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Recent developments in migraine

Two large American migraine studies found that the prevalence of migraine in the USA was 18% in women and 6% in men.[1] The recent American Migraine Prevalence and Prevention Study found similar results, which indicate that the prevalence of migraine in the USA has been stable over 15 years.[1] There have been new developments in migraine research and treatment since I last reviewed this topic.[2]

Migraine is associated with cardiovascular disease. Two recent re-analyses,[3,4] from the Women's Health and Physicians' Health Studies, found that migraine with aura was a risk factor for myocardial infarction (odds ratio 2·08, 95% CI 1·3 to 3·3), coronary revascularisation (1·74, 1·2 to 2·5), angina (1·71, 1·2 to 2·5), and death from ischaemic cardiovascular disease (2·33, 1·2 to 4·5).[3] Migraineurs, particularly those with aura, had an increased likelihood of an unfavourable cholesterol profile, high blood pressure (for the non-diagnosed migraineurs with aura), and a parental history of early myocardial infarction.[5]

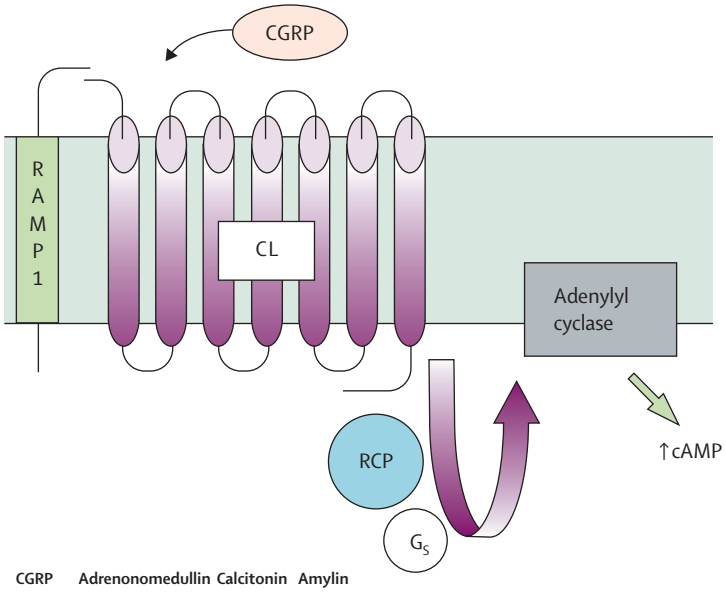
Patent foramen ovale is more common than expected in migraineurs with aura. The MIST placebo-controlled (sham procedure) randomised trial of closure of patent foramen ovale found a high prevalence (38%) of moderate-to-large patent foramen ovale in migraineurs with aura who had frequent but not daily headaches and were refractory to preventive drugs. Unlike open-label reports, this trial found that closure of patent foramen ovale had no significant effect on migraine.[6]

Familial hemiplegic migraine (FHM) is an autosomal dominant disorder associated with attacks of migraine with hemiparesis. FHM1 is due to a missense mutation in the *CACNA1A* gene, which codes for the α_1 subunit of a voltage-dependent P/Q Ca^{2+} channel. FHM2 arises from a mutation in the α_2 subunit of the Na/K pump.[1] The new type, FHM3, is caused by a missense mutation in *SCN1A* (Gln1489Lys), which encodes an α_1 subunit of a neuronal voltage-gated Na^+ channel ($Na_v1.1$). Functional analysis of the FHM3 mutation revealed markedly slowed inactivation and a two-fold faster recovery from fast inactivation compared with controls, which predicts enhanced neuronal excitation. Enhanced neuronal excitation results in excessive firing of neurons and could facilitate cortical spreading depression.[7]

The migraine aura is probably due to cortical spreading depression.[1] Headache probably results from activation of meningeal and blood vessel nociceptors combined with a change in central pain modulation.[1] How does a headache begin in the absence of aura? Cortical spreading depression may occur in silent areas of the cortex or the cerebellum. Stress can also activate meningeal plasma cells via a parasympathetic mechanism, leading to nociceptor activation. How does this relate to therapy? Ayata and colleagues[8] recently showed that, if given chronically rather than acutely, drugs to prevent migraine block cortical spreading depression.

Migraine headache was believed to be associated with cerebral or meningeal vasodilation. Nitroglycerine can induce migraine attacks. In a magnetic-resonance angiography study, migraineurs randomly received nitroglycerin or placebo. Schoonman and co-workers[9] measured blood flow in the basilar and internal carotid arteries, and diameters of the middle meningeal, external carotid, internal carotid, middle cerebral, basilar, and posterior cerebral arteries. With nitroglycerin infusion, but not with placebo, there was a transient 6·7–30·3% vasodilation ($p<0·01$) of all blood vessels, with no change in blood flow. During migraine, there was no vasodilation or change in blood flow.

Does coordinated headache treatment make a difference? Matchar and colleagues[10] assessed whether



CGRP	Adrenonomedullin		Calcitonin	Amylin		
CGRP1	AM1	AM2	CT	AMY1	AMY3	AMY2
CL	CL	CL	CT	CT	CT	CT
RAMP1	RAMP2	RAMP3	None	RAMP1	RAMP2	RAMP3

Figure: **Calcitonin gene-related peptide (CGRP) and related receptor family during migraine attacks**
CL=calcitonin-receptor-like receptor. CT=calcitonin receptor. RAMP=receptor-activity-modifying protein. RCP=receptor-component protein. G_s=G-stimulating protein. Table shows CGRP and related receptor family.

coordinated headache treatment would reduce headache disability. The patients in their randomised study were at least 21 years old, had chronic tension-type migraine, or mixed-aetiology headache and a Migraine Disability Assessment (MIDAS) score greater than 5, and were not receiving treatment from a neurologist or headache clinic currently or within the previous 6 months. Active intervention consisted of: a headache class informing patients about headache types, triggers, and treatment options; diagnosis and treatment by a headache professional; and proactive follow-up by a case manager. Control patients received usual care. The intervention improved MIDAS scores by 7·0 points (95% CI 2·9 to 11·1) more than the control did at 6 months. Quality of life and satisfaction with headache treatment were similarly improved. Coordinated headache management significantly improved outcomes for patients who had substantial unmet needs.

Migraine pharmacotherapy can be acute or preventive, and patients might require both approaches. Early intervention prevents escalation and might increase efficacy. Our work[11] investigated the efficacy and tolerability of a fixed-dose single-tablet formulation of sumatriptan 85 mg, formulated with fast-release technology, and naproxen sodium 500 mg as an early intervention in acute migraine. Patients treated a migraine within 1 h of head-pain onset, while the pain was mild, with sumatriptan plus naproxen or placebo. Intention-to-treat analyses in two trials included 576 and 535 migraineurs. At 2 h, 52% and 51%, respectively, of patients on the combination were pain-free, compared with 17% and 15% of placebo-treated patients (p<0·001).

Preventive treatment is often recommended for only 6–9 months, but what happens after the end of prophylaxis? Diener and co-workers[12] assessed the effects of discontinuing topiramate. After an open-label treatment period of 6 months, patients were randomly assigned to continue on topiramate or switch to placebo, for a 26-week double-blind phase. The mean increase in number of migraine days was greater in the placebo group (1·19 days in 4 weeks, 95% CI 0·71 to 1·66, p<0·0001) than in the topiramate group (0·10, –0·36 to 0·56, p=0·5756). Topiramate had a sustained benefit after it was discontinued, although the number of migraine days increased. Not all antiepileptic drugs are effective for migraine prevention. In a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial,[13] we have found that oxcarbazepine (1200 mg per day), while well tolerated, was not effective in preventing migraine.

What might feature in the treatment of migraine in the future? Calcitonin gene-related peptide (CGRP), a 37-aminoacid neuropeptide, is released during migraine attacks. An intravenous CGRP antagonist, olcegepant, was effective in acute migraine headache (figure). Olesen and colleagues (quoted in Doods[14]) found that the 2-h headache response rate was 66% compared with 27% for placebo. Ho and co-workers[15] studied the oral CGRP receptor antagonist telcagepant for acute migraine treatment in a randomised, double-blind, parallel-group trial with a two-stage, adaptive, dose-ranging design. Patients treated a moderate or severe migraine attack with oral telcagepant 25–600 mg, rizatriptan 10 mg, or placebo. The four lowest doses of telcagepant (25–200 mg) were discontinued because of insufficient efficacy. The 300 mg dose was the most promising: the proportion of patients experiencing pain relief at 2 h was 68·1% (placebo 46·3%, rizatriptan 69·5%); the proportion pain-free at 2 h was 45·2% (placebo 14·3%, rizatriptan 33·4%); and the proportion

with sustained freedom from pain at 24 h was 39·6% (placebo 11·0%, rizatriptan 18·4%). Telcagepant was effective and generally well tolerated for acute migraine treatment. Phase III trials are positive with results similar to those with zolmitriptan (5 mg) and an adverse-event profile similar to placebo and lower than that with zolmitriptan.[16]

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Advances in conspiracy theory

The past half-century has seen a steady erosion of trust in authority of all sorts, ranging from a healthy scepticism to conspiracy theories, which say that governments and their agencies or associates are capable of anything, even murder. To put it in a more scholarly fashion,[1] conspiracy theories are "attempts to explain the ultimate cause of an event…as a secret plot by a covert alliance of powerful individuals or organizations". The phrase conspiracy theories is often seen as pejorative and belief in them as irrational, but researchers from the University of Kent, Canterbury, UK, are asking for more research into "why people overtly reject conspiracy theories but privately accept them as true". For that is what we do, apparently.

Karen Douglas and Robbie Sutton inquired of two groups of 48 undergraduate students what they and their peers in the other group thought of conspiracy theories (though the phrase itself was avoided) about the death of Diana, Princess of Wales.[1] The experimental group was given a briefing about the evidence for non-accidental death. The findings, from quite a complex analysis, suggest, with other research, that conspiracy theories can influence people without their being aware of it. "Whereas participants perceived themselves to be relatively invulnerable to persuasion when they clearly were not, they suggested that other members of their class were more influenced." Some support for this surprising conclusion can be found via a questionnaire on the BBC's *Conspiracy Files* website.[2] To protest complete incredulity on five specific alleged conspiracies (Kennedy's assassination, Diana's death, collapse of the World Trade Center twin towers, the US moon landings, and aliens) while responding neutrally to the ten non-specific questions is not enough, for you will still find yourself labelled as retaining a "medium level of belief" in conspiracy theories. A gross misdiagnosis? Perhaps, but complete immunity to conspiracy chatter does seem to be difficult to prove, to psychologists anyway. Try it.[2]