

Bandolier **Extra**

Evidence-based health care

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MIGRAINE SPECIAL ISSUE

Introduction

This special issue of *Bandolier* concentrating solely on migraine is a new development. It is intended to reflect the contents of *Bandolier's* migraine Internet resource, where large amounts of information about migraine have been gathered and abstracted, and which also contains a number of new systematic reviews. Neither the Internet resource nor this special issue can cover all the nuances, but can touch on the main sources of evidence and describe how the evidence was obtained.

Special Internet resource centres include:

Resource centres updated regularly	Resource centres expanding
Arthritis & bones	Allergy & asthma
Atrial fibrillation	Cancer
Cardiac	Dental
Complementary	Drug abuse
Diagnostics	EBM
Healthy living	ENT
Management	Family health
Men's health	Gastrointestinal
Migraine	Genetics
Older people	Mental health
Pain	Neurological
Palliative care	NNTs
Sexual health	Operations
Stroke	Trial Methods etc
Vaccines	Urinary
Web essays	Women's Health

Although many readers of the paper version of *Bandolier* also access the Internet site, many do not. This special issue is by way of a "taster" for those not using the Internet site. On the Internet site can be found every issue of *Bandolier* and *ImpAct* in both html and printable PDF forms. That means that they can be read on-screen, and downloaded onto your computer to be read or printed.

In addition *Bandolier* has been assiduously gathering good evidence from systematic reviews and other quality sources in a number of other areas.

Migraine

Migraine is characterised by episodic severe headaches, commonly but not always unilateral, typically described as throbbing or pulsating, sometimes as a tight band or pressure. Migraine is often associated with photophobia or phonophobia, and with nausea and vomiting at the height of an attack. There is sometimes a visual aura of flashing lights, zig-zag castellations, balls or filaments of light. Many people with severe migraine find lying down in a dark room all they can do, as headaches often last up to 24 hours.

There are no simple causes of migraine, but a meta-analysis [1] tells us which clinical features are important, and which irrelevant, in diagnosing migraine. Headache features in migraine compared with tension-type headache are shown in Table 1, with nausea and photo- and phonophobia being more discriminating features.

The review also examined a whole range of possible precipitating factors often quoted as key migraine precipitants. These included stress, alcohol, weather change, menstruation, missed meals and sleep, or perfume or odour, and compared the frequency they were present for migraine compared with tension headache. There was no difference for

Sponsorship

The *Bandolier* migraine resource was sponsored by the Gwen Bush Foundation, and by MSD. For the avoidance of doubt, neither sponsoring organisation had or has any form of control over content, and sponsorship is accepted only when this condition is accepted.

Bandolier believes migraine to be an important topic, not least because of the impact it has on young women, and because only a minority of sufferers seek treatment.

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Table 1: Symptoms associated with migraine

	Likelihood ratios			
	Positive		Negative	
	LR+	95% CI	LR-	95% CI
Nausea	19.2	15-25	0.2	0.19-0.21
Photophobia	5.8	5.1-6.6	0.25	0.24-0.26
Phonophobia	5.2	1.5-5.9	0.38	0.36-0.40
Activity makes it worse	3.7	3.4-4.0	0.24	0.23-0.26
Unilateral	3.7	3.4-3.9	0.43	0.41-0.44
Throbbing/pulsing	2.9	2.7-3.1	0.36	0.34-0.37

Table 2: Precipitants and history associated with migraine

	Likelihood ratios			
	Positive		Negative	
	LR+	95% CI	LR-	95% CI
Chocolate	7.1	4.5-11.2	0.82	0.73-0.93
Cheese	4.9	1.9-12.5	0.68	0.62-0.73
Any food	3.6	2.8-4.6	0.59	0.56-0.62
Family history of migraine	5	4.4-5.6	0.47	0.46-0.49
Childhood vomiting attacks	2.4	1.9-2.9	0.79	0.75-0.82
Motion sickness	2.2	1.9-2.5	0.79	0.75-0.82

these factors, but there was a difference for chocolate, cheese, and any food (Table 2). Family history of migraine, childhood vomiting attacks and motion sickness were also more common in migraineurs (Table 2).

Diagnostic criteria

In 1988 the International Headache Society published criteria for the diagnosis of a number of different headache types [2]. Those for migraine are reproduced below.

Migraine without aura

A. At least five headache attacks lasting 4 - 72 hours (untreated or unsuccessfully treated), which have at least two of the four following characteristics:

- 1 Unilateral location
- 2 Pulsating quality
- 3 Moderate or severe intensity (inhibits or prohibits daily activities)
- 4 Aggravated by walking stairs or similar routine physical activity

B. During headache at least one of the two following symptoms occur:

- 1 Phonophobia and photophobia
- 2 Nausea and/or vomiting

Migraine with aura

A. At least two attacks lasting 4 - 72 hours fulfilling at least three of the following:

- 1 One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem functions
- 2 At least one aura symptom develops gradually over more than four minutes, or two or more symptoms occur in succession

- 3 No aura symptom lasts more than 60 minutes; if more than one aura symptom is present, accepted duration is proportionally increased
- 4 Headache follows aura with free interval of at least 60 minutes (it may also simultaneously begin with the aura)

B. At least one of the following aura features establishes a diagnosis of migraine with typical aura:

- 1 Homonymous visual disturbance
- 2 Unilateral paresthesias and/or numbness
- 3 Unilateral weakness
- 4 Aphasia or unclassifiable speech difficulty

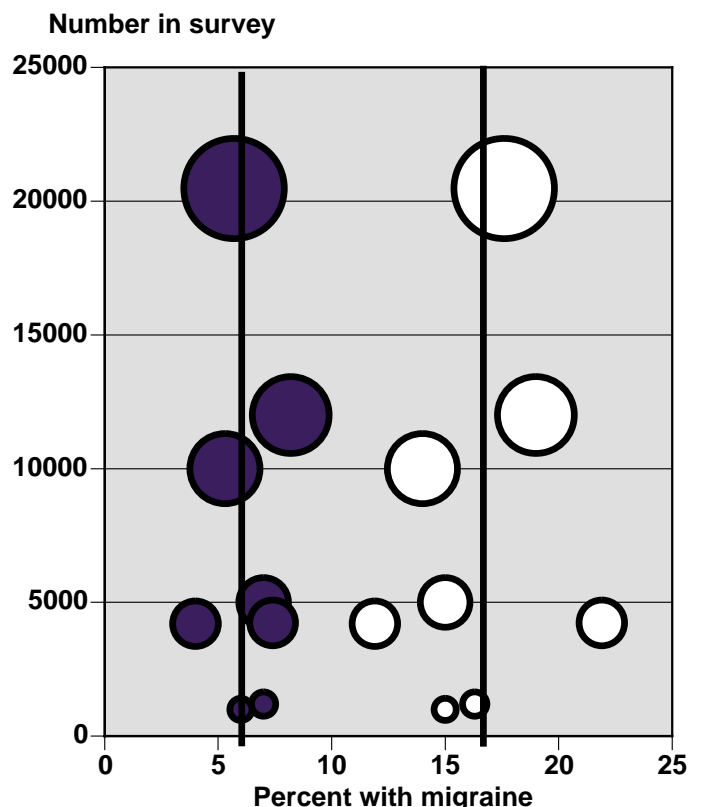
Prevalence

The earliest migraine attacks occur in children younger than 10 years (in a third of patients), but a diagnosis may be missed without a clear description of headache and visual and sensory experiences. Most migraineurs have their first attack before they are 30 years old, and first attacks at over 40 years are rare, and probably mean that some other pathology is involved.

Eight surveys have investigated the prevalence of migraine in adult populations in Europe or North America since 1989. All used International Headache Society criteria for diagnosing migraine, with telephone surveys and/or questionnaires or interviews. Sample sizes were between 1,000 and 20,500.

The results of the surveys are shown in Figure 1. The range of results for women was between 11.9% and 21.9%, and for men between 4.0% and 8.2%. The weighted mean prevalence for women was 17% and for men was 6%.

Figure 1: Prevalence of migraine in men (solid) and women (open)



Associated conditions

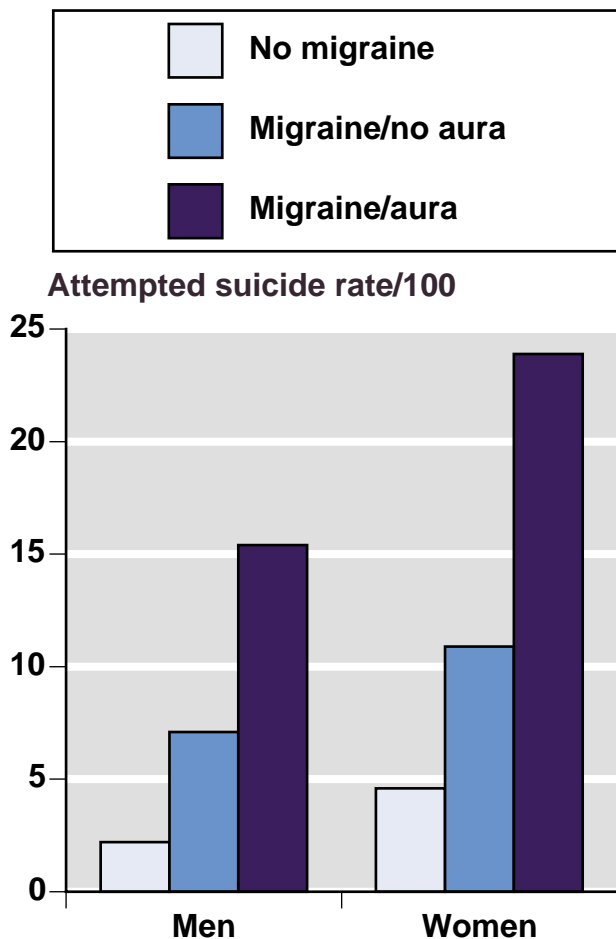
There is limited evidence of an important association between migraine and psychiatric disorder and suicide in young adults [3]. It is worth noting, though, that the study has yet to be replicated.

It examined 1,007 young adults aged 21 to 30 years old in Michigan. They participated in a structured interview using the International Headache Society definitions of migraine and the National Institute of Mental Health diagnostic interview schedule to gather information on psychiatric disorders.

The results showed a lifetime prevalence of migraine of 7% in men and 16% in women, agreeing with other studies. But there were higher lifetime rates of psychiatric disorders in persons with migraine. For instance, major depression occurred in 9% of people without migraine, but in 22% of people with migraine without aura and in 32% of people with migraine with aura. Panic occurred 10 times more frequently, at 17%, than in people without migraine. Anxiety occurred in 21% of people without migraine and 54% of people with migraine.

Perhaps the most startling result, though, was that suicide attempts were very much commoner in migraine sufferers, especially in those with aura (Figure 2).

Figure 2: Attempted suicide rate without migraine, and migraine without and with aura



Impact of migraine on individual and society

The *Bandolier* Migraine Resource has a compendium of health economics papers on migraine. They differ and are not always easy to compare, but each one confirms that migraine is a disorder of major economic consequence to individuals and society. Some examples demonstrate the scale of the problem.

Migraine is associated with a substantial amount of time lost from work. A major survey based on clinical trials underlines this [4]. In screening 2670 patients for phase III clinical trials, the average estimates for lost work were 8.3 days lost due to absence because of migraine, and 11.2 days lost because of reduced efficiency. The estimated cost to employers was US\$3,309 (year 2000 prices).

Study

A questionnaire (Migraine background Questionnaire) was developed to estimate the economic burden of illness associated with migraine. It was tested for clarity in migraine patients in 25 countries, and captured the following information:

- ◆ migraine frequency in past 12 months
- ◆ days worked with migraine symptoms in past four weeks
- ◆ percentage effectiveness when at work with migraine in past four weeks
- ◆ hours at work negatively affected by migraine in past four weeks
- ◆ days of paid and unpaid work missed because of migraine in past four weeks
- ◆ emergency treatments for migraine in past 12 months
- ◆ medical office or clinic visits for migraine in past 12 months
- ◆ hospitalisation for migraine in past 12 months

The questionnaire was self-administered in patients at screening visits at 23 US and 73 non-US sites for phase III clinical trials of rizatriptan. These were people aged 18 to 65 years with 1-8 moderate to severe migraines per month in the past six months.

Results

There were 2670 completed questionnaires from 2674 patients, 55% in Europe, 17% in Latin America, and 23% in North America. Thirty-nine patients reported no migraine in the previous four weeks, giving 2631 evaluable questionnaires. The mean age of patients was 39 years, 82% were women, with 3.7 episodes of migraine in the previous four weeks. Full or part-time employment was reported by 68%, self-employment by 7%, 15% were students or home-makers and others were looking for work, were retired, or were unable to work for health reasons. The type of employment was managerial or professional in 23%, in a service industry in 14%, secretarial or clerical in 16% and other in 47%.

Use of medical services

Healthcare use was recorded as annual use. The overall average was 2.8 doctor or clinic visits, 0.5 emergency room visits and 0.06 hospital admissions. This means that for every 10,000 patients with migraine there would be 28,000 visits to the doctor, 5000 visits to the emergency room, and 6 patients admitted to hospital. These rates were similar across all geographical regions, though emergency room visits were lower in Europe and higher in the Americas.

Work and productivity loss

On average, every four weeks each migraine sufferer was absent from paid work on 0.64 days, and worked with migraine for 3.6 days. There were 12.7 hours worked with migraine, during which they were only about half (46%) as effective as usual, so that every four weeks an average of 6.9 hours of work were lost due to ineffectiveness. These rates were similar across all geographic regions.

The annual loss of paid work was equivalent to 19.5 days per migraine sufferer. This was similar across the world. In the USA, the economic impact of lost work hours would be equivalent to US\$3,309 per migraine sufferer per year.

The amount of unpaid work and productivity loss was greater than that for paid work. On average there were 1.4 lost workdays, and they worked with migraine for 3 days a month. There were 10.6 lost work hours per month through lower effectiveness while at work.

Comment

The paper gives detailed information for each of the countries, from the 14 respondents in Iceland to the 469 in the USA and 402 in the UK. There are some interesting country-by-country variations, but much of that is likely to be due to the small numbers in some countries. Monthly work hours lost through lost workdays were highest in Norway (2.3) and Canada (2.1) and lowest in Mexico and Colombia (0.7). Monthly work hours lost through ineffectiveness while at work with a migraine were highest in Belgium (36) and Canada (15) and lowest in South Africa (5) and Israel (7).

Are the findings credible? Well, another estimate of migraine-associated productivity loss in the USA [5] put the figure at about US\$14 billion. This paper estimates US\$3,300 per worker. So for this to be credible there would need to be 4 million US workers aged 16-65 years with 1-8 migraines a month. With a US population of about 260 million, of whom, say, half were economically active, to suggest that 3% fell in the clinical category of migraine described here is reasonable. A Dutch summary of a number of economic analyses on migraine confirms that the US experience is shared with other developed economies [6].

What do migraineurs want?

An interesting question this for any disease, and one that is so often missed or ignored. A large study [7] that asks useful questions of patients, and obtains interesting answers, cannot be ignored.

Study

Representative American households were identified by random digit survey in 1998. About 5100 were contacted by telephone using a computer assisted interview to identify people with migraine according to International Headache Society criteria.

Results

There were 688 individuals identified as having migraine in the past year, a prevalence of 18% in women and 6% in men. Their mean age was 43 years. About a third had never consulted a doctor. Half did not think their headaches that bad, and the other half had a treatment that worked for them. Underlying this was that significant minorities (40%) did not think that doctors had any useful remedies or seeing the doctor was too inconvenient, and about a third thought seeing a doctor too expensive (this being the USA).

About a fifth had seen doctors previously, but had not done so in the past year. This was predominantly because treatments were working or the headaches had improved. But about half also thought that their doctor could do nothing for their migraine, could not help them, or was not interested in headache.

Patient satisfaction with their current treatment was predominantly positive (Figure 3). Of the 70% who were not in the group who were "very satisfied", the reasons for dissatisfaction (Figure 4) were generally to do with lack of efficacy of treatments rather than about adverse effects. When questioned, most people thought that satisfactory pain relief should be within one hour, and more than half thought it should be within 30 minutes.

Figure 3: Patient satisfaction with treatment

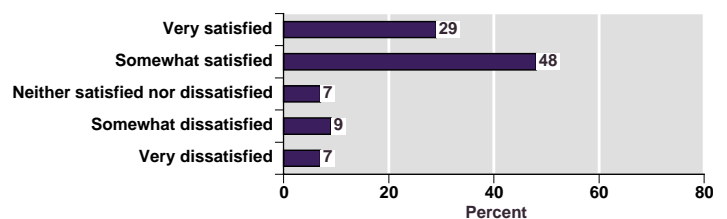


Figure 4: Patient complaints about migraine

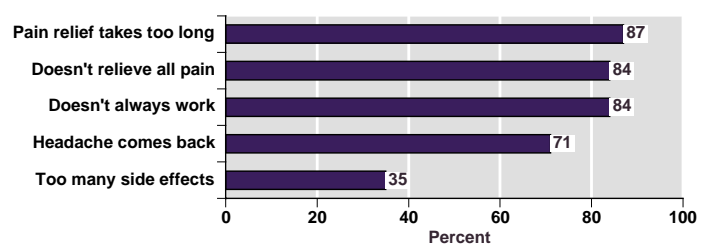


Figure 5: What patients want from treatment

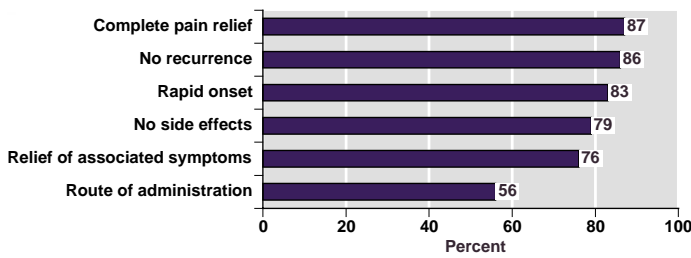
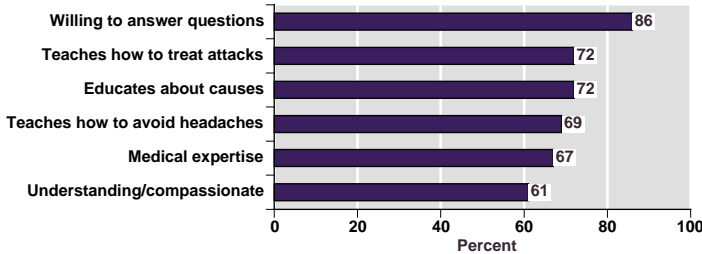


Figure 6: What patients want from professionals



What patients want from treatment

Bit of a no-brainer, this. Patients want the headache to go away now, completely, and not come back (Figure 5). They also want any associated symptoms, like nausea, to be relieved. The bulk of them want a tablet or rapidly dissolving tablet, and are not impressed by subcutaneous or intranasal delivery systems.

What patients want from their doctor

The responses to questions about what patients wanted from their doctors produced a constellation of answers, all of which demonstrate clearly that patients see their relationship with their doctor as a partnership (Figure 6). They want questions answered, and to be educated about controlling their migraines to prevent them happening and how to treat attacks.

Outcomes of migraine trials

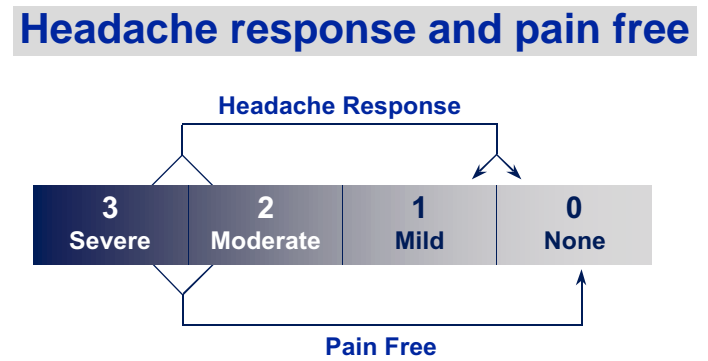
People with migraines have a whole range of symptoms. Pain is perhaps the most obvious, but many are nauseated and may have other associated symptoms like photophobia or phonophobia. This page describes some of the outcomes measured in clinical trials, and that might be expected to be reported in trials and collected in systematic reviews.

Pain

Pain is usually measured using a simple scale, in which sufferers describe it as no pain, mild pain, moderate pain, or severe pain. Pain has to be moderate or severe before a treatment is taken in clinical trials, and the reason is that if there is no pain, or the pain is only mild, the effectiveness of treatments in taking away the pain cannot be measured.

These scales have proved highly robust in clinical trials in acute and chronic pain over decades. Pain is measured before a treatment is taken, and then at 0.5, 1, 1.5, 2 hours, and possibly longer, though after two hours the relevance declines because headaches get better by themselves.

Figure 7: Short-term outcomes



• Pain free at 2 hours is now the preferred IHS primary endpoint for clinical trials

The two outcomes most often reported and used are:

Headache response

This is when pain which is initially moderate or severe becomes mild, or where there is no pain. This can be measured at any time, but usually the two-hour response is taken (Figure 7).

Pain free

This is when pain which is initially moderate or severe becomes no pain. This can be measured at any time, but usually the two-hour response is taken (Figure 7).

Sustained response

Patients who have a headache response at two hours have headache that becomes no worse, and take no other headache medicine over the period of 2-24 hours (Figure 8).

Sustained pain free

Patients who are pain free at two hours have no recurrence of headache, and take no other headache medicine over the period of 2-24 hours (Figure 8).

Figure 8: Long-term outcomes

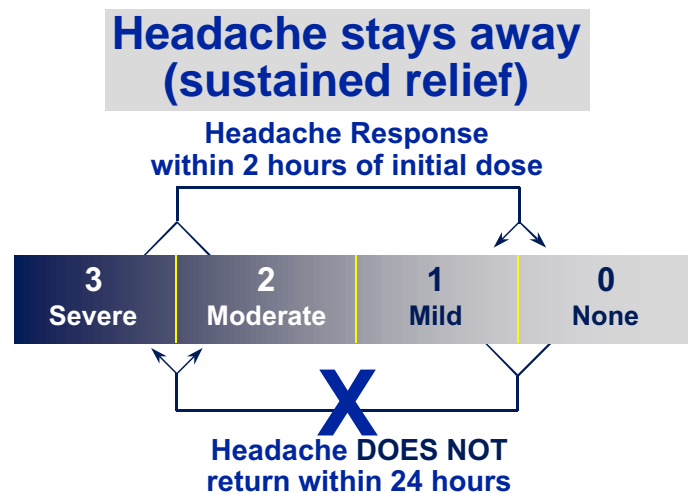


Table 3: Complementary and alternative therapies for migraine (in full on *Bandolier* Internet site)

Intervention	Outcome
Acupuncture for recurrent headache	There is no evidence from high quality trials that acupuncture is effective for the treatment of migraine and other forms of headache. The trials showing a significant benefit of acupuncture were of dubious methodological quality.
Chiropractic for migraine	There is limited evidence that spinal manipulative therapy may reduce the frequency and intensity of migraine attacks, but the evidence that spinal manipulation is better than amitriptyline, or adds to the effects of amitriptyline, is insubstantial.
Feverfew for migraine prophylaxis	Overall, these studies suggest that feverfew may be beneficial for the prevention of migraine attacks. However, the effectiveness has not been established beyond reasonable doubt. More data are needed to determine which dose and formulation should be prescribed, and how effective it is.
Homeopathic prophylaxis for migraine	In a systematic review the three studies with the strongest methods showed no difference between homeopathy and placebo. One methodologically weak study did show a difference, and some de-blinding was reported to have been possible.
Relaxation and biofeedback training in paediatric headache	Relaxation training probably reduces chronic headache and migraine in children and adolescents. Relaxation is probably as effective as other non-pharmacological interventions. There appear to be long-term benefits. Based on one trial, biofeedback with relaxation training reduced migraine. It is not possible to say whether the addition of biofeedback increased the benefits of relaxation or not.

Table 4: Treatments for acute migraine attacks where there is limited evidence (in full on *Bandolier* Internet site)

Treatment	Result
Aspirin	Aspirin, in a variety of doses and formulations, is effective for the treatment of an acute migraine attack. Approximately 45 to 55% of patients had moderate to severe headache reduced to mild or none at 2 hours with oral aspirin, and 60 to 65% patients had at least 50% pain relief by one hour with intravenous aspirin.
Aspirin plus metoclopramide	Aspirin plus metoclopramide has been fully tested in three randomised trials with about 550 patients. The NNT for two hour headache response was 3.2 (2.6 to 4.0).
Cafergot	Cafergot (ergotamine tartrate 2 mg plus caffeine 200 mg) has been fully tested in one randomised trial with about 250 patients. It is probably unreliable to extrapolate too much from a single trial.
Diclofenac	The evidence from a small number of randomised, double blind trials shows diclofenac to be more effective than placebo for the relief of migraine headache. In all studies, diclofenac 50 to 100 mg (oral) or 75 mg (intramuscular) provided significantly better pain relief than placebo.
Ibuprofen	Ibuprofen is an effective treatment for acute migraine. Ibuprofen at doses ranging from 400 to 1200 mg provided significantly better pain relief than placebo in three out of four placebo controlled studies. One trial of ibuprofen-arginine, a more rapidly absorbed formulation, was effective with an NNT of about 2 for the complete or near complete relief of migraine by two hours (but see concluding remarks).
Ketoprofen	Ketoprofen given as a rectal suppository or an intramuscular injection is effective for the acute treatment of migraine. These results are based on a small number of patients, and should be interpreted with caution. No trials of oral ketoprofen were found.
Naproxen	Naproxen is an effective treatment for acute migraine. Naproxen at doses ranging from 750 to 1250 mg/day provided significantly better pain relief than placebo in four placebo controlled studies.
Paracetamol	Paracetamol 1000 mg was more effective than placebo in one trial with an NNT for at least 50% pain relief by 2 hours of 7.8 (4.8 to 21). The lower dose, 650 mg, was not effective. Compared with NSAIDs, three out of five trials showed that the NSAID was significantly better at reducing migraine pain than paracetamol 500 to 1000 mg.
Tolfenamic acid	Oral tolfenamic acid has been tested in only a single small trial in acute migraine, involving about 80 patients. It is unsafe to draw any conclusions.

Other outcomes

Symptoms associated with migraine are nausea, photophobia or phonophobia. Not every patient with migraine has some, or all, of these associated symptoms. The number or proportion of patients who have these symptoms initially, but where the symptoms are completely relieved by (say) two hours, are important outcomes.

Functional disability is measured on a four point scale, from grade 0 where there is no functional disability to grade 3 where patients are restricted to bed. The number or proportion of patients who have some functional disability initially, but where there is no disability at (say) two hours, is an important outcome.

Clearly other outcomes could be measured, and sometimes are, but these are the main ones used in clinical trials.

Treating migraine

Migraine treatments come in a number of guises. Clearly, if there are obvious precipitating factors, the first thing to do is to try and remove them, though this may not always be possible. For those who have infrequent migraines, treating the headache and associated symptoms is a sensible goal. For those who have frequent migraines, prophylactic interventions to reduce the number may make sense. Choice is an important factor, and some may prefer unconventional to conventional treatments.

This brief review of available treatments can only be an overview. Fuller details of the evidence will be found in *Bandolier's* Migraine Resource. Even that can never capture all the nuances of diagnosis and treatment that will be necessary for some patients.

Complementary therapies

There have been several systematic reviews of complementary therapies for migraine or migraine-type headaches, mainly but not exclusively for prophylaxis to prevent headaches. The main results of these are shown in Table 3.

The stark message is that these do not work, or there is no evidence that they do work. What we know from both homeopathy and acupuncture is that the better the trials, and the more the trial designs minimise bias, the more negative are the results. These interventions are a waste of money and time.

The one exception may be feverfew for migraine prophylaxis. In common with a number of other herbal remedies, there is some evidence that it works, but even here that is not entirely convincing. Feverfew is a chemical, or mix of chemicals, and may not be without adverse effects.

Treating acute migraine

To be able to compare treatments across trials, we need the trials and outcomes to be the same. For migraine, trial design has become standardised, with patients having mi-

Figure 9: NNTs for two hour headache response

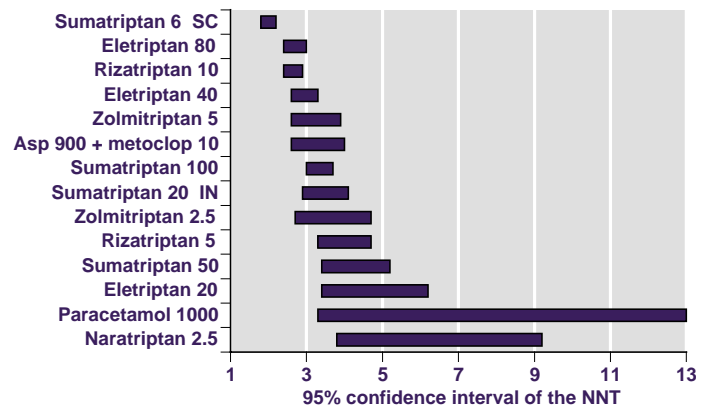


Figure 10: Percentage of patients with two hour headache response

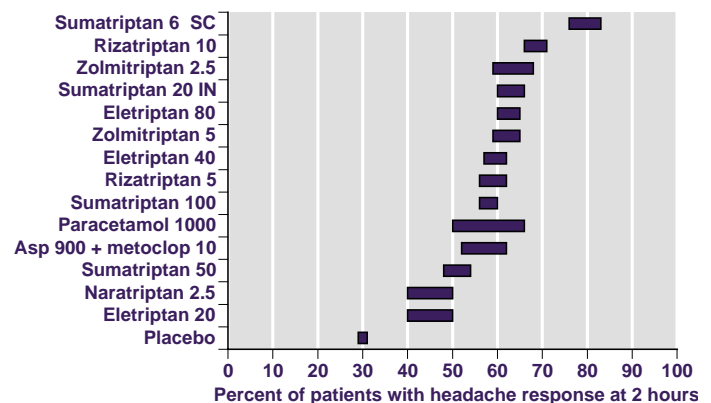


Figure 11: NNTs for two hour pain free

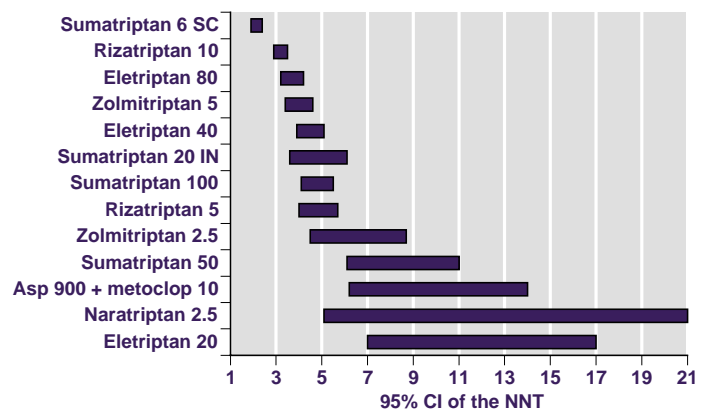
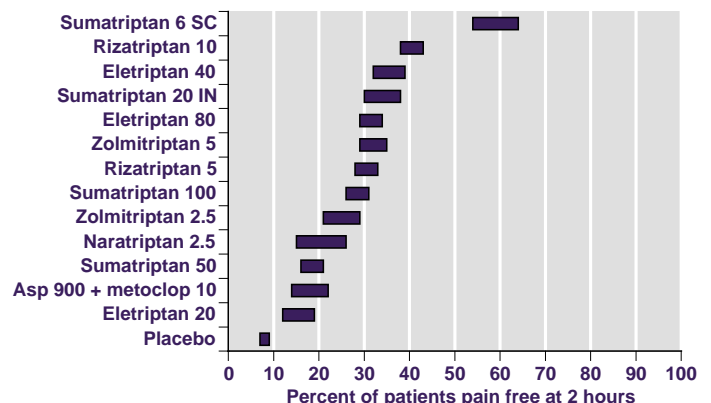


Figure 12: Percentage of patients with two hour pain free



graine diagnosed according to IHS criteria, having pain of moderate or severe initial intensity, and measuring the pain (or other symptom) using standard criteria at times up to two hours.

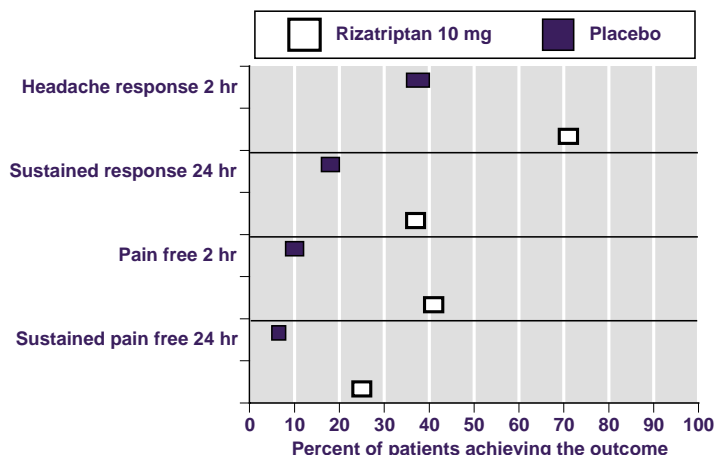
For a number of common remedies, these criteria are often not filled. For some there are only a few small trials, of limited quality. Brief summaries of these are shown in Table 4. Full references are available in the *Bandolier* Migraine Resource, with systematic reviews of each.

For many other interventions, notably the triptans, trials have been conducted that are large and fulfil the requirements above. Almost all used a placebo group, allowing comparison of their relative efficacy. Reports of systematic reviews are to be found in the *Bandolier* Migraine Resource. For some, like sumatriptan and rizatriptan, there are several systematic reviews each coming to broadly similar results.

The outcomes where we have results for most of the triptans are those of headache response at two hours and pain free at two hours, though some systematic reviews report other outcomes, for instance sustained response, or pain at times shorter than two hours.

The Figures on page 7 take information from a Canadian systematic review [8]. Figures 9 and 10 show the results for two hour headache response, firstly as the 95% confidence limits of the number needed to treat, and the second as the absolute percentage of people with headache response. An analysis based on somewhat larger numbers, and showing the number of patients on which the results are based, is in Table 5. Figures 11 and 12 show the results for two hour pain free response, as both the 95% confidence limits of the number needed to treat, and as the absolute percentage of people free of headache pain. Updated information and references can be found on the *Bandolier* Internet site, with details of any systematic reviews done by *Bandolier*.

Figure 13: Percentage benefiting with rizatriptan 10 mg and placebo for different outcomes



The single most detailed review available [9] is of rizatriptan from individual patient data, and gives additional information about headache response sustained over 24 hours, and pain free sustained over 24 hours. The percentage of patients with these outcomes with rizatriptan and with placebo is shown in Figure 13. The abstracted version on the paper on *Bandolier's* Migraine Resource also gives information about photophobia, phonophobia, nausea and functional disability, demonstrating how powerful can be pooled information based on the responses of individual patients.

Comparing reviews

Having one good review of a topic is good, but having three is remarkable. We now have three migraine reviews that have examined the efficacy of rizatriptan 10 mg for the treatment of acute migraine. All have been abstracted by *Bandolier*, and the abstracts can be accessed from the links above.

Table 5: Results for triptans for two hour headache response (refernces and data on Bandolier Internet site)

Treatment	Route	Number of trials	Active		Placebo		NNT (95% CI)
			Number/ Total	Percent	Number/ Total	Percent	
Sumatriptan 6 mg	SC	8	379/477	79	131/461	28	2.0 (1.8 to 2.2)
Eletriptan 80 mg	Oral	6	763/1221	62	191/779	25	2.6 (2.4 to 3.0)
Rizatriptan 10 mg	Oral	7	1219/1783	68	303/987	31	2.7 (2.4 to 2.9)
Eletriptan 40 mg	Oral	6	724/1224	59	191/779	25	2.9 (2.6 to 3.3)
Zolmitriptan 5 mg	Oral	4	583/943	62	85/285	30	3.1 (2.6 to 3.9)
Sumatriptan 100 mg	Oral	13	1346/2311	58	336/1211	28	3.3 (3.0 to 3.7)
Sumatriptan 20 mg	l'nasal	6	571/907	63	185/546	34	3.4 (2.9 to 4.1)
Zolmitriptan 2.5 mg	Oral	2	279/438	64	74/213	35	3.5 (2.7 to 4.7)
Rizatriptan 5 mg	Oral	4	548/933	59	234/713	33	3.9 (3.3 to 4.7)
Sumatriptan 50 mg	Oral	6	532/1042	51	137/510	27	4.1 (3.4 to 5.2)
Naratriptan 2.5 mg	Oral	2	154/340	45	61/229	27	5.4 (3.8 to 9.2)

Table 6: Comparison of results for rizatriptan 10 mg from three systematic reviews

Number needed to treat (95% confidence interval) for rizatriptan 10 mg

	At 2 hours		Over 24 hours	
	Headache response	Pain free	Sustained response	Sustained pain free
Gawel et al [8]	2.8 (2.6 to 3.2)	3.2 (2.9 to 3.5)		
Ferrari et al [9]	3.0 (2.8 to 3.4)	3.2 (3.0 to 3.5)	5.3 (4.6 to 6.2)	5.5 (4.9 to 6.4)
Oldman et al [10]	2.7 (2.4 to 2.9)	3.1 (2.9 to 3.4)	5.6 (4.5 to 7.4)	

Notes: Gawel review used only tablet data from 6 trials. Ferrari review used data from tablets and wafers in 7 trials, but had individual data from trial records. Oldman review combined tablet and wafer from 7 trials, but probably used a different definition of intention to treat as numbers of patients differed.

How do they compare? Table 6 gives the NNTs for four pain outcomes. All three reviews [8-10] had two hour outcomes, two reported the outcome of sustained relief, and one sustained pain free.

The agreement was very close. What differences there were derived from two sources - which trials were combined and the definition of intention to treat (Table 6).

Rizatriptan 10 mg is available as a tablet and a wafer for buccal dissolution. Two trials combined tablet and wafer data, while one used only tablets.

Then there is the issue of intention-to-treat. In migraine studies some patients can be randomised to treatment, but not have a migraine and not take the tablets. One review used only information from patients who did have a migraine attack, rather than all randomised.

Despite the nuances of methodology, the results were consistent. This gives us great confidence in the results, and demonstrates that here we have class 1 evidence.

Prophylactic interventions to prevent migraine

Bandolier has done its own systematic review on valproate for migraine prevention. The clinical bottom line was that sodium valproate is effective for the prevention of migraine attacks. About half of the patients had a reduction in the number of migraine attacks or days with migraine by about 50%. NNT for at least 50% reduction in migraine frequency for individual studies were three to four in three trials, with a pooled result of 3.5 (2.6 to 5.3) in three trials with 350 patients. The incidence of adverse effects was not insignificant, with nausea, dizziness and drowsiness associated with its use. Women of childbearing age should use the drug with caution due to the possibility of birth defects.

A review of beta-blockers from 1991 [11] suggests that prophylactic propranolol was associated with a 34% reduction in migraine activity, derived from weighted trial scores. The review may have included studies with bias and methodological weaknesses.

Comments on NNTs for migraine

Not every researcher in the migraine world likes NNTs. Other ways of describing results, like therapeutic gain, have also been tried, and liked by some and not by others. The therapeutic gain is merely the absolute risk increase, the percentage of patients having an outcome with treatment minus the number having that outcome with placebo.

Part of this derives from suggestions that there are different placebo effects between trials, that the placebo effect is greater for injected rather than oral treatments [12] and that the proportion randomised to placebo might alter results [13]. Both these conclusions are likely to be based on inadequate numbers. The bigger placebo response was examined using only sumatriptan trials, with a 7% higher placebo response with subcutaneous sumatriptan than oral sumatriptan. A full examination of all trials showed no difference (unpublished observations). The latter depended on the results in only 56 patients given placebo.

For those wanting to explore criticisms of different ways of presenting trial results, the key references are 14-16. One paper [14] complains that trials done for registration do not adequately reflect the clinical situation, where people may treat before pain becomes severe. It also suggests that they do not reflect *how* clinical decisions can best be made. So it is worth examining studies that address these issues.

The STEP trial

A number of strategies can be used to treat acute migraine attacks, each utilising some part of the evidence base.

For instance, the initial attack could be treated with aspirin or simple analgesic, and if or when that fails, a triptan could be used. That is a **step strategy within an attack**.

A different approach may be to try aspirin or simple analgesic for a few attacks. It will work for some, but for those for whom it does not work, a triptan may be an alternative treatment. That is a **step strategy across attacks**, and is probably the strategy most likely to be used in the UK as it is probably seen as the cheapest.

A third way would be to assess the individual patient for the severity of the disorder, and then to treat appropriately: mild disease might be treated with aspirin or simple analgesics, while more severe disease might be treated with a triptan. This would be **stratified care**.

It just so happens that a randomised controlled trial indicates that stratified care produces the best results [17].

Trial

The trial was randomised, but open-label, and examined multiple migraine attacks for patients with established diagnosis of migraine according to International Headache Society criteria. Patients completed the MIDAS questionnaire [18], measuring lost time in three domains of activity. Patients were assigned a grade of disability from I (little or infrequent disability), grade II (mild or infrequent disability), grade III (moderate disability) to grade IV (severe disability). Patients with grade II-IV disability were included.

Randomisation was to:

Stratified care: grade II patients received aspirin 800 to 1000 mg plus metoclopramide 10 mg for all six attacks. Those with grade III or IV received zolmitriptan 2.5 mg.

Step care across attacks: Patients treated the first three attacks with aspirin 800 to 1000 mg plus metoclopramide 10 mg. Those without adequate relief took zolmitriptan 2.5 mg for the next three attacks.

Step care within attacks: Patients treated all attacks with aspirin 800 to 1000 mg plus metoclopramide 10 mg first. If adequate relief was not obtained by two hours, they then took zolmitriptan 2.5 mg.

Figure 14: Two hour headache response according to treatment strategy

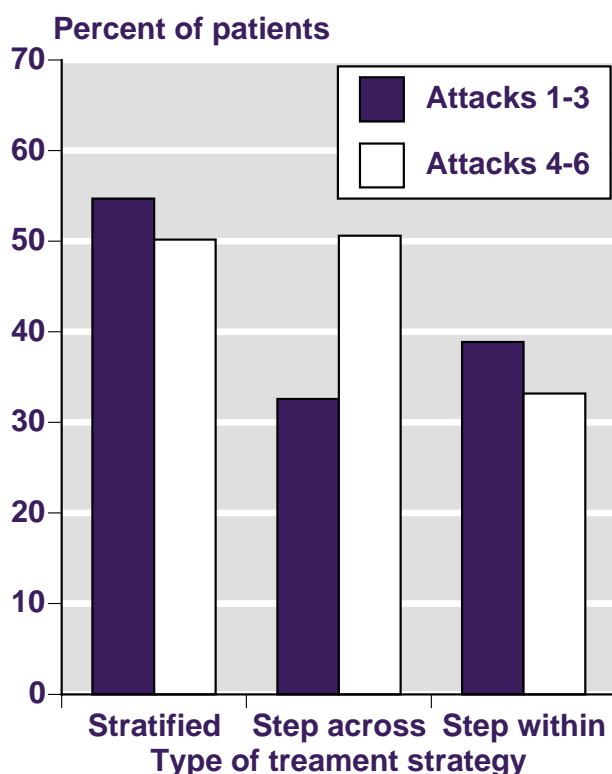
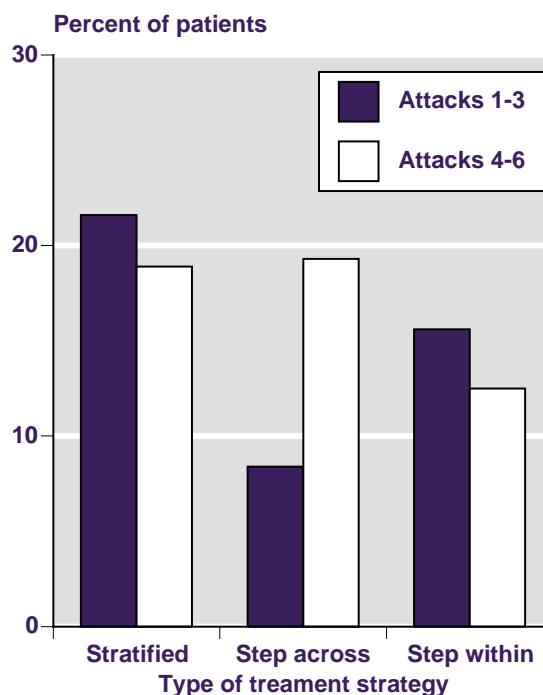


Figure 15: Two hour pain free according to treatment strategy



Results

In the three treatments groups, 1062 patients were randomised. Twenty percent of patients withdrew or were lost for various reasons, mostly innocuous. Only 3% withdrew because of an adverse event, and 0.2% because of deteriorating condition. Groups were well balanced.

More patients had a two-hour headache response in the stratified care strategy than for either step care strategy (Figure 14).

More patients were pain free at two hours in the stratified care strategy than for either step care strategy (Figure 15).

Adverse events were equally common in all three groups, and were predominantly mild and transient. Adverse event study withdrawals were evenly distributed across the groups.

Comment

Most guidelines would probably accept a step up approach, similar to that of step up across attacks, but with many more steps. Because of the time involved, and because of repeated failure of treatment, some patients simply become disenchanted and seek other forms of treatment.

Treating the appropriate patient appropriately from the beginning is a better bet. It takes less time, is more effective, and is without the "hassle factor" for patient and doctor. This is exactly what evidence-based medicine is supposed to be about, and reading the definition of EBM in the context of this trial is rewarding.

It is also worth noting that at least one analysis has attempted, albeit retrospectively, to examine the effect of triptans in patients with mild, rather than moderate or se-

vere pain [19]. It suggests that treatment earlier in an attack, with mild pain, may interrupt the progression of pain, decrease associated symptoms and disability, and improve patient outcomes.

Using tables of relative efficacy

“Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients” [20].

Studies like the STEP trial should help us realise that relative efficacy is only part of the equation in deciding about what to prescribe for whom, and issues like patient and professional preference, cost of prescribing, and adverse effects all become part of the complex decision-making process.

The good news is that we have a whole range of interventions that work in acute migraine, from aspirin, NSAIDs, paracetamol and triptans. However, it is only for the triptans that we have large amounts of good evidence from standardised, validated RCTs. For the triptans, we can be confident that they work well, with numbers needed to treat in the range of 2 to 5 for a number of interventions, both for headache response and pain free at two hours. Increasing amounts of information are becoming available that tell us if other aspects of treatment are important.

Tables of relative efficacy should not be used to proscribe treatments (as they have been in the past), but should be used as tools for better prescribing. Different patients will

have different needs. A young woman executive travelling the world may need the security that comes from rapid and effective treatment with subcutaneous sumatriptan. An old fogey pottering in his garden in rural Oxfordshire may be happy with an over-the-counter medicine.

The impact of triptans on lost time from migraine

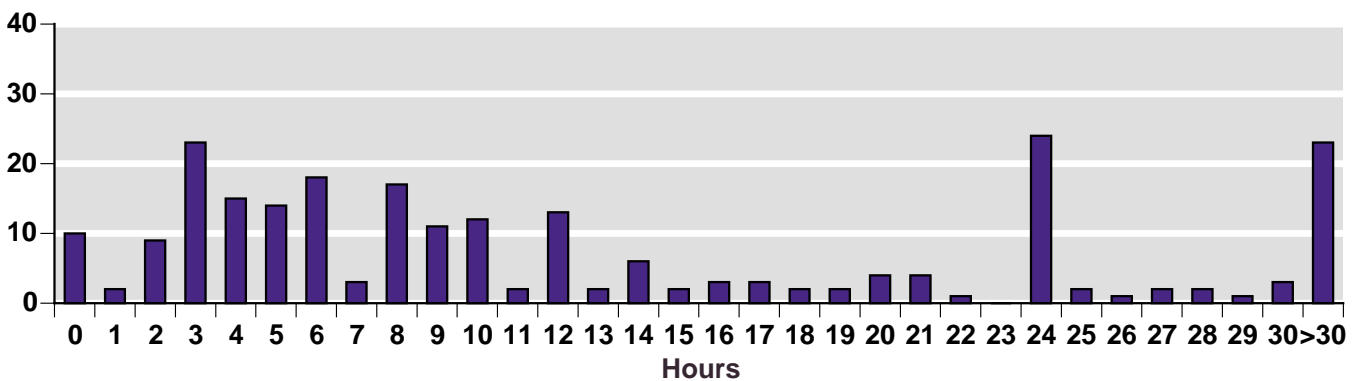
Migraine attacks usually mean that sufferers are unable to carry out those functions, both activities of daily living and paid employment, that they would normally do. Results from a randomised trial [21] put some numbers on how much of that lost time can be regained by using an effective triptan.

The total time lost with placebo (Figure 16) was a median of 9 hours. This reflected a very wide distribution. For example, while half of the patients lost fewer than 9 hours, at least 60 patients lost more than 20 hours. The mean value was 14.5 hours of total time lost. The total time lost with eletriptan was 4 hours (mean about 7 hours, Figure 17 for 40 mg eletriptan). The distribution was very different with eletriptan, with only a small proportion losing more than 9 hours.

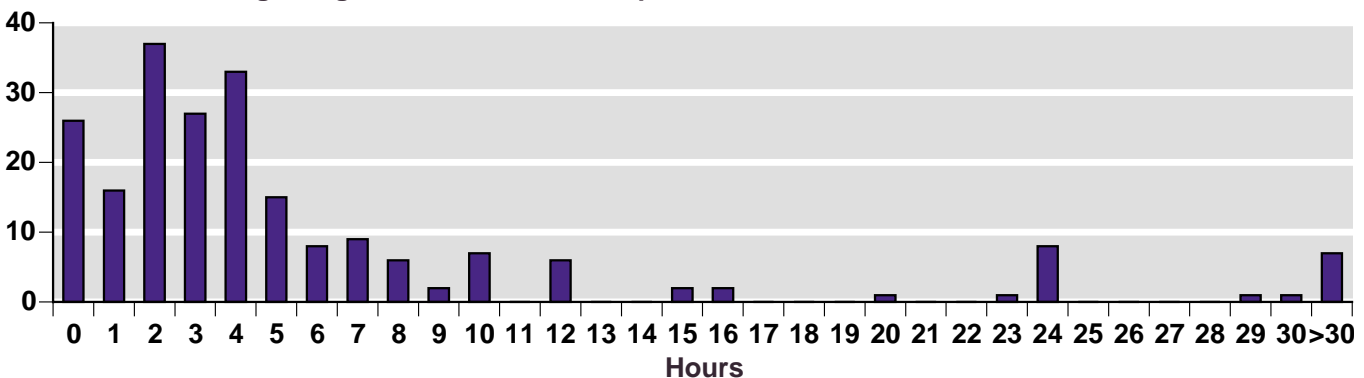
Thus for each migraine attack, treatment with an effective dose of a triptan, with use of a further dose if the first fails to provide adequate relief, will result in a saving of a median of five hours of total time, and 1-1.5 hours of work time. This is exactly the same result as that of 1.1 hours saved in another randomised trial with rizatriptan [22].

Figure 16: Hours lost to a migraine attack with placebo or 40 mg eletriptan

Hours lost with a single migraine attack with placebo



Hours lost with a single migraine attack with eletriptan



Multiplying the median savings in work time with the gross hourly wages in the UK would suggest an economic gain of £12.50 per attack for a triptan compared with placebo.

Overall comments and conclusions

Migraine has been a fascinating area in which to assemble good quality evidence.

One comment is that much of the good evidence is quite recent, for epidemiology, for diagnosis, and for treatment. For older treatments, like paracetamol or NSAIDs the evidence is limited in scale and quality. Newer information tends to disappoint. For instance, the *Bandolier* Internet site has a review of ibuprofen for migraine, suggesting an NNT of about 2 based on one small study. In a new large, randomised trial in about 700 patients [23], done to high standards, ibuprofen 200 mg and 400 mg each had an NNT for two hour headache response of 7.5 (4.5 to 22).

Another comment is that people can get fixated on league tables of relative efficacy. *Bandolier* gets irritated when people choose one treatment which *has* to be used. The point is that we have many treatments that work. Some treatments are more efficacious, others are cheaper, some migraineurs are happy with the treatment they are taking. The evidence base around migraine is there as a *tool* to inform better diagnosis and treatment. It is not there to enforce *rules* about what should be prescribed to what patient and when.

Finally, it is worth pointing out that trying to tackle the evidence base in any area of medicine, however narrow, is a job that can only be done with humility, and in the full and certain knowledge that no knowledge applies to every patient, everywhere, and without exception. We hope that readers, professional and lay, will accept this for what it is: a broad brush attempt to help people know more, to point them to better knowledge, and with the goal of improved treatment of migraine.

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