Seminar

Migraine

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Migraine is a very common neurobiological headache disorder that is caused by increased excitability of the CNS. It ranks among the world's most disabling medical illnesses. Diagnosis is based on the headache's characteristics and associated symptoms. The economic and societal effect of migraine is substantial: it affects patients' quality of life and impairs work, social activities, and family life. There are many acute and preventive migraine treatments. Acute treatment is either specific (triptans and ergots) or non-specific (analgesics). Disabling migraine should be treated with triptans. Increased headache frequency is an indication for preventive treatment. Preventive treatment decreases migraine frequency and improves quality of life. More treatments are being developed, which provides hope to the many patients whose migraines remain uncontrolled.

Introduction

Migraine is a primary episodic headache disorder characterised by various combinations of neurological, gastrointestinal, and autonomic changes. The word migraine is derived from the Greek word hemicrania (Galen about 200 AD).[1] Diagnosis is based on the headache's characteristics and associated symptoms.[2] The International Headache Society diagnostic criteria for headache disorders (1988)[3] have been revised (2004) and provide criteria for seven subtypes of migraine.[4] Migraine was last reviewed in *The Lancet* in 1998.[5] For this review I have relied on the technical reports of the Agency for Healthcare Policy and Research,[6–9] US Headache Consortium Guidelines,[10,11] and the triptan meta-analysis.[12]

Epidemiology

Migraine prevalence is similar and stable in western countries and the USA.[13] In the USA, 18% of women and 6% of men had had at least one migraine attack in the previous year.[14] A second study 10 years later had similar prevalence estimates (figure 1).[15] Migraine prevalence varies by age, sex, ethnic origin, and income. Before puberty, migraine prevalence is about 4%.[16] After puberty, prevalence increases more rapidly in girls than in boys. Prevalence increases until about age 40 years, then declines. Prevalence is lowest in Asian-Americans, intermediate in African-Americans, and highest in white people.[16] In the USA, migraine prevalence decreases as household income increases.[14,16,17]

Migraine greatly affects quality of life. WHO ranks migraine among the world's most disabling medical illnesses.[18] About 28 million Americans have severe, disabling migraine headaches.[15] Migraine's yearly cost to employers is about US$13 billion and yearly medical costs exceed $1 billion.[16] Methods to quantify migraine disability include the Migraine Disability Assessment Scale (MIDAS)[19] and the Headache Impact Test (HIT).[20]

Pathophysiology

Genetics

Migraine is a group of familial disorders with a genetic component. Familial hemiplegic migraine is an autosomal dominant disorder associated with attacks of migraine, with and without aura, and hemiparesis. The gene has been mapped to chromosome 19p3 in about two-thirds of cases.[21,22] The defect is caused by at least ten different missense mutations in the *CACNA1A* gene, which codes for the α1 subunit of a voltage dependent P/Q calcium channel.[23] The same gene is associated with episodic ataxia with cerebellar vermal atrophy.[21] P-type neuronal calcium channels mediate 5-HT and excitatory neurotransmitter release. Dysfunction can impair release of 5-HT and predispose patients to migraine attacks or impair their self-aborting mechanism. Voltage-gated P/Q-type calcium channels mediate glutamate release, are involved in cortical spreading depression, and might be integral in initiating the migraine aura.[24] A second gene has been mapped to chromosome 1q21–23; the defect is a new mutation in the α2 subunit of the sodium/potassium pump.[25]

Aura

The migraine aura was thought to be caused by cerebral vasoconstriction and the headache by reactive vasodilation,[26] which explained the headache's throbbing quality and its relief by ergots. The aura is now thought to be caused by neuronal dysfunction, not ischaemia; ischaemia rarely, if ever, occurs. Headache often begins while cortical blood flow is reduced;[27–29] thus, headache is not caused by simple reflex vasodilation.[30,31]

The migrainous fortification spectrum corresponds to an event moving across the cortex at 2–3 mm/min.[32] Noxious stimulation of the rodent cerebral cortex produced a spreading decrease in electrical activity that moved at 2–3 mm/min (cortical spreading depression, figure 2).[33] Cortical spreading depression is characterised by shifts in cortical steady state potential, transient increases in potassium, nitric oxide, and glutamate, and transient

Search strategy and selection criteria

I did a search of MEDLINE for articles on migraine that were published in the past 2 years using the search terms migraine or headache and pathogenesis, epidemiology, or treatment. I also reviewed abstracts of headache and neurological meetings, recent reviews about migraine, and technical reports of the Agency for Healthcare Policy and Research, US Headache Consortium guidelines, and the triptan meta-analysis.

Lancet 2004; **363:** 381–91

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Figure 1: **Adjusted age-specific prevalence of migraine by sex**
Data taken from Lipton and colleagues.[1]

increases in cortical blood flow, followed by sustained decreases.[27]

The aura is associated with an initial hyperaemic phase followed by reduced cortical blood flow, which moves across the cortex (spreading oligaemia).[34] Olesen and Lauritzen[34,35] found 17–35% reductions in posterior cortical blood flow, which spread anteriorly at 2–3 mm/min. It crossed brain regions supplied by separate vessels and is thus not caused by segmental vasoconstriction.[35] Reduced cortical blood flow persisted from 30 min to 6 h, then slowly returned to baseline or increased. The rates of progression of spreading oligaemia are similar to those of migrainous scotoma and cortical spreading depression, suggesting that they are related.[31,33,36]

Additional studies[28,29,37–40] support the hypothesis that cortical spreading depression produces the aura.[27] During visual auras, cortical blood flow decreased by 15–53%, cerebral blood volume decreased by 6–33%, and mean transit time increased by 10–54% in the occipital cortex contralateral to the aura. The perfusion defect moved anteriorly.[29] The absence of diffusion abnormalities suggests that ischaemia does not occur during the aura.[41]

Blood oxygenation level-dependent (BOLD) functional MRI reflects the relative concentration of deoxyhaemoglobin in venous blood. Visual stimulation was used to trigger headache in patients with migraine.[37] A wave of increased (hyperoxygenated blood) and then decreased (possibly reflecting neuronal metabolic-flow coupling) BOLD signal propagated into the contiguous occipital cortex at a rate of 3–6 mm/min. When visual stimulation was used to test the visual cortex response, the BOLD signal and the BOLD response to visual activation diminished after progression of the visual aura.[30]

Magnetoencephalography shows changes in patients with migraine, but not controls, consistent with cortical spreading depression.[42,43] Use of transcranial magnetic stimulation applies magnetic fields of increasing intensity to assess occipital cortex excitability. Aurora and colleagues[44] and Young and colleagues,[45] but not Afra and co-workers,[46] found that phosphenes were generated in patients with migraines at lower thresholds than controls, and that it was easier to visually trigger headaches in those with lower thresholds. Other evidence of increased CNS excitability comes from studies of visual and brainstem auditory evoked potentials.[47] Migraine with aura might be caused by neuronal hyperexcitability, perhaps because of cortical disinhibition.

Headache

Headache probably results from activation of meningeal and blood vessel nociceptors combined with a change in central pain modulation. Headache and its associated neurovascular changes are subserved by the trigeminal system. Reflex connections to the cranial parasympathetics form the trigeminoautonomic reflex. Activation results in vasoactive intestinal polypeptide release and vasodilation.[31]

Trigeminal sensory neurons contain substance P, calcitonin gene-related peptide, and neurokinin A.[48] Stimulation results in release of substance P and calcitonin gene-related peptide from sensory C-fibre terminals[49] and neurogenic inflammation.[50] The neuropeptides interact with the blood vessel wall, producing dilation, plasma protein extravasation, and platelet activation.[51] One study[52] suggests that neurogenic inflammation occurs in human beings. Neurogenic inflammation sensitises nerve fibres (peripheral sensitisation) that now respond to previously innocuous stimuli, such as blood vessel pulsations,[53] causing, in part, the pain of migraine.[54] Central sensitisation can also occur. After meningeal irritation, c-fos expression (a marker for neuronal activation) occurs in the trigeminal nucleus caudalis[55] and in the dorsal horn at the C1 and C2 levels.[56,57]

Superior sagittal sinus stimulation results in release of calcitonin gene-related peptide, but not of substance P.[58] That calcitonin gene-related peptide and not substance P is raised in external jugular venous blood during migraine is important.[59] Sumatriptan reduced high concentrations of calcitonin gene-related peptide in a migraine attack and in animals during trigeminal ganglion stimulation.[60,61] Calcitonin gene-related peptide might have a role in migraine headache,[62,63] and a potent specific calcitonin gene-related peptide antagonist[64] has been reported to be effective in acute migraine treatment.[65]

Application of an inflammatory soup to the dura sensitises second order trigeminovascular neurons (increased spontaneous activity and response to mechanical and thermal skin stimulation).[53] Triptans administered early prevented central sensitisation: dural and facial receptive fields did not expand; spontaneous activity and mechanical and thermal sensitivity did not increase. Late triptan intervention did not reverse central sensitisation but shrunk the expanded dural receptive fields and normalised intracranial mechanosensitivity. Central sensitisation might play a key part in maintaining the headache.[66,67]

Patients frequently develop cutaneous allodynia during migraine attacks because of trigeminal sensitisation.[66] Triptans can prevent, but not reverse, cutaneous allodynia.[67] Cutaneous allodynia can be used to predict the effectiveness of triptans.[66] Without allodynia, triptans completely relieved the headache and blocked development of allodynia. In 90% of attacks with established allodynia, triptans provided little or no headache relief and did not suppress allodynia. However, late triptan therapy eliminated peripheral sensitisation (throbbing pain aggravated by movement) even when pain relief was incomplete and allodynia was not suppressed.[66] Early intervention might work by preventing cutaneous allodynia and central sensitisation.

Brainstem activation occurs in migraine without aura. By use of positron emission tomography, patients with right-sided migraine headache showed increased regional cortical blood flow in the left brainstem. Sumatriptan relieved the headache and associated symptoms but did not normalise regional cortical blood flow in the

brainstem, suggesting that activation is caused by factors other than, or in addition to, increased activity of the endogenous antinociceptive system.[68] A second report corroborates these findings.[69]

A link exists between the migraine aura and headache. Cortical spreading depression activates trigeminovascular afferents causing a long-lasting increase in middle meningeal artery blood flow and plasma protein extravasation within the dura mater.[70] Cortical spreading depression results in upregulation of inducible nitric oxide synthetase and inflammatory cytokines. This mechanism couples meningeal blood flow and neurogenic inflammation to cortical spreading depression, but does not explain headache ipsilateral to the aura.[31,70]

Serotonin (5-HT) receptors and migraine treatment

There are seven classes of 5-HT receptors: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7.[71] In human beings, there are five 5-HT_1 receptor subtypes: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}.[72] The 5-HT_{1B} receptor is located on intracranial blood vessels and CNS neurons. The 5-HT_{1D} receptor is located on CNS neurons and trigeminal nerve endings. 5-HT_{1F} receptors are located on trigeminal nerve endings.[73] Ergots and triptans act at the 5-HT_{1B}, 5-HT_{1D}, and, in part, at the 5-HT_{1F} receptors. They constrict extracerebral intracranial vessels, inhibit trigeminal neurons, and block transmission in the trigeminal nucleus. They minimally constrict human coronary arteries. They block plasma protein extravasation[50] by activating prejunctional trigeminal 5-HT_{1D} and 5-HT_{1F} heteroreceptors, blocking neuropeptide release. Plasma protein extravasation can also be blocked by non-steroidal anti-inflammatory drugs,[74] γ aminobutyric acid agonists,[75,76] neurosteroids,[77] substance P antagonists,[78] and the endothelin antagonist, bosentan.[79] Dihydroergotamine and the centrally penetrant triptans label nuclei in the brainstem and spinal cord involved in pain transmission and modulation.[80] The caudal trigeminal nucleus is activated by stimulation of the sagittal sinus, and this activity is transmitted to the thalamus. Ergots and triptans suppress this activation.

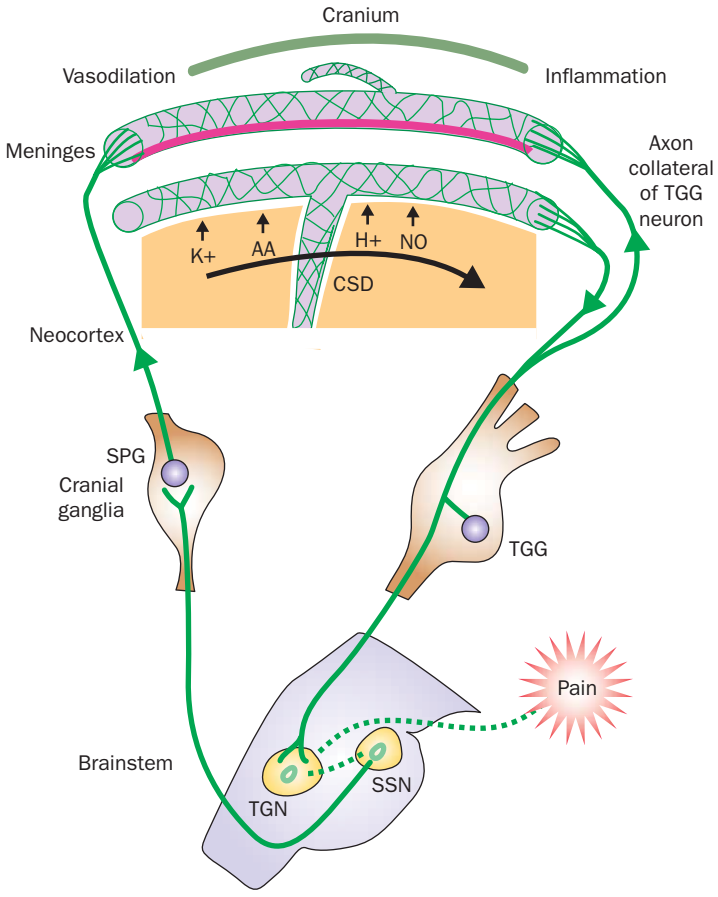

Figure 2: **Cortical spreading depression**
The relation between cortical spreading depression (CSD) and headache in migraine with aura. Cortical spreading depression releases hydrogen ions (H+), potassium ions (K+), and other agents, including arachidonic acid (AA) and nitric oxide (NO), in the extracellular space of the neocortex. These agents diffuse toward local blood vessels and depolarise perivascular trigeminal terminals that, in turn, causes activation of the caudal portion of the trigeminal nucleus (TGN) in the brainstem. At the same time, collateral axons of activated neurons in the trigeminal ganglion (TGG) release proinflammatory peptides in the meninges and their vessels, leading to a local inflammatory reaction. The activation of TGN caused by CSD produces vasodilations of meningeal vessels through a pathway originating from the superior sagittal sinus (SSN) and reaching meningeal blood vessels via the sphenopalatine ganglion (SPG). The perception of pain is mediated by higher-order projections from the TGN. The dashed lines between TGN, SSN, and regions generating the pain indicate that these connections are either unknown or have not been depicted.
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Description of the migraine attack

The migraine attack can consist of premonitory, aura, headache, and resolution phases. Premonitory symptoms occur in 20–60% of patients with migraines, hours to days before headache onset. They can include psychological, neurological, constitutional, or autonomic features, such as depression, cognitive dysfunction, and bouts of food cravings.[81] Patients who reported premonitory symptoms accurately predicted their full-blown headaches 72% of the time. The most common symptoms were feeling tired or weary (72%), difficulty concentrating (51%), and a stiff neck (50%). Poor functioning commonly predicted headache.[82]

Aura

The migraine aura consists of focal neurological symptoms that precede, accompany, or (rarely) follow an attack. Aura usually develops over 5–20 min, lasts for less than 60 min, can be visual, sensory, or motor, and can involve language or brainstem disturbances.[3] Headache usually follows within 60 min of the end of the aura. Patients can have multiple aura types: most patients with a sensory aura also have a visual aura.[83]

Auras vary in complexity. Simple auras include scotomata, simple flashes (phosphenes), specks, geometric forms, and shimmering in the visual field. More complicated visual auras include teichopsia or fortification spectra (characteristic aura of migraine), metamorphopsia, micropsia, macropsia, zoom vision, and mosaic vision. Paraesthesias are often cheiroaural: numbness starts in the hand, migrates up the arm, and jumps to involve the face, lips, and tongue.[2,84] Weakness is rare, occurs in association with sensory symptoms, and is unilateral.[85] Apraxia, aphasia, and agnosia, states of altered consciousness associated with déjà vu or jamais vu, and elaborate dreamy, nightmarish, trance-like, or delirious states can occur.[81]

Headache phase

The median frequency of migraine attacks is 1·5 per month (IQR 1–2).[14] The typical headache is unilateral, of gradual onset, throbbing (85%),[86]

Diagnostic criteria for migraine

Without aura

A At least five attacks

B Headache attack lasts 4–72 h (untreated or unsuccessfully treated).

C Headache has at least two of the following characteristics:
- Unilateral location
- Pulsating quality
- Moderate or severe intensity
- Aggravation by or avoidance of routine physical activity (ie, walking or climbing stairs)

D During headache at least one of the following:
- Nausea, vomiting, or both
- Photophobia and phonophobia

E Not attributed to another disorder

With aura (classic migraine)

A At least two attacks

B Migraine aura fulfills criteria for typical aura, hemiplegic aura, or basilar-type aura.

C Not attributed to another disorder

Typical aura

1 Fully reversible visual, sensory, or speech symptoms (or any combination) but no motor weakness

2 Homonymous or bilateral visual symptoms including positive features (eg, flickering lights, spots, lines) or negative features (eg, loss of vision), or unilateral sensory symptoms including positive features (eg, visual loss, pins and needles) or negative features (ie, numbness), or any combination

3 At least one of:

a) At least one symptom develops gradually over a minimum of 5 min, or different symptoms occur in succession, or both

b) Each symptom lasts for at least 5 min and for no longer than 60 min

4 Headache that meets criteria for migraine without aura begins during the aura or follows aura within 60 min

moderate to marked in severity, and aggravated by movement.[3] Pain can be bilateral (40%) or start on one side and become generalised. It lasts 4–72 h in adults and 1–72h in children.[3]

Anorexia is common. Nausea occurs in almost 90% of patients, while vomiting occurs in about a third.[87] Sensory hypersensitivity results in patients seeking a dark, quiet room.[2,87] Blurry vision, nasal stuffiness, anorexia, hunger, tenesmus, diarrhoea, abdominal cramps, polyuria, facial pallor, sensations of heat or cold, and sweating might occur. Depression, fatigue, anxiety, nervousness, irritability, and impairment of concentration are common. Symptom complexes may be generated by linked neuronal modules.[88]

Resolution phase

After the headache, the patient often feels tired, washed out, irritable, or listless, and can have impaired concentration, scalp tenderness, or mood changes. Some feel unusually refreshed or euphoric after an attack; others experience depression and malaise.

Formal diagnostic criteria

The International Headache Society subdivides migraine into with and without aura.[4,89] To diagnose migraine without aura (panel), five attacks are needed. No single feature is mandatory, but recurrent episodic attacks must be documented.[3] Migraine persisting for longer than 3 days defines status migrainosus.[3,4]

Migraine with aura is subdivided into typical aura, aura, sporadic and familial hemiplegic migraine, and basilar-type migraine. The International Headache Society classification now allows aura to be associated with other headache types. Persistent aura lasts for longer than 1 week without radiological evidence of infacrtion. If neuroimaging shows a stroke, a migrainous infarction has occurred.

Periodic neurological dysfunction (scintillating scotomata and recurrent sensory, motor, and mental phenomena) can occur without headache.[90] Visual phenomena, which are usually benign, occurred in 1·33% of women and in 1·08% of men in a general population sample.[91] Scintillating scotomata, numbness, aphasia, dysarthria, and motor weakness might occur for the first time after age 45 years and be confused with transient ischaemic attacks of cerebrovascular origin.[92] In general, migrainous symptoms are slower to develop (>5 min) and can be positive or negative.

Migraine variants

Basilar-type migraine aura has brainstem symptoms: ataxia, vertigo, tinnitus, diplopia, nausea and vomiting, nystagmus, dysarthria, bilateral paraesthesia, or a change in level of consciousness and cognition.[3] It should be considered when patients have paroxysmal brainstem disturbances. Some investigators have suggested that hemiplegic migraine should be diagnosed if weakness is present.[85]

Ophthalmoplegic migraine is caused by an idiopathic inflammatory neuritis.[93] The cisternal segment of the oculomotor nerve is enhanced, followed by resolution over several weeks as symptoms resolve.

Hemiplegic migraine can be sporadic or familial.[2] Attacks are frequently precipitated by minor head injury.[85] Familial hemiplegic migraine is an autosomal dominant, genetically heterogenous disorder with variable penetration. It includes attacks of migraine without aura, migraine with typical aura, and episodes of prolonged aura, fever, meningismus, and impaired consciousness.[23] Headache can precede the hemiparesis or be absent and its onset is sometimes abrupt and simulates a stroke. In 20% of unselected families with familial hemiplegic migraine, patients have cerebellar symptoms and signs (nystagmus, progressive ataxia). All have mutations within *CACNA1A*.[22]

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited arterial disease of the brain caused by a mutation in the *Notch3* gene on chromosome 19.[94,95] Symptoms include recurrent subcortical lacunar infarctions (84%), progressive or stepwise subcortical dementia with pseudobulbar palsy (31%), migraine with aura (22%), and mood disorders with severe depressive episodes (20%).[96] MRIs of at-risk individuals are often abnormal, with extensive areas of increased white matter T2 signals. The arteriopathy involves the media of small cerebral arteries and to a lesser extent extracerebral arteries, including skin arterioles. Skin biopsy revealing abnormal patches of agranular osmiophilic material within the basal membranes of vascular smooth-muscle cells is diagnostic.[97]

Treatment

Treatment of migraine begins with making a diagnosis,[2] explaining it to the patient, and developing a treatment plan that takes into account coincidental or comorbid conditions.[98] Headache calendars record headache duration, severity, and treatment response. Comorbidity

indicates an association between two disorders that is more than coincidental.

Conditions that occur in patients with migraine with a higher prevalence than would be expected include stroke, epilepsy, Raynaud's syndrome, and affective disorders, which include depression, mania, anxiety, and panic disorder. Possible associations include essential tremor, mitral valve prolapse, and irritable bowel syndrome.

Pharmacotherapy can be acute (abortive) or preventive (prophylactic); patients might need both approaches. Acute treatment attempts to reverse or stop a headache progressing once it has started. Preventive treatment is designed to reduce attack frequency and severity. Acute treatment is appropriate for most attacks and should be restricted to 2–3 days a week.

Pharmacotherapy of acute migraine headaches

Acute treatment can be specific (ergots and triptans), or non-specific (analgesics and opioids) (table 1). Non-specific drugs control the pain of migraine or other pain disorders, whereas specific drugs are effective in migraine (and certain other) headache attacks but are not useful for non-headache pain disorders. Triptans are effective in the range of mild, moderate, and severe migraine attacks.[99]

The choice of treatment depends on the severity and frequency of the attack, associated symptoms, coexistent disorders, previous treatment response, and the drug's efficacy, potential for overuse, and adverse events. A non-oral route of administration and an antiemetic should be considered for severe nausea or vomiting.[11] Injections provide rapid relief. Headaches can be stratified by severity and disability (using MIDAS or HIT). Analgesics are used for mild to moderate headaches.[11] Triptans or dihydroergotamine are first-line drugs for severe attacks and for less severe attacks that do not adequately respond to analgesics.[11] Patients with moderate or severe headaches with moderate or severe disability (based on MIDAS) who were stratified to a triptan did better than did those given aspirin and metoclopramide.[100]

Early intervention prevents escalation and can increase the effectiveness of the treatment.[101] Triptans can prevent development of cutaneous allodynia, and cutaneous allodynia predicts triptans' effectiveness.[66] Before deciding that a drug is ineffective, at least two attacks should be treated. It might be necessary to change the dose, formulation or route of administration or add an adjuvant. When the response is inadequate, the headache recurs, or adverse events are bothersome, a change in the drug might be needed. Restricting acute treatment to 2–3 days a week can prevent drug-overuse headache. When headaches are very frequent, early intervention might not be appropriate.

All treatment fails occasionally, therefore rescue drugs (opioids, neuroleptics, and corticosteroids) are needed. They provide relief, but often restrict function because of sedation or other adverse events.

	Contraindications	Indication
Acute migraine		
Acetaminophen (paracetamol)	Liver disease	Pregnancy
Aspirin	Kidney disease, ulcer disease, peptic ulcer disease, gastritis (age <15 years)	Coronary artery disease, transient ischaemic attack
Non-steroidal anti-inflammatory drugs	Kidney disease, peptic ulcer disease, gastritis	Arthritis
Butalbital, caffeine, and analgesics	Use of other sedative, history of medication overuse	
Caffeine adjuvant	Sensitivity to caffeine	
Isometheptene	Uncontrolled hypertension, coronary artery disease, peripheral vascular disease	
Opioids	Drug or substance misuse	Pregnancy, rescue medication
Neuroleptics	Parkinson's disease, prolonged QTc	Nausea, vomiting, pregnancy, rescue
Dihydroergotamine		
Injections	Coronary artery disease, peripheral vascular disease, uncontrolled hypertension	Prominent nausea or vomiting
Intranasal	Coronary artery disease, peripheral vascular disease, uncontrolled hypertension	Prominent nausea or vomiting
Ergotamine		
Tablets	Prominent nausea or vomiting	
Suppositories	Coronary artery disease, peripheral vascular disease, uncontrolled hypertension	
Triptans*	Coronary artery disease, peripheral vascular disease, uncontrolled hypertension	
Preventive drugs		
β blockers	Asthma, depression, congestive heart failure, Raynaud's disease, diabetes	Hypertension, angina
Antiserotonin		
Pizotifen	Obesity	
Methysergide	Angina, peripheral vascular disease	Orthostatic hypotension
Calcium-channel blockers		
Verapamil	Constipation, hypotension	Migraine with aura, hypertension, angina, asthma
Flunarizine	Parkinson's disease	Hypertension, FHM
Antidepressants		
Tricyclic antidepressants	Mania, urinary retention, heart block	Other pain disorders, depression, anxiety disorders, insomnia
Serotonin specific reuptake inhibitor	Mania	Depression, obsessive-compulsive disorder
Monoamine oxidase inhibitors	Unreliable patient	Refractory depression
Anticonvulsants		
Divalproex/valproate	Liver disease, bleeding disorders	Mania, epilepsy, anxiety disorders
Gabapentin	Liver disease, bleeding disorders	Mania, epilepsy, anxiety disorders
Topiramate	Kidney stones	Mania, epilepsy, anxiety disorders
Non-steroidal anti-inflammatory drugs (Naproxen)	Ulcer disease, gastritis	Arthritis, other pain disorders

*Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, zolmitriptan (tablets or intranasal), sumatriptan (subcutaneous injection, intranasal, or tablets).

Table 1: **Drugs for acute migraine and for prevention: efficacy, adverse effects, relative contraindications, and indications**

	Headache response (2 h)†	Therapeutic gain (2 h)†	Pain–free frequency (2 h)†	Pain–free therapeutic gain (2 h)†	Recurrence rate
Almotriptan (12·5 mg)	61% (57–65)	25% (14–36)	36% (32–40)	21% (17–25)	26% (22–30)*
Eletriptan					
40 mg	60% (58–64)	35% (27–41)	27% (25–29)	22% (18–26)	21% (18–24)*
80 mg	66% (62–70)	42% (36–48)	33% (28–38)	28% (23–33)	20% (12–28)*
Frovatriptan (2·5 mg)	42% (40–44)	17% (27–44)	..	..	..
Naratriptan (2·5 mg)	49% (46–92)	22% (17–27)	22% (20–24)	14% (11–17)	21% (13–28)* 24% (21–27)†
Rizatriptan					
5 mg	62% (60–64)	28% (23–33)	30% (28–32)	22% (20–24)	39% (36–42)*
10 mg	69% (67–71)	35% (30–40)	40% (38–42)	30% (27–33)	37% (35–39)*
Zolmitriptan					
2·5 mg	64% (59–69)	34% (27–41)	25% (21–29)	19% (14–24)	30% (26–34)*
5 mg	66% (62–70)	37% (30–44)	34% (30–38)	28% (23–33)	34% (25–43)*
5 mg (intranasal)	69% (62–75)	38% (30–47)	36% (29–42)	29% (22–36)	27% (20–34)*
Sumatriptan					
50 mg	63% (60–64)	31% (24–38)	28% (26–30)	18% (12–24)	28% (29–31)*
100 mg	59% (57–61)	29% (25–33)	29% (27–31)	20% (18–22)	30% (27–33)*
20 mg (intranasal)	61% (55–78)	31% (28–43)	27–37%	11–28%	
6 mg (subcutaneous)‡	69% (70–88)	50% (38–77)	48–49%	46–43%	

All administered orally except where indicated. *2–24 h. †4–24 h. ‡All 2 h except for sumatriptan SC=1 h. Adapted from Ferrari and colleagues,[12] Tfelt-Hansen,[112] Physicians' Desk Reference,[113] and Dahlöf.[114]

Table 2: **Triptans**

Non-specific drugs

Analgesics and non-steroidal anti-inflammatory drugs—aspirin, ibuprofen, tolfenamic acid, naproxen sodium, acetaminophen, and acetaminophen, aspirin, and caffeine combination are effective in treatment of acute migraine.[11,102,103]

Barbiturate hypnotics—no randomised, placebo-controlled studies have established the efficacy of butalbital-containing agents.[104] They are used in the USA, but have been withdrawn from the market in many European countries. Because of the potential of drug-overuse headache and withdrawal, their use should be restricted and carefully monitored.

Opioids—opioids are effective.[2,11] However, because of the risk of drug overuse they should be used less than twice a week in patients who have severe, infrequent headaches.[105] They are used in the USA for patients who do not respond to simple analgesics (or cannot take ergots or triptan) and as a rescue drug. They are often used in pregnant women in the absence of controlled data.[106]

Neuroleptics and antiemetics—prochlorperazine is safe and effective for treatment of migraine and associated nausea and vomiting.[7,9,11,107,108] Droperidol, a parenteral neuroleptic, was effective in a recent placebo-controlled, double-blind trial, at a dose of 2·75 mg intramuscularly. Sedation, akathisia, and other extrapyramidal reactions can be treated with diphenhydramine or benzotropine.[109]

Specific drugs

Ergots and triptans are potent 5-$HT_{1B/1D}$ agonists and in some cases 5-HT_{1F} receptor agonists. Ergots have much greater receptor affinity at 5-HT_{1A}, 5-HT_2, adrenergic, and dopaminergic receptors than triptans, leading to more adverse events. All are indicated for treatment of acute migraine. If the initial (appropriate) dose is not effective, it is unlikely that subsequent doses will be effective within the same attack, and rescue drugs should be used. Contraindications include documented or suspected ischaemic heart disease, Prinzmetal's angina, uncontrolled hypertension, basilar or hemiplegic migraine, and pregnancy. Patients with sepsis, renal or hepatic failure, and cerebral or peripheral vascular disease should avoid ergots. There is little consensus as to how many risk factors preclude triptan use and what constitutes an appropriate assessment.[110]

Selective 5-HT_1 agonists (triptans)—the first triptan was sumatriptan, followed by zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan. All are more centrally penetrant than sumatriptan. Eletriptan's central penetrance is limited, since it is a substrate for the p-glycoprotein pump.[111] P-glycoprotein pump inhibitors allow higher central penetrance. Table 2 shows data for all formulations of triptans.[11,12] All are effective, even if given after the onset of migraine, and are sometimes more effective when pain is mild than when severe.[115] They relieve head pain and nausea and vomiting. Efficacy is measured by 2-h response rates and therapeutic gain (difference between active drug and placebo) (table 2). Therapeutic gain is used to compensate for differences in placebo rates in different trials. Other measures include 2-h pain-free and recurrence rates. Common adverse events include subcutaneous injection site pain, tingling, flushing, burning, warm or hot sensations, dizziness, paraesthesias, somnolence, fatigue, heaviness, neck pain, and dysphoria.[116,117] Here, I discuss mainly non-oral formulations.

Sumatriptan (6 mg subcutaneously, 20 mg nasal spray, 25 mg, 50 mg, or 100 mg tablets, and 25 mg suppository).[12,118] Subcutaneous sumatriptan has a rapid onset of action, reaching peak plasma concentrations within 12 min. Oral sumatriptan has a T-max of 2 h. Bioavailability is 97% subcutaneous, 19·2% for suppository, 15·8% for intranasal, and 14·3% for tablet.[116] The terminal elimination half-life is 2 h. Sumatriptan is metabolised mainly by the monoamine oxidase (MAO)-A; therefore, the oral, nasal, and suppository formulations are contraindicated in patients using monoamine oxidase inhibitors.

Subcutaneous sumatriptan (6 mg) has a 1-h response of 69% with a therapeutic gain of 50%.[112] The 1-h pain-free rate was 48–49%.[113] Intranasal sumatriptan (20 mg) had a 2-h response of 61% with a therapeutic gain of 31%.[112,114] Sumatriptan 25 mg suppository 2-h efficacy ranges from 64–72% (five studies). Pain-free rate ranged from 34–50%. In a comparative study, a combination (ergotamine 2 mg and caffeine 100 mg) suppository was more effective than sumatriptan (73% versus 63%) but had more adverse events.[117] The meta-analysis of oral triptans by Ferrari and colleagues uses 100 mg sumatriptan as the standard.[12]

Zolmitriptan (2·5 mg and 5 mg regular and orally-disintegrating tablets, and a 5 mg nasal spray) has a 40% oral bioavailability, a time to maximum concentration (T-max) of about 2·5 h, and is metabolised by the cytochrome P450 system to an active metabolite that is degraded by MAO-A. Patients taking monoamine oxidase are restricted to a total dose of 5 mg per day. Nasal spray is absorbed in the nasopharynx; is detectable in the blood within 5 min, and 40% of C-max is achieved within 10–15 min.[119,120] First-attack 2-h headache response rates for 5 mg nasal spray are 69%, with a therapeutic gain of 38%.[119–121]

Naratriptan (1 mg and 2·5 mg oral tablets)—the recommended dose is 2·5 mg. Bioavailability is 60–70%, T-max is 2 h (outside an attack), and the terminal elimination half-life is 5 h. Naratriptan is excreted largely as unchanged drug in the urine.[122]

Rizatriptan (5 mg and 10 mg oral tablet and rapidly dissolving wafer)—the recommended dose is 10 mg except for patients taking propranolol, which increases rizatriptan's plasma concentration, in which case the recommended dose is 5 mg, T-max is 1 h, bioavailability is 40–45%, and plasma half-life is 2–3 h. Rizatriptan is metabolised mainly by MAO-A, with metabolites being excreted in the urine. It should not be used by patients taking inhibitors of monoamine oxidase.

Almotriptan (6·25 mg and 12·5 mg oral tablet): The recommended dose is 12·5 mg with a maximum of two doses in 24-h. Bioavailability is 70%, T-max 1–3 h, and mean half-life 3–4 h. It is partly metabolised in the liver (monoamine oxidase 27%, P450 [3A4 and 2D6; 12%]) to inactive metabolites. Almotriptan does not interact with propranolol, selective serotonin reuptake inhibitors, or monoamine oxidase inhibitors.

Frovatriptan (2·5 mg tablet): Daily limit is three tablets. Frovatriptan has a bioavailability of 22% in men and 30% in women. T-max is 2–3 h. It is metabolised by P4540 (CYP-1A2) and excreted in urine.[123] The mean half-life is 26 h.

Eletriptan (40 mg and 80 mg oral tablets) has a 50% bioavailability, a half-life of 5 h, and is rapidly absorbed.[124] Eletriptan interacts with drugs that are metabolised by cytochrome P450 (including CYP-3A4). Adverse events are more common with eletriptan 80 mg than with other triptans.

Seven triptans are available. They are safe (for patients without cardiovascular risk factors), effective, and appropriate first-line treatment for patients who have a moderate to severe migraine headache or for whom analgesics have failed to provide adequate relief. Although safe, no evidence supports their effectiveness during the aura phase of a migraine attack.[125]

Headache severity, rapidity of onset, and duration are important factors when deciding which triptan should be used. When the headache intensifies rapidly (<30 min), or nausea and emesis are early and there are severe associated symptoms, non-oral administration is appropriate. Subcutaneous sumatriptan is the fastest and most effective. Sumatriptan or zolmitriptan nasal spray sometimes provide a faster onset of action than oral triptans, but sumatriptan nasal spray is often associated with a disagreeable taste.

The oral formulations can be divided into two classes. Almotriptan, eletriptan, rizatriptan, sumatriptan, and zolmitriptan have the highest 2-h effectiveness, can provide headache relief within 30–60 min, and would be the first choice when patients require effectiveness and speed of onset and do not have multiple recurrences. The meta-analysis suggests that almotriptan, eletriptan, and rizatriptan are most effective.

All triptans have the same contraindications and safety concerns. None is safer than another; however, the response to triptans is often idiosyncratic. One triptan might work for one patient and cause no adverse events, and a different triptan might work for another patient. The triptan of choice is the one that restores the patient's ability to function by swiftly and consistently relieving pain and associated symptoms with minimum adverse events and without recurrence of symptoms.

Ergotamine and dihydroergotamine—The evidence supporting ergotamine's efficacy is inconsistent.[126] Some patients respond preferentially to rectal ergotamine than to that administered by any other method.[127] Dihydroergotamine can be administered intramuscularly, subcutaneously, or intravenously. It usually has a low headache recurrence rate (<20%), fewer adverse events, and is less likely than ergotamine to produce rebound headache.[126] Limited evidence exists for the effectiveness of dihydroergotamine nasal spray. No placebo-controlled trials have shown the efficacy and safety of dihydroergotamine subcutaneously, intramuscularly, or intravenously as monotherapy. Repetitive intravenous dihydroergotamine is commonly used in North America in intractable headache treatment.[126,128]

Corticosteroids—Open-label studies have suggested that corticosteroids are effective. Hydrocortisone, methyl prednisolone, and dexamethasone have been used.[2]

Preventive treatment

Preventive drugs reduce attack frequency, duration, or severity.[2,129] According to the US Headache Consortium Guidelines,[10] indications for preventive treatment include: Migraine that substantially interferes with the patient's daily routine despite acute treatment; failure of, contraindication to, or troublesome adverse events from acute drugs; acute drug overuse; very frequent headaches (more than two per week) (risk of drug overuse); patient preference; special circumstances, such as hemiplegic migraine or attacks with a risk of permanent neurologic injury.

Preventive drug groups include β-adrenergic blockers, antidepressants, calcium-channel antagonists, serotonin antagonists, anticonvulsants, and non-steroidal anti-inflammatory drugs. Choice is based on effectiveness, adverse events, and coexistent and comorbid conditions (table 1). Every drug should be started at a low dose and increased slowly until therapeutic effects develop or the maximum dose is reached. A full therapeutic trial can take 2–6 months. Acute headache drugs should not be overused. If headaches are well controlled, treatment can be tapered and discontinued. Dose reduction usually provides a better risk-to-benefit ratio. Women of childbearing potential should be on adequate contraception.

Behavioural and psychological interventions used for prevention include relaxation training, thermal biofeedback combined with relaxation training, electromyography biofeedback, and cognitive-behavioural treatment.[130]

β *blockers*

Propranolol, nadolol, atenolol, metoprolol, and timolol are effective.[8] Their relative effectiveness has not been established; choice is based on β selectivity, convenience, adverse events, and patients' reactions.[2] β blockers can produce behavioural adverse events, such as drowsiness, fatigue, lethargy, sleep disorders, nightmares, depression, memory disturbance, and hallucinations; they should be avoided when patients are depressed. Decreased exercise tolerance restricts their use by athletes. Less common

adverse events include impotence, orthostatic hypotension, and bradycardia. β blockers are useful for patients with angina or hypertension. They are contraindicated for patients with congestive heart failure, asthma, Raynaud's disease, and insulin-dependent diabetes.

Antidepressants

Amitriptyline (a tricyclic antidepressant) is the only antidepressant with limited support for effectiveness.[8] Adverse events include increased appetite, weight gain, dry mouth, and sedation; cardiac toxic effects and orthostatic hypotension occasionally occur.[131] There is one positive trial for fluoxetine. Sexual dysfunction is a common adverse event.[132] Antidepressants are especially useful for patients with comorbid depression and anxiety disorders.

Calcium-channel blockers

The Agency for Healthcare Policy and Research analysed 45 controlled trials.[8] Flunarizine was effective, nimodipine had mixed results, and nifedipine was difficult to interpret. Verapamil was more effective than placebo in two of three trials, but both positive trials had high dropout rates, rendering the findings uncertain.[2] Its most common adverse event is constipation. Flunarizine is the most effective drug of this class, but it is not available everywhere. Adverse events include parkinsonism, depression, and weight gain.

Anticonvulsant drugs

Divalproex sodium (500–1000 mg) and sodium valproate are effective, as is the extended release formulation.[8] The most frequent adverse events were nausea (42%), alopecia (31%), tremour (28%), asthenia (25%), dyspepsia (25%), somnolence (25%), and weight gain (19%).[133] Toxic effects in the liver and pancreas are the most serious adverse events, but irreversible hepatic dysfunction is extremely rare in adults. Baseline liver function studies should be obtained, but follow-up studies are probably not needed in adults on monotherapy.[134] Divalproex carries a high risk of congenital abnormality.

Gabapentin (1800–2400 mg) was effective in a placebo-controlled, double-blind trial,[135] only when a modified intent-to-treat analysis was used. Migraine attack frequency was reduced by 50% in about a third of patients. The most common adverse events were dizziness or giddiness and drowsiness.

Topiramate, a D-fructose derivative, has been associated with weight loss, not weight gain. In two large, double-blind, placebo-controlled, multicentre trials,[136,137] topiramate, both 100 mg and 200 mg, was effective in reducing migraine attack frequency by 50% in half the patients. Dropouts because of adverse events were common in the topiramate groups, but did not affect significance.

Divalproex and topiramate are useful in patients with epilepsy, anxiety disorder, or manic-depressive illness. They can be used in patients with depression, Raynaud's disease, asthma, and diabetes, circumventing the contraindications to β blockers.

Serotonin antagonists

Methysergide is effective.[8,138] Adverse events include transient muscle aching, claudication, abdominal distress, nausea, weight gain, and hallucinations. The major complication is rare (1/2500) retroperitoneal, pulmonary, or endocardial fibrosis.[138] To prevent this complication, a 4-week drug-free interval is recommended after 6 months of continuous treatment.[2,138]

Pizotifen, a benzocycloheptathiophene derivative, is also effective.[10] Adverse events include drowsiness, increased appetite, and weight gain. It is not available in the USA.

Natural products

Feverfew (Tanacetum parthenium) is a medicinal herb, the effectiveness of which has not been established.[139] Riboflavin (400 mg) was effective in one placebo-controlled, double-blind trial.[140] More than half the patients responded. *Petasites hybridus* root (butterbur) is a perennial shrub.[16] A standardised extract (75 mg twice daily) was effective in a double-blind, placebo-controlled study.[141] The most common adverse event was belching. Coenzyme Q10 was effective in one double-blind, placebo-controlled trial.[142]

Newer treatments

Botulinum toxin type A (0, 25 U, or 75 U) showed promising results in one placebo-controlled, double-blind trial.[143] It was injected into glabellar, frontalis, and temporalis muscles. The 25 U treatment group was significantly better than the placebo group in reducing mean frequency of moderate to severe migraines during days 31–60, incidence of 50% reduction in all migraine at days 61–90, and reduction in all migraine at days 61–90.[143]

Setting treatment priorities

The preventive drugs with the best documented effectiveness are the β blockers, divalproex, and topiramate. Choice is made on the basis of a drug's proven effectiveness, the doctor's informed belief about drugs not yet assessed in controlled trials, the drug's adverse events, the patient's preferences and headache profile, and the presence or absence of coexisting disorders.[2] Coexistent diseases have important implications for treatment. In some instances, two or more conditions can be treated with a single drug. If individuals have more than one disease, certain categories of treatment might be contraindicated.

Conflict of interest statement

S Silberstein is on the advisory panel, speakers' bureau, or serves as a consultant for Abbott, Allergan, AstraZeneca, Elan, Eli Lilly, OrthoMcNeil, Merck, and GlaxoSmithKline. He receives research support from Allergan, AstraZeneca, Eli Lilly, GlaxoSmithKline, Janssen, Merck, OrthoMcNeil, Pfizer, UCB Pharma, and Vernalis. He has received educational grants from Abbott, Allergan, AstraZeneca, BristolMyers Squibb, Eli Lilly, GlaxoSmithKline, Merck, OrthoMcNeil, and ParkeDavis.

Acknowledgments

I thank William B Young and David Dodick for reviewing the manuscript and offering helpful suggestions, and Linda Algarin Kelly and Lynne Kaiser for their wordprocessing and editing efforts.

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