonest cause of new headache in older patients

- Usually bilateral
- Pain can radiate forwards to the frontal region
- Steady pain
- No nausea or vomiting
- Worsened by moving the neck

- Management:-
  Rest, deep heat, massage.
  Anti-inflammatory analgesics.
  Over-manipulation may be harmful.
Cervical Spondylosis
TEMPORAL ARTERITIS

- Virtually unknown below the age of 55.
- Incidence rises 10-fold between the 6th and 9th decades.
- Three times commoner in females.
- The majority present with constant headache, generalised or unilateral.
- The temporal arteries are usually inflamed and tortuous.
- Generalised scalp tenderness is common.
- **Involvement of the posterior ciliary arteries can lead to blindness.**
- 25% have Polymyalgia Rheumatica.
- The majority have an elevated ESR
- Biopsy shows inflammation and Giant Cells.
  Stable for 48hrs after steroids
- **High daily doses (80mg) of Prednisolone are curative.**
  Remember to protect against osteoporosis and dyspepsia
- Disease is self-limiting over 3-4 years
ATYPICAL FACIAL PAIN

Most commonly in middle aged women. Depressed or anxious. Daily, constant, poorly localised deep aching or burning. Facial or jaw bones, but may extend to the neck, ear or throat. Not lancinating. Not conforming to the strict anatomical distribution of any nerve in the head. 11 out of 93 cases in one series bilateral. No sensory loss. Pathology in teeth, TM joints, eye, nasopharynx and sinuses must be excluded.

Unresponsive to conventional analgesics, opiates and nerve blocks. Mainstay of management tricyclics.
Headache in cerebrovascular disease

- **Transient ischaemic attacks**
  6 - 44%, mild to moderate, appropriately localised

- **Stroke**
  20-30% of large artery occlusions, usually ipsilateral

- **After carotid endarterectomy**
  Ipsilateral
  ? Interference with sympathetic nerves
  ? Sudden reperfusion of distal vessels

- **Venous sinus thrombosis**
  Overlap with Benign Intracranial Hypertension

- **Carotid Dissection**
  Horner’s common
Sinusitis

Malaise, headache, fever.
Blocked nasal passages.
Loss of vocal resonance (esp. ethmoiditis).
Anosmia or cacosmia.
Nasal or postnasal catarrh.
Local pain and tenderness.

Frontal pain characteristically starts 1-2 hours after rising and clears up during the afternoon.
Sphenoid pain may be widespread or localised
Prevalence of Post traumatic headache

- 36% at discharge
- 24% at 6 months
- 16% at 12 months

- Correlates with previous history of headache
- Unrelated to duration of post-traumatic amnesia
- Depends on the nature of the head injury:
  - High in victims of car accidents
  - Low in perpetrators of car accidents
  - Low in sports injuries
- Multiple mechanisms:
  - Neck injury
  - Scalp injury
  - Vasodilatation ? autonomic damage
  - Depression - often delayed
- Fewer patients with migraine after head injury have a family history of migraine
Management of Post Traumatic Headache

- Explanation
- Analgesic abuse?
- NSAID’s
- Valproate
- Tricyclic antidepressants - Amitriptyline

Be patient - 3-4 years
<table>
<thead>
<tr>
<th>Migraine</th>
<th>Cluster Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>About 33% men</td>
<td>Up to 90% men</td>
</tr>
<tr>
<td>Usually last 3-12 hours</td>
<td>Last ¼ - 3 hours</td>
</tr>
<tr>
<td>Usually 1-8 attacks monthly</td>
<td>Usually 1-3 attacks daily,</td>
</tr>
<tr>
<td></td>
<td>often at night</td>
</tr>
<tr>
<td>Long remissions unusual</td>
<td>Long remissions common</td>
</tr>
<tr>
<td>Visual or sensory auras seen</td>
<td>Eye waters, nose blocked,</td>
</tr>
<tr>
<td></td>
<td>ptosis etc</td>
</tr>
<tr>
<td>Nausea &amp; vomiting frequent</td>
<td>Nausea rare</td>
</tr>
<tr>
<td>Pulsating hemicranial pain</td>
<td>Steady, exceptionally severe,</td>
</tr>
<tr>
<td></td>
<td>well localised pain,</td>
</tr>
<tr>
<td></td>
<td>unilateral in each cluster</td>
</tr>
<tr>
<td>Patients lie in the dark</td>
<td>Patients pace about</td>
</tr>
</tbody>
</table>
Cluster Headache
International Classification of Headache Diseases 2004

- Severe unilateral pain lasting 15-180 minutes untreated.
- At least one of the following, ipsilaterally:
  - Conjunctival injection and/or lacrimation
  - Nasal congestion and/or rhinorrhoea
  - Eyelid oedema
  - Forehead and facial sweating
  - Miosis and/or ptosis
  - A sense of restlessness or agitation
- Frequency between one on alternate days to 8 per day.
- Not attributable to another disorder
Cluster Headache

- Population prevalence 1-4 per 1000 (Sjaastad 2004)
- Ratio M:F now thought to be 3.5-7 :1
- 1% bilateral
- 25% have some form of aura
Figure 13.2. The site of pain in 60 patients (from Lance and Anthony, 1971)
Secondary Cluster Headache

Favier Arch Neurol 2007 64 25-31

Review of 31 cases, often clinically typical, sometimes episodic

**Principal diagnosis:**

- Pituitary tumour 11
- Meningioma 4
- Carotid or vertebral aneurysm 4
- Sinus disease 3
- AVM 3
- Arnold-Chiari 1
- Ganglioglioma 1
- Brainstem glioma 1
- Nasopharyngeal Ca 1
- Subclavian steal 1
- Orbital haemangioma 1

**Consider** Pontine MS, Carotid dissection

SUNCT and SUNA are more likely to have a structural cause
THERAPY OF CLUSTER HEADACHE

**Acute**
- Inhaled oxygen
- S/C or Nasal Sumatriptan
- Zolmitriptan 10mg

**Prevention**
- Verapamil - 120 mg tds, or more
- Prednisolone - 40 mg daily > zero. 2 weeks only!
- Lithium - Priadel 800-1200mg daily. Chronic
- Valproate
- Gabapentin
- Methysergide
- Ergotamine
- Pizotifen
- Topiramate

**Ineffective**
- Propranolol
THERAPY OF CLUSTER HEADACHE

Intractable cases of Chronic Cluster Headache may justify Surgical management:

- (Percutaneous thermocoagulation)
- Trigeminal Nerve Section
- Stereotactic Hypothalamic Stimulation
Occipital Nerve Stimulation for intractable Cluster Headache

- £22,000 total cost – battery life-span
- Mechanism not fully understood. Convergence of 2nd order nociceptors in the brain stem
- Paraesthesiae preclude full blinding, and can be unbearable
- Benefit builds up over several weeks
- Worsening over hours or days if switched off or battery fails

- Fatal haemorrhage from hypothalamic stimulation (Schoenen Brain 2005 128 940)
Occipital Nerve Stimulation for intractable Cluster Headache

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Follow-up months</th>
<th>Substantial improvement (&gt;90%)</th>
<th>Moderate Improvement (&gt;40-85%)</th>
<th>Mild improvement (&lt;40%)</th>
<th>No benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burns</td>
<td>14</td>
<td>17.5</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>London</td>
<td>Lancet 2007 369 1009 Neurology 2009 72 341</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magis</td>
<td>8</td>
<td>18</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>Nil</td>
</tr>
<tr>
<td>Liege</td>
<td>Lancet Neurology 2007 6 314</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PAROXYSMAL HEMICRANIA

- Episodic or Chronic
- Commoner in females (about 3:1)
- Frequent, short lasting, (lasting 2 – 45 min) attacks of unilateral pain, usually in or above the eye, or in the temple.
- Can have unilateral ‘jabs and jolts’.
- Usually at least 5 attacks daily; published range 1-40.
- At least one autonomic symptom.
- *Complete* sensitivity to Indomethacin 150mg daily, and often to less.

Goadsby & Lipton Brain 1997 120 193
Short-lasting Unilateral Neuralgiform headache with Conjunctival injection and Tearing. “SUNCT”

- Predominately Males
- Paroxysms of pain lasting 5 sec-4 mins
- Usually 5-6 per hour, range 1 per week to 30 per hour. In one series mean 28 per day
- Conjunctival injection and Tearing.
  Nose can run, sweating on the forehead

Remarkably refractory to all treatments so far described; Lamotrigine and Carbamazepine among the better; also IV Lignocaine, Gabapentin, and Topiramate

Goadsby & Lipton 1997 Brain 120 193
Cluster Headache: Comparison with other Trigeminal-Autonomic Cephalgias

<table>
<thead>
<tr>
<th></th>
<th>Cluster</th>
<th>CPH</th>
<th>SUNCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender M:F</strong></td>
<td>3:1</td>
<td>1:3</td>
<td>3:1</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>15min-3hrs</td>
<td>2-45 min</td>
<td>5sec-4min</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>1-3/day</td>
<td>1/40/day</td>
<td>1/day-30/hr</td>
</tr>
<tr>
<td><strong>Autonomic features</strong></td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Indomethacin</strong></td>
<td>+/-</td>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>
Hypnic Headache

- Rare; 1:1400 at the Mayo headache clinic
- Older subjects; 40-73 years
- At least 15 attacks monthly; usually 4 nights weekly
- Wakes from sleep consistently at 1-3am, often more than once
- Duration 5-60 min
- Frequency and severity unchanged over time
- Usually generalised or bilateral
- Nausea and autonomic features rare
- No evidence of alternative pathologies—must scan!
- Spontaneous remissions rare

Treatment:- Indomethacin (75 mg at night), Lithium, Caffeine (75mg at bedtime), or combinations.

Modified from Goadsby & Lipton Brain 120 193 1997 Dodick Headache 38 152 1998; 40 830 2000
TENSION TYPE HEADACHE

Episodic or Chronic

Consider:-

- Psychogenic and emotional factors, and especially depression.
- Referred cervicogenic pain
- Drug induced headache
- Female sex hormones
- Referred pain from inflammatory lesions in the facial skeleton.
Epidemiology of Chronic Headache in Spain

4,855 inhabitants interviewed prospectively:

<table>
<thead>
<tr>
<th>Subjects</th>
<th>1.41% (70 women)</th>
<th>2.6% Women</th>
<th>0.19% men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache &gt; 10 days/month</td>
<td>332</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary Headache</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDH with analgesic overuse</td>
<td>74</td>
<td>1.41%</td>
<td></td>
</tr>
<tr>
<td>Transformed Migraine</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Tension-type headache</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New daily persistent Headache</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Colas Neurology 2004 62 1338
De Novo Chronic Headache

Rare: 2 of 89 with chronic headache from a population of 1883 in Northern Spain

Exclude Low pressure headache
Meningitis
Cerebral Venous Sinus Thrombosis

Lumbar Puncture may be required for diagnosis
Criteria for Transformed Migraine
Silberstein & Lipton  Neurology 1996  47 871-5

- History of episodic migraine
- Pain >15 days/month for >1 month
- Untreated duration > 4 hours
- Increasing frequency and decreasing duration for > 3 months
- No other cause
- ? Medication overuse:-
  - >1000mg Aspirin/ Paracetamol for >5 days/week
  - Caffeine or barbiturates > 3tabs/day > 3 days/week
  - Opiates >1 tab/day >2 days/week
  - Ergotamine 1mg orally >2 days/week
Chronic Migraine

The most frequent migraine??

Responsiveness to Sumatriptan relates to lifetime history of migraine
Lipton et al Headache 40 783 2000

Does Tension Headache exist?
Chronic headache - management

- Consider analgesic abuse and depression
- NSAID’s preferred
  - Ibuprofen, Naproxen, Diclofenac
  - May be better given regularly
- Tricyclic antidepressants:
  - Amitriptyline 50-75mg daily
  - 30-60% derive some symptomatic relief
- SSRI’s probably less effective
- Biofeedback and relaxation unproven
- Botox! Publicity > availability
Pain and focal symptoms = Migraine with aura
- (Classical)

Pain alone = Migraine without aura - (Common)

Focal symptoms alone = Acephalalgic migraine
A. At least 5 attacks fulfilling B-D
B. Headache attacks lasting 4-72 hours (Untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe intensity (inhibits or prohibits daily activities)
   4. Aggravation by walking stairs or similar routine physical activity
D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. At least one of the following:
   1. History, physical- and neurological examinations do not suggest one of the disorders listed in groups 5-11
   2. History and/or physical- and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations
   3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

International Headache Society Criteria for Migraine Revised 2004
Hormones and Headache

- Menarche
- Menstruation
- Falling levels of oestrogen
- Combined oral contraceptives – POP, Mirena
- Pregnancy
- Menopause - HRT
Hormones and Headache

Remember these patients are complaining of headache!
- headache is the priority
Keep hormone levels stable
  Off the pill. Mirena!
Timing of exogenous hormones in the cycle
Minimum HRT if really necessary
Treatment of Migraine

- Analgesic
- Prophylactic
- Don’t forget about other drugs!
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Cost (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>600 mg</td>
<td>0.02</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400 mg</td>
<td>0.08</td>
</tr>
<tr>
<td>Naproxen</td>
<td>500 mg</td>
<td>0.07</td>
</tr>
<tr>
<td>Ergotamine (Cafergot)</td>
<td>1 mg</td>
<td>0.13</td>
</tr>
<tr>
<td>Sumatriptan (Generic)</td>
<td>100 mg</td>
<td>0.51</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>2.5 mg</td>
<td>4.00</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>2.5 mg</td>
<td>4.09</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>10 mg</td>
<td>4.46</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>12.5 mg</td>
<td>3.02</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>40 mg</td>
<td>3.75</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>2.5 mg</td>
<td>2.78</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>20 mg nasal</td>
<td>5.90</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>5 mg nasal</td>
<td>6.08</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>6 mg s.c.</td>
<td>20.21</td>
</tr>
</tbody>
</table>
Most patients will have tried paracetamol, Aspirin, and Ibuprofen

Try Naproxen, Diclofenac, Mefenamic acid, Domperidone
Ergotamine
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effect</th>
<th>Ergot</th>
<th>Triptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT$_{1A}$</td>
<td>Dysphoria</td>
<td>++++</td>
<td>±</td>
</tr>
<tr>
<td>5-HT$_{1B}$</td>
<td>Less Headache!</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>5-HT$_{1D}$</td>
<td>Less Headache!</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>5-HT$_{1F}$</td>
<td>Blocks plasma extravasation</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>5-HT$_{2A}$</td>
<td>Vasoconstriction</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>$\alpha$-adrenergic</td>
<td>Dizziness</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Dopaminergic D$_2$</td>
<td>Nausea</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Triptans</td>
<td>Trade name</td>
<td>Tablets</td>
<td>Melt</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>------------</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Imigran</td>
<td>£4.42-£7.15</td>
<td>£4.14 (Radis)</td>
</tr>
<tr>
<td></td>
<td>Generic</td>
<td>£0.51-£2.26</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Zomig</td>
<td>£4</td>
<td>£4</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Naramig</td>
<td>£4.09</td>
<td></td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Maxalt</td>
<td>£4.46</td>
<td>£4.46</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>Relpax</td>
<td>£3.75</td>
<td></td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Almogran</td>
<td>£3.02</td>
<td></td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Migard</td>
<td>£2.78</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Advantages</td>
<td>Disadvantages</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------------------</td>
<td>----------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Well established</td>
<td>Expensive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subcutaneous available</td>
<td>Poorly absorbed</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Cheaper; S/L tastes better.</td>
<td>Occasional confusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Melt available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Cheaper; Long acting; low recurrence rate</td>
<td>Slow onset of relief</td>
<td></td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>More rapid action</td>
<td>High recurrence rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Melt available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Cheaper; ± Fast acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long acting; low recurrence rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eletriptan</td>
<td>Cheaper; Long acting; low recurrence rate</td>
<td>Pumped out of CNS; High doses; more side-effects</td>
<td></td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Cheaper</td>
<td>Slow onset of relief</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very long acting</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Percentage of patients with two hour headache response for each treatment (bars are 95% confidence intervals of the percentage)

Bandolier April 2007
Triptans balance scores for efficacy and tolerability

Source: Ferrari MD, et al. 2002
Triptans for mild headache

Most trials require at least a moderate headache; these are protocol violators

Response in open almotriptan trials:

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hour pain-free</td>
<td>47%</td>
<td>14%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 hours pain-free</td>
<td>84%</td>
<td>53%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Early recurrence</td>
<td>28%</td>
<td>33%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Pascual  Headache 42 28 2002
Early versus delayed treatment with Almotriptan 12.5mg

Headache 2002 42 S12
There is experimental evidence that Naproxen enhances the antinociceptive effects of sumatriptan, even if it is delayed. Possible synergism in migraine?

Burstein et al Neurology 2006 66(Suppl2) A69
INDICATIONS FOR MIGRAINE PROPHYLAXIS

Two attacks monthly.
Less frequent attacks proving intractable.

Note
- Cost benefit.
- Abolition of the first hour or so of each headache if successful.
- Persistent symptoms after 2 hours, eg:-
  - Mild Headache
  - Nausea
  - Photophobia
  - Disability

Quality of life can be impaired despite ‘effective’ treatment.
Principles of Prevention

Migraine Prevention

Consider Prevention if any of the following criteria are met:

1. Migraine significantly interferes with patients' daily routine, despite acute treatment
2. Frequency attacks (>2/month) with risk of acute medication overuse
3. Acute medications ineffective, contraindicated, troublesome AEs, or overused
4. Patient preference
5. Presence of uncommon migraine conditions
   a. Hemiplegic Migraine
   b. Basilar Migraine
   c. Migraine with Prolonged Aura
   d. Migrainous Infarction

Patients may be candidates for preventive treatment if any of above criteria apply.
US Headache Consortium Guidelines.
Migraine Prevention Utilization

53% of migraineurs meet criteria for prevention based on disability and frequency

Less than 5% of migraineurs are using preventive therapy

Source: IMS MIDAS; 2002 RXs; N2C Migraine Products + top products used for G43 diagnosis code (which includes off-label products).
### Preventative treatment

<table>
<thead>
<tr>
<th>Amine modulation</th>
<th>Channel modulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pizotifen</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Methysergide</td>
<td>Topiramate</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Valproate</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>Flunarizine</td>
</tr>
<tr>
<td>Flunarizine</td>
<td></td>
</tr>
<tr>
<td>Phenelzine</td>
<td></td>
</tr>
</tbody>
</table>

Both groups are likely to act in the Brain Stem  [Diener PET studies]
Migraine - Preventive Treatment

First choice
- betablockers
- antiepileptic drugs

Second choice
- antidepressants
- calcium-antagonists
- serotonin antagonists

Third choice
- riboflavin, coenzyme Q10, magnesium

“Special cases“
- menstrual migraine: NSAIDs, continuous contraceptive pill, naratriptan, frovatriptan
- exercise induced: betablockers, indomethacin
Consensus view on migraine prophylaxis

Offered:- Patients with 6 or more headache days per month; 4 or more days with some impairment; or 3 or more days with severe impairment.

Considered:- Patients with 4 or 5 headache days per month with normal functioning; 3 days with some impairment; or 2 days with severe impairment.

Not indicated:- Patients with <4 headache days per month with normal functioning; or no more than 1 day per month regardless of impairment.

Lipton Neurology 2007 68 343
RESULTS FROM PREEMPT 1

Week

0 4 8 12 16 20 24 28 32 36 40 44 48 52 56

Headache Days/28 Days*
(Mean Change From Baseline)

After week 24 all patients received BOTOX®

Double-Blind Phase

Open-Label Phase

BOTOX® (n = 341)
Placebo (n = 338)

\(^aP \leq .05\)
PREEMPT Trials

Botox had a greater effect in shortening the attacks, without reducing their number.

8.4 → 6.6 on placebo

Hence the results were better if one counted the days and not the number of episodes.

Patients given placebo first do improve once given Botox, but they do not catch up.

Response lasts too long to be an acupuncture effect.

It is not clear what proportion of patients do not respond at all.
PREEMPT Trials

The trial was careful to avoid detoxifying. Patients were not told to stop analgesics. Placebo group too.

‘If it helps you to get off.............’

Subjective opinion of the patients more favourable than diaries.
More convincing effect on HIT scores:

<table>
<thead>
<tr>
<th></th>
<th>Botox n=513</th>
<th>Placebo n=492</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent with score &gt;60</td>
<td>62.6</td>
<td>78.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-5.5</td>
<td>-2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent with &gt;5 point reduction</td>
<td>44.1</td>
<td>25.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
79% of the effect can be attributed to the placebo.

Difference between active and placebo is 2 headache days per month.

Nevertheless 70% of the patients achieve a >50% reduction in headache days in 56 weeks.

Scottish Medicines Consortium did not approve!

NICE did approve ..................
NICE Guidance 2012

Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine, defined as headaches on at least 15 days per month of which at least 8 days are with migraine

• that has not responded to at least three prior pharmacological prophylactic therapies and

• whose condition is appropriately managed for medication overuse
Daily headache is less likely to respond

Need to have negative and positive stopping rules

< £20,000 per QUALY!

Rothrock EHMTIC London 2012
Neurology 78 2012
Conclusions

• A majority of the population have headaches from time to time.
• Almost all are benign.
• Sudden and/or worsening headache may need investigating.
• Patients with tumours almost always present with seizures or focal symptoms.
• A few have a specific cause, requiring specific treatment.
• A lot will be disabling, and may require specific analgesics, and perhaps regular preventative treatment.