

READERS REQUESTS EDITION

FOLATE, HOMOCYSTEINE AND DEMENTIA

Bandolier receives many fascinating requests asking it to find the evidence on such-and-such a topic. Many, most even, are difficult, or even border on the impossible. But increasingly even for the seemingly impossible it is becoming easier to find at least some level of evidence to support a course of action. It may not be the answer to the world, the universe, and everything, but it's usually better than what we had before.

Take homocysteine and dementia, for instance. We had never heard of any connection, nor had anyone we knew, but a few hours of searching found some really interesting literature supporting a connection. Or restless legs - hardly anything hove into view until three rather good randomised trials showed pergolide to have substantial effects. Some are more difficult, and all we can do is point to where the best available evidence can be found.

Gastroenteritis in children

The assessment and clinical management of children and adults with gastroenteritis, and the evidence on which it is based, is one of the questions asked of *Bandolier*. There is a thoroughly researched article dealing with managing acute gastroenteritis in children [1], but the details are too complex for summary in *Bandolier*.

This article has a highly developed searching strategy, and is likely to have found most of the relevant articles published up to 1997. It has 70 references for those who want to dig deeper or read more widely. For those who want *the* document to read for now, this is it. Your local library should be able to get it for you within a few days.

Reference:

- 1 MS Murphy. Guidelines for managing acute gastroenteritis based on a systematic review of published papers. Archives of Diseases in Children 1998 79: 279-84.

In this issue

Gastroenteritis in children	p. 1
Folate, homocysteine and dementia	p. 1
Hand washing evidence	p. 2
Preventing catheter-related bacteriuria	p. 4
Migraine, economics, depression and suicide	p. 5
Restless leg syndrome - pergolide review	p. 6

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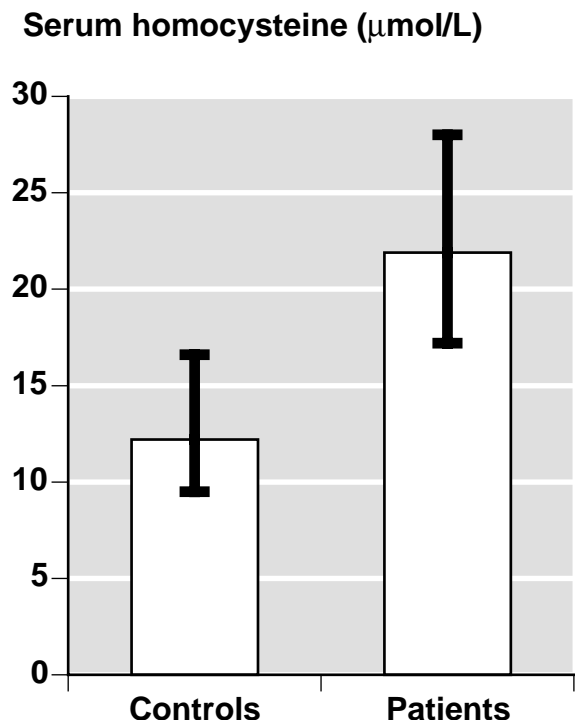
High folic acid intake is associated with reduced incidence of both heart disease (*Bandolier* 57) and colon cancer (*Bandolier* 60). For heart disease at least, the mechanism is thought to be that of reducing homocysteine levels. The bottom line is that low folate and high homocysteine are bad, while high folate and low homocysteine are good. The question was asked of *Bandolier* whether there was a similar association with dementia.

Some quick searching revealed that there is, indeed, a literature on this. It seems to confirm a similar relationship between high folate intake (or at least levels), low serum homocysteine and low risk of dementia. Three epidemiological studies are briefly reviewed.

Wrexham [1]

Thirty patients aged 65 years or more (mean age 79 years) and presenting consecutively with features compatible with primary degenerative dementia of Alzheimer's type were matched with controls from the local general practice population without dementia. There were several sensible exclusions.

Figure 1: Homocysteine levels in patients with dementia and age-matched controls

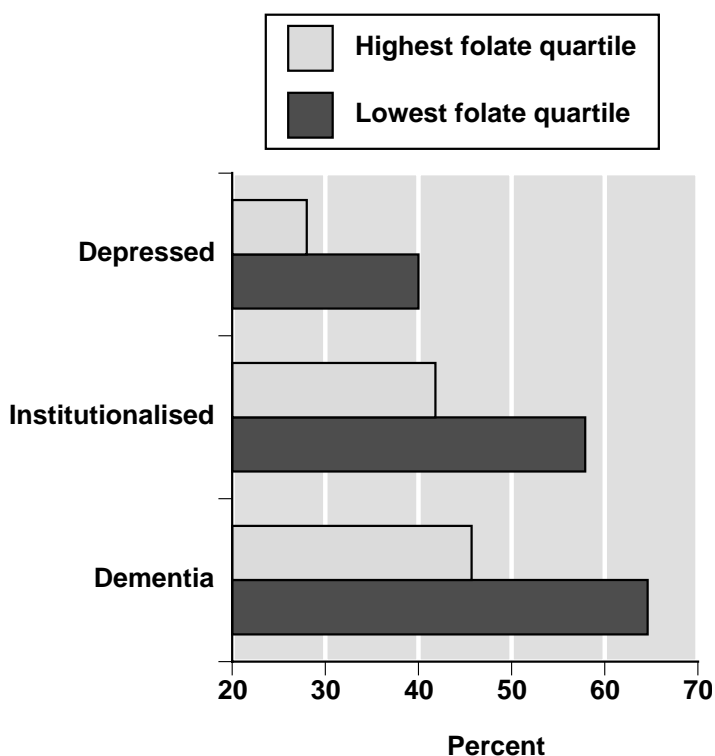


Homocysteine levels were much lower in controls than in patients with dementia (Figure 1), which was significant at the 1 in 10,000 level. Folate levels were somewhat lower in controls, but the two major discriminating factors between patients and controls were homocysteine and folate.

Canada [2]

In Canada, a population study of people over 65 had 1171 individuals in whom serum folate was measured as part of a clinical examination in a study of ageing. The clinical features of the patients were then examined according to the quartile of folate results. Those in the highest quartile had lower rates of dementia and depression, and were less likely to be institutionalised (Figure 2). When dementias were examined closely, there were significant differences between the quartile with the highest level of folate and the lowest for any type of dementia, for probable plus possible Alzheimer's disease, and for other types of dementia than vascular or unclassified types. Older age groups were selectively sampled (mean age 82 years), explaining the high incidence of dementia.

Figure 2: Comparison between outcomes with high and low serum folate in elderly people



Oxford [3]

Perhaps the most detailed of these three studies was that conducted in Oxford on 164 patients over 55 with a clinical diagnosis of Alzheimer's disease and 108 matched controls. This looked at a range of markers in blood, including some genetic markers. Importantly, 76 of the patients subsequently died, and their Alzheimer's disease was confirmed by histology on post mortem examination.

Serum homocysteine was significantly lower, and folate higher, in controls than in patients. The frequency of the Apo E lipoprotein allele ϵ -4 occurred at about 40% in patients with Alzheimer's disease than in controls. Moreover, in 43 patients with clinically diagnosed Alzheimer's disease with CAT scans over four years there was significantly radiological evidence of disease progression in those with the middle and highest tertiles of homocysteine compared to those in the lowest.

Comment

The association between high serum homocysteine and low serum folate and dementia appears to be reproducible. Is it cause or effect? One suggestion is that people with dementia have poor diets – they may lose weight and have low serum albumin levels – because of their disease. So that could explain the low folate intake and high homocysteine levels. There is no easy answer to this, but the Oxford study demonstrated that homocysteine and vitamin levels were stable over several years while dementia got worse.

Clearly some prospective trials will be needed to sort out the benefits of treatment, and more about the underlying processes. The bottom line is that taking a daily multivitamin for whatever reason is likely to prevent cardiovascular disease, cancer and possibly dementia also.

References:

- 1 A McCaddon et al. Total serum homocysteine in senile dementia of Alzheimer type. *International Journal of Geriatric Psychiatry* 1998 13: 235-9.
- 2 EM Ebly et al. Folate status, vascular disease and cognition in elderly Canadians. *Age and Ageing* 1998 27: 485-491.
- 3 R Clarke et al. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. *Archives of Neurology* 1998 55: 1449-55.

NOW WASH YOUR HANDS

The relevance of hand washing to hospital acquired infection has long been of interest to *Bandolier*. Clearly it is considered an issue of importance, and a BMJ editorial [1] pointed out how infrequent and sporadic hand washing is in health care workers. One classic paper quoted showed that while doctors estimated that they washed their hands 73% of the time before patient contact, the observed frequency was just 9%.

That hands can be a repository of nasty germs, and that hand washing can reduce infection rates has been known for a long time. A cracking little paper [2] showed that *Klebsiella* species can live quite happily on hands for up to two and a half hours, and that instituting hand washing regimens can reduce infections in patients by a significant amount (down from 23 to 16%). Hand washing with chlorhexidine regularly gave 98-100% reductions in hand counts.

There is even a systematic review [3] looking at compliance issues with hand washing and barrier precautions, which is a useful source of literature. It highlighted two other studies which showed that increased compliance with hand washing before and after patient contact resulted in large (50% or more) decreases in infection rates. Three more recent papers of interest are examined here.

Iowa [4]

Over eight months a multiple cross-over study was conducted in which two hand washing systems, chlorhexidine and soap plus alcohol rinse, were compared. The primary outcome was the patient nosocomial infection rate.

By observation, the proportion of opportunities for hand washing (after one patient and before the next) in which hands were actually washed was 42% during chlorhexidine use and 38% for soap/alcohol. With chlorhexidine during 4001 patient days there were 152 infections. With soap/alcohol during 3984 patient days there were 202 infections. This was statistically lower.

London [5]

Following cases of *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* in three acute medical wards for elderly people, infection control measures were monitored to examine the effect on infection, and use of cephalosporin antibiotics. The interventions were:

- ◆ Emphasis on hand washing between patient contacts – using 4% chlorhexidine scrub if contact was prolonged and alcoholic 0.5% chlorhexidine handrub if it was less prolonged. This was consultant led, involved nurses, and handrub was available in bays and side-rooms and on the medical notes trolley for ward rounds.

- ◆ There was considerable feedback to all members of staff about new cases, and about infection rates.
- ◆ A low cephalosporin antibiotic policy was introduced aiming to limit the length of antibiotic courses to no more than seven days.

The result of the infection control policy was to reduce the amount of cephalosporin drug use by more than two-thirds. Compared with the nine months before the intervention, the nine months following the intervention resulted in a 42% drop in *C difficile* infections and a 51% reduction in MRSA infections (Figure). For MRSA this did not include a period when an isolation unit was in action during March to June 1995.

One year later this policy had had a significant impact on ward closures and bed availability. There was a net gain of 5 beds a day.

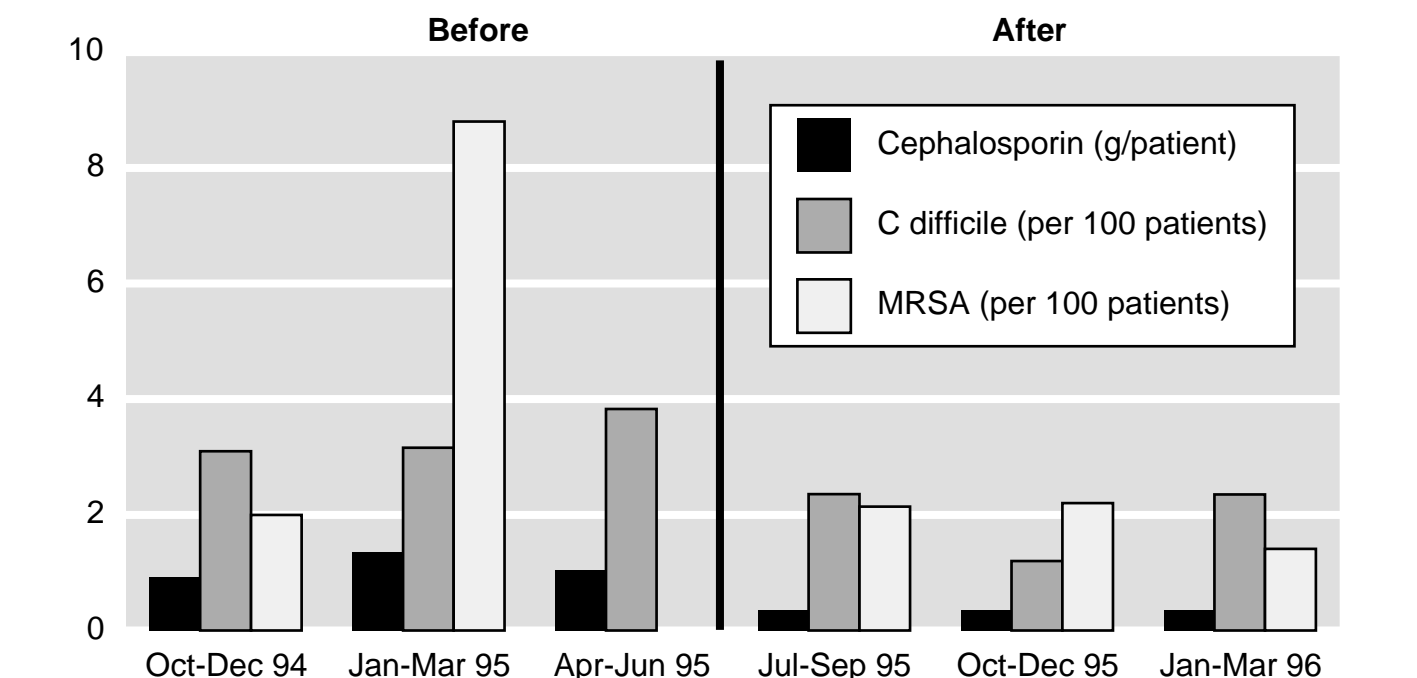
Geneva [6]

So just how contaminated do hands get during episodes of routine patient care? A study in Geneva answered this question by examining the previously-washed hands of health care workers by looking at the number of colony forming units (CFU) from the five fingertips of a dominant hand. There were 417 episodes, lasting a median of five minutes.

The total number of counts ranged from 0 to 300 CFU, with a mean 100 CFU. As well as normal skin flora, 11% were contaminated with *Staphylococcus aureus* and 15% with gram negative bacteria. Gloved hands acquired only 3 CFU per minute, while ungloved hands acquired 16 CFU per minute. The longer the episode of patient care, the larger the number of bacteria acquired.

For ungloved hands, direct patient contact, respiratory care (endotracheal tube), handling bodily secretions and episodes of care interrupted by a telephone call, for instance,

Figure: Before and after institution of infection control policies



were associated with highest rates of acquisition, from 16 to 20 CFU per minute. Most types of hospital setting were associated with similar rates of acquisition except septic orthopaedic and paediatric intensive care. Prior hand washing with antiseptics containing chlorhexidine was associated with lower rates of bacterial acquisition.

Comment

The bottom line appears to be simple, that hand washing with agents containing chlorhexidine really does lower the rate at which bacteria get onto the hands, and that hand washing protocols properly enforced reduce hospital acquired infections. It's more than that, though. There would appear to be clear evidence of effectiveness, and of benefits of quality and cost-effectiveness. It may even be a clinical governance issue.

Bandolier and *ImpAct* would love to hear from people who have found ways in making a policy work, in addition to that from London above.

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- 6 D Pittet et al. Bacterial contamination of the hands of hospital staff during routine patient care. *Archives of Internal Medicine* 1999 159: 821-6.

PREVENTING CATHETER-RELATED BACTERIURIA

An evidence-based review of the literature on preventing catheter-associated urinary tract infection aims to provide clinicians with an overview of the advances made in the last 20 years [1]. It uses an extensive literature search which should have located most English-language articles published up to 1997.

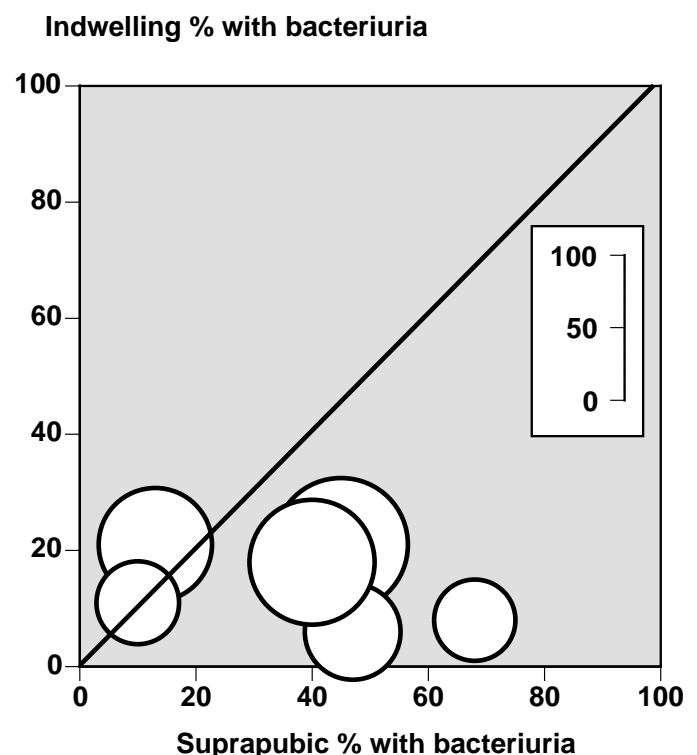
Background

About a quarter of hospital patients have a urinary catheter some time during their stay, and an average of 5% (range 3-10%) will acquire a urinary tract infection every day. Clearly, then, almost all patients will have an infection after about a month. This can extend hospital stay by about

Main recommendations

- 1 Avoid using a urinary catheter whenever possible. When used, remove as soon as possible.
- 2 Always insert a catheter aseptically, use a closed drainage system, and properly maintain the catheter.
- 3 Consider systemic antibiotics only during short term (3-14 days) in patients at high risk for complications of catheter-associated bacteriuria.
- 4 Consider using a silver alloy catheter in patients at high risk of complications.
- 5 Suprapubic catheters may be desirable in patients needing long-term catheterisation.
- 6 A condom catheter may be sensible for incontinent men who will not manipulate the device.
- 7 Prophylaxis with trimethoprim-sulphamethoxazole should be given to patients undergoing renal transplantation who need a catheter.
- 8 Systemic antibiotic prophylaxis should probably be given to men undergoing transurethral resection of the prostate.
- 9 No good evidence that bladder irrigation, antibacterial instillation in the drainage bag, rigorous meatal cleaning, and use of meatal lubricants and creams prevent bacteriuria. They should not be used.

Figure: Trials comparing bacteriuria rates with indwelling and suprapubic catheters



three extra days, and patients with a urinary tract infection are three times more likely to die. The case-fatality rate from urinary tract related bacteraemia is 13%.

Main findings

This review examines so many different aspects that it is all but impossible to summarise for *Bandolier*, other than re-cap the main recommendations (Box). There are two major findings. One relates to the use of silver alloy catheters, which have an NNT to prevent one infection of 4.6 (95% confidence interval 3.4 to 6.9), as shown in *Bandolier* 58.

The other major finding is that suprapubic catheters give overall lower rates of bacteriuria than do indwelling catheters. For suprapubic catheters, 15% of 227 patients in six trials (four randomised) had bacteriuria, compared with 37% of 208 patients with indwelling catheters. Use of suprapubic catheters rather than indwelling catheters would prevent bacteriuria for one patient in every five so treated (NNT 4.6, confidence interval 3.4 to 7.4).

Comment

This is a super paper, and a “must-read” for anyone responsible for urinary catheters. It emphasises in strong language the need for thorough hand washing to prevent nosocomial infections. The main recommendations, based on the evidence, are shown in the box.

The other important point that makes this paper worth reading is that it deals with issues relating to catheters in particular clinical situations, like renal transplantation or transurethral resection of the prostate.

Reference:

- 1 S Saint, BA Lipsky. Preventing catheter-related bacteriuria. Should we? Can we? How? *Archives of Internal Medicine* 1999 159: 800-808.

MIGRAINE: COSTS AND CONSEQUENCES

Bandolier 59 examined numbers needed to treat for treatments for acute migraine, but there's more to migraine than that. There is a large economic burden, mostly outside the NHS, and interesting and important associations with depressive illness and suicide risk.

Costs

Health economic papers are usually impenetrable, but a superbly sensible and readable report examines the burden of migraine in the United States [1]. It draws on a wide range of data sources to do its computations, and the major assumptions on migraine are interesting:

- ◆ Migraine prevalence is about 7% in men and 20% in women over the ages 20 to 64.
- ◆ The average number of migraine attacks per year was 34 for men and 37 for women.
- ◆ Men will need nearly four days in bed every year. Women will need six.
- ◆ The average length of bed rest is five to six hours.
- ◆ Only about 1 in 5 sufferers seek help from a doctor.

The bottom line on the costs is given in Table 1. Only 8% of costs were for medical care – and the bulk of this was in physician visits and prescribed drugs. Most of the burden

was in missed workdays and lost productivity. The figures used to calculate these were not out of line with the British equivalent (average wage cost was lower, for instance), and translated on a population basis the equivalent figure for the UK would be £1,913 million. This is about as much as a 1p on the standard rate of income tax, or about 0.5% of GDP. A Dutch summary of a number of economic analyses on migraine confirms that the US experience is shared with other developed economies [2].

Consequences

Perhaps more like very important association than consequence, but an epidemiological study of young adults linking migraine to psychiatric disorder and suicide attempts [3] is worth considering.

This study examined 1,007 young adults aged 21 to 30 years old who were part of an HMO in Michigan. The participated in a structured interview which used 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. There were higher lifetime rates of psychiatric disorders in persons with migraine. For in-

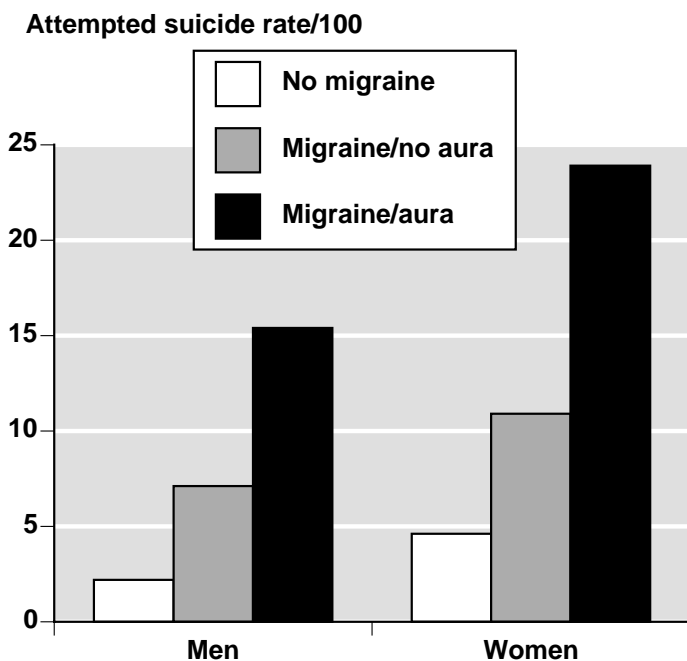
Table 1: Economic burden of migraine in the USA

Cost element	US\$ million		
	Men	Women	Total
Medical	193	1,033	1,226
Missed workdays	1,240	6,662	7,902
Lost productivity	1,420	4,026	5,446
Total			14,574

Table 2: Association between migraine, depression and suicide attempts

Migraine	Depression	Number	Suicide attempts/100
None	None	786	2.2
Migraine/no aura	None	51	5.9
Migraine/aura	None	33	9.1
None	Major	91	16.5
Migraine/no aura	Major	18	22.2
Migraine/aura	Major	26	38.5

Figure: Suicide rates in men and women according to type of migraine



stance, 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 higher in migraine sufferers, especially in those with aura (Figure). When stratified according to the type of migraine and the presence and absence of major depression, the figures confirm this remarkable trend (Table 2).

Comment

Confirmation of the association between migraine, depression and suicide attempts could not be found in a search of the literature, so this 1992 paper stands on its own as far as *Bandolier* can see. It looks sufficiently important to require replication in a UK context, especially when suicide has become a health improvement target, and migraine is so common. Clearly there is much more to migraine than expensive and effective new drugs, and a significant economic drag on the economy.

References:

- 1 XH Hu et al. Burden of migraine in the United States. *Archives of Internal Medicine* 1999 159: 813-8.
- 2 MD Ferrari. The economic burden of migraine to society. *Pharmacoeconomics* 1998 13: 667-76.
- 3 N Breslau et al. Migraine, psychiatric disorders, and suicide attempts: an epidemiological study of young adults. *Psychiatry Research* 1992 37: 11-23.

RESTLESS LEG SYNDROME

Originally defined by a Swedish neurologist in the 1940s, restless leg syndrome is now thought to affect up to 15% of the population, particularly older people. Four basic elements must be present to make the diagnosis:

- 1 A desire to move the limbs, often associated with paresthesia or dysaesthesia
- 2 Symptoms exacerbated by rest and relieved by activity
- 3 Motor restlessness
- 4 Nocturnal worsening of the symptoms

What helps? L-dopa and benzodiazepines have been tried, but there are now three high-quality randomised studies of

pergolide (a dopamine receptor agonist) which show it to be highly effective. Details of the studies are shown in the Table. All of the studies were well-designed and highly detailed in the outcomes they examined, and all of them allowed a period of dose-escalation with both pergolide and comparator with drug formulations of identical appearance.

Göttingen [1]

This study showed a dramatic drop in night time restless leg movement time from a pre-treatment control mean of 165 minutes to 35 minutes with pergolide but a non-significant drop to 91 minutes with L-dopa. All 11 patients had complete (9) or almost complete (2) relief with pergolide as against only one of 11 with placebo.

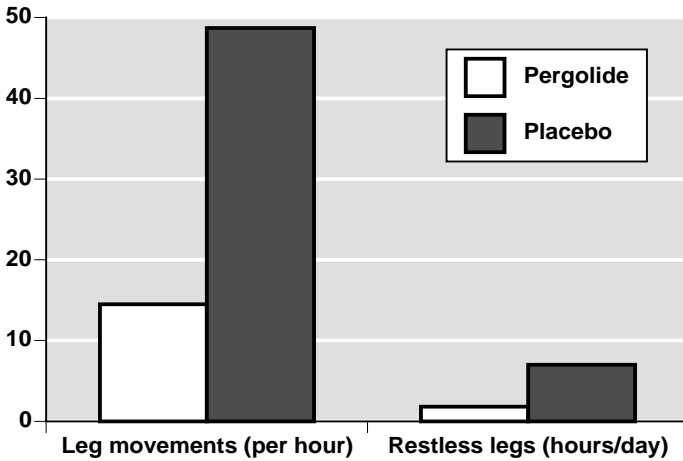
Table: Randomised, double-blind trials of pergolide in restless legs syndrome

Reference	Design	Pergolide	Comparator	Main outcomes	Main results	Adverse effects
Staedt et al, 1997	Randomised, double-blind crossover study in 11 patients, two 16-day phases	0.125 mg at night increased to 0.250 mg if needed (mean final dose 0.159 mg)	L-dopa 250 to 500 mg (final dose 363 mg)	Patient outcomes, poly-somnography	11/11 complete or nearly complete resolution with pergolide, 1/11 on L-dopa Significant improvement in sleep and reduced movement times from 165 minutes at baseline to 35 minutes on pergolide	Initial nausea with pergolide successfully treated with domperidone 60 mg. No discontinuations because of adverse effects.
Earley et al, 1998	Randomised, double-blind parallel group study in 16 patients over 18 days	Self-adjusted schedule, 0.05 to 0.65 mg a day (final median dose 0.35 mg)	Placebo	Poly-somnography, sleep measures, periodic limb movements of sleep	Significant reduction in sleep limb movements from 49 to 14 per hour on pergolide. Improved sleep and hours a day of restless legs. No change with placebo. 5/8 complete resolutions on pergolide	Mild adverse effects with pergolide and placebo. No discontinuations because of adverse effects.
Wetter et al, 1999	Randomised, double-blind crossover study in 28 patients, two 6-week phases	Up to 0.75 mg titrated up from starting dose of 0.05 mg (final mean dose 0.51 mg)	Placebo	Poly-somnography, sleep measures, periodic limb movements of sleep, sleep diaries, patient and physician outcomes	Significant improvement in all sleep measures. Periodic limb movements reduced from 55 per hour on placebo to 5 per hour on pergolide. Patient severity of restless leg average below 1 on scale of 10.	Nausea, headache and rhinitis were main adverse effects on pergolide. Headache, abdominal pain, constipation and nausea with placebo. 1 patient withdrew on placebo because of abdominal pain.

Baltimore [2]

Compared with placebo, pergolide reduced periodic limb movements of sleep and the numbers of hours a day with restless legs by a very considerable extent, while placebo was without effect (Figure 1). Five of eight patients had almost no restless leg symptoms with pergolide.

Figure 1: Pergolide effects on leg movements compared with placebo

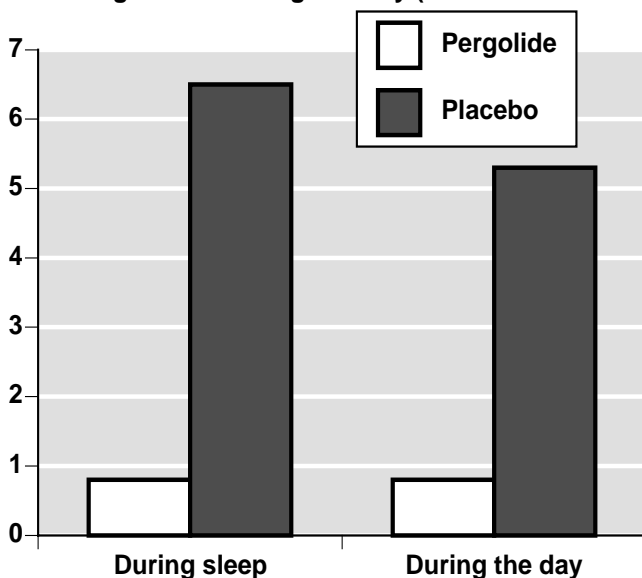


Munich [3]

This was a longer-term trial with six weeks of treatment, and had more patients than the other trials. There were highly statistically significant improvements on almost every measure of sleep and leg movement. Using a scale from zero (no restless legs) to 10 (severe symptoms), patients on pergolide rated their symptoms below 1 on average, while on placebo the same patients rated their symptoms at 5 to 7 during the day and at night respectively (Figure 2). The absolute number of periodic leg movements during sleep and wakefulness was 46 on pergolide and 438 on placebo.

Figure 2: Patient rating of restless legs severity on pergolide and placebo

Patient rating of restless leg severity (0=none/10=severe)



Adverse effects

There were no adverse effect withdrawals on pergolide and one on placebo. Adverse effects were usually nausea, headache and constipation, and usually mild. Nausea was treated with domperidone 60 mg.

Comment

These results, albeit in three relatively small but high-quality trials, look very good. Using the outcome of complete or almost complete relief of restless leg symptoms, the best information is that 16/19 patients benefited with pergolide compared with 1/19 controls. This would give a relative benefit of 11 (95% confidence interval 2.3 to 52) and a number needed to treat of 1.3 (1.0 to 1.7).

Whether this is sufficient evidence to institute this treatment in primary care is another matter. The results are such that local prescribing committees might like to examine it as part of formulating guidelines, and update that as more studies are reported. Because the studies we have were done on patients with bad symptoms (they were referred to neurologists, after all), a trial in primary care might be justified. An old-fashioned review has some interesting comments on diagnosis [4].

As always, *Bandolier* shows that evidence can be found, and where it can be found, even if, as here, it is for an unlicensed indication. Whether and how it should be used is up to the reader.

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ISSN 1353-9906