HOME IS WHERE THE HEART IS

A care assistant asked an elderly lady living in Oxford where her home was. “Pontypridd”, she replied, with a description of the beauty of the valleys. The immediate response was a call to the doctor to report a case of dementia.

A wise old doctor asked her where her home was. “Pontypridd”, came the reply. And where do you live now. “Why in Oxford, you fool!”

Many exiles from the Celtic fringe and the English regions are of two minds when it comes to answering a question about what constitutes home, which is why Bandolier’s friends support football clubs like Blackburn and Liverpool rather than Oxford United. But it is easy to see how complicated the issue of dementia can be, and therefore little surprise that clinical schemes for diagnosing dementia may give different results.

But what about ten times different? This month Bandolier reports on a paper which says just that. And in addition, we report on a superb trial of Ginko biloba in dementia which demonstrates how to do trials in this difficult area, and how to report them to allow us to make sense of the results.

Moving home - ode to the trailer park

This month sees Bandolier’s fifth birthday. For the first four years home has been a leaky portacabin. Many of the visitors who visit Bandolier's Internet pages 6,000 times every day don’t know what a leaky portacabin is, and for their benefit we have a picture.

In April Bandolier moves into palatial accommodation in a new Pain Unit building, and after four cold winters and three scorching summers, it can’t come fast enough. No split personality for us as to where home will be!

Not for NHS patients or dogs

Your indoor games editor has angrily rebutted the charge that she is yet another fashionable lifestyle columnist. Bitterly hurt she went off on your behalf to watch the film Regeneration (see book review Bandolier 43). The electrical treatment for shell shock is stunning (sic, Ed). An NNT of 1 claimed compared with therapy. The advent of electricity produced ‘one spark and you’re better’ cures - we will return to this next month (and explain the cryptic title).

We see the same attitude in broadsheet medical pages - uncritical testimonials for hardware from lasers to TENS machines (see Bandolier 37). For some devices you could argue that if it’s harmless then that’s the consumer’s choice. Seems strange though that the self-criticism which EBM brings, and which patients are always surprised wasn’t always there, hasn’t filtered through to journalists. Perhaps the ‘cures everything from corns to cancer’ belief is another delusional crutch. We all need them. At teetotal meetings speakers took laudanum for Dutch courage.

Finally, two more for dementia diagnosis. What’s the price of a first class stamp? Where is Northern Ireland, and what’s going on there now? Answers on a postcard.............
DEMENTIA
DIAGNOSIS AND TREATMENT

In Bandolier 40 we examined a trial of a new dementia drug, donepezil, and criticised it because of the unhelpful and preliminary way the information had been presented. So this month it is a pleasure to report a really well designed study of Ginkgo biloba extract which is much easier to interpret. But first our Finnish correspondent brought to Bandolier’s attention an important investigation of how different ways of diagnosing dementia produce wildly differing results.

Diagnosis

A detailed study of systems of diagnosing dementia has shown a 10-fold variation in prevalence in 1879 subjects, from 3.1% to 29% [1].

A Canadian study of health and ageing surveyed 10,263 people aged 16 years or more. Of these 1879 had a full clinical examination, including a neuropsychological examination. Records were then examined independently by a neurologist, a neuropsychologist and a nurse to agree whether each patient met criteria included in each of a number of different diagnostic systems:

- Diagnostic and Statistical Manual of Mental Disorder (DSM)-III
- DSM-III-R
- DSM-IV
- International Classification of Disease (ICD)-9
- ICD-10
- Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)

Results

The mean age of the 1879 included in the study was 80 years, and two-thirds lived in the community. The results for the different schemes in this population are shown in the Figure. The lowest prevalence was 3.1% with ICD-10, and the highest was DSM-III with 29.1%. Clinical consensus in the Canadian study was 20.9%. Only 20 people were given a diagnosis of dementia by all six systems.

Treatment

Bandolier 18 reported on a systematic review pointing out the efficacy of Ginkgo biloba in cerebral insufficiency. Now a trial of an extract of Ginkgo biloba has shown efficacy in patients with dementia [2]. It is a cracking study, beautifully reported, and has exactly the sort of information Bandolier found lacking earlier in a trial of donepezil (Bandolier 40).

Study

This was a randomised, double-blind study in which patients with dementia were given extract of Ginkgo (called EGb, now licensed in Germany) as a 40 mg tablet before each main meal, or matched placebo. The planned duration was 52 weeks with assessments at baseline, and 2, 12, 26 and 52 weeks.

Patients

Patients were 45 years or older with a diagnosis of uncomplicated dementia according to the DSM-III-R and ICD-10 criteria, with either Alzheimer’s disease or multi-infarct dementia.

Outcomes

There were three main outcomes. The first was ADAS-Cog, an Alzheimer Disease Assessment scale. The total score can range from 0 to 70, and the higher the score, the poorer the performance (we got that wrong in Bandolier 40). A daily living and social behaviour score (GERRI) was completed by family members. The third was a Clinical Global Impression of Change (CGIC) score, completed by the physician.

Results

A total of 549 patients were screened, 327 were randomised, and data from 309 patients was used for analysis. There was a high rate of withdrawal after baseline, and 50% of patients on Ginkgo completed 52 weeks, compared with 38% with placebo.

In the Ginkgo group the ADAS-Cog score was unchanged at 52 weeks compared with a mean increase (worsening) of 1.5 points for placebo patients. The GERRI scores worsened on average with placebo, but showed a continuing small im-

![Prevalence of dementia according to system of diagnosis in 1879 subjects](image)
improvement with Ginkgo. These differences were highly significant between groups. There was no significant difference for the physician score.

**NNTs**

Categorical results were also available. So the number of patients with 2 and 4 point ADAS-Cog improvement, and improved and worsened GERRI scores were provided. This allowed calculation of NNTs, which are shown in the Table for all patients and for just those with Alzheimer’s disease. For ADAS-Cog scores showing an improvement of 4 points or more, the NNT was 7.9 (4.2 to 67) for all patients and 6.3 (3.5 to 32) for those with Alzheimer’s disease.

This means that about seven patients have to be treated with 120 mg of Ginkgo extract daily for one year for one of them to have an improved ADAS-Cog score of four points which they would not have had with placebo. For a two point improvement, about four patients have to be treated for one year. For a patient’s family member to notice an improvement in their daily living and social behaviour about 7 patients have to be treated for one year.

**Comment**

High-quality clinical research in dementia will never be easy, but the authors of this study have done a brilliant job in making the study and its results transparent and usable. They comment on the clinical value of changes in the scores, particularly the ADAS-Cog score. They say that an improvement of four points may be equivalent to a six month delay in progress of the disease. But the trial does not permit conclusions about sustained effects, even though at one year it was longer than many studies in dementia. And because of the way in which they have made conservative decisions about the way data were treated, Ginkgo extract may be undervalued by their treatment.

But there is another point. The difference in ADAS-Cog score between treatment and placebo of 1.5 points after one year should be compared with 3.2 after treatment with donepezil for 14 weeks (though 12 weeks seems to be the time of peak improvement). There is a need for someone to define what is a useful outcome, and how long it must be sustained. As more treatments for dementia and Alzheimer’s disease appear, the need for some common sense to allow the right drugs to be used for the right patients at the right time increases.

What constitutes dementia to begin with? As the authors of the study on diagnosis comment, a diagnosis of dementia might mean not being able to drive, or make a will, or manage one’s own affairs. Prevalence estimates differing by a factor of 10 have huge implications for individuals and for health care planners. A paper published a few years ago [3] showed a 15-fold variability in Alzheimer prevalence. The authors concluded that methodological issues were to blame, but without being able to identify the sort of diagnostic criteria that were important. *Bandolier* thought that maybe the fact that the largest difference was between southern California and China might have given them a clue.

The ability to make an accurate diagnosis underscores the estimation of efficacy of any treatment. The implications are enormous.

**References:**

1. T Erikinjuntti, T Østbye, R Steenhuis, V Hachinski. The effect of different diagnostic criteria on the prevalence of dementia. New England Journal of Medicine 1997 337: 1667-74.
2. PL Le Bars, MM Katz, N Berman et al. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. JAMA 1997 278: 1327-32.
3. M Corrada, R Brookmeyer, C Kawas. Sources of variability in prevalence rates of Alzheimer’s disease. International Journal of Epidemiology 1995 25: 1000-5.
Asthma

Bandolier is frequently asked to “do more on asthma”. There is no “quick fix” because asthma is a complicated subject, but there are some good trials being done and at least one systematic review.

Inhaled steroids in childhood asthma

A systematic review from Toronto [1] picked up 24 randomised, double-blind, placebo-controlled studies published in English on inhaled steroids in children. All involved prophylactic inhaled steroids, and included trials with clinical outcomes like symptoms and concomitant drug use, or laboratory outcomes like lung function tests. The 24 studies involved 1087 children, and 5 studies examined only children dependent on oral steroids. Trial duration was from 4 to 88 weeks, but only eight of the studies were 12 weeks or longer.

Outcome reporting

Because of different outcome data in the original trials, the authors of the review tried to standardise treatment effect for clinical outcomes by using a relative improvement in mean (RIM) measure. This was calculated as:

\[
\text{RIM} = \frac{(\text{mean outcome placebo}) - (\text{mean outcome steroid})}{\text{mean outcome placebo}}
\]

This works for clinical scoring because higher scores are worse. They did the same for surrogate markers like use of \(\beta_2\) agonists and oral steroid use. Peak expiratory flow rate (PEFR) was as absolute mean increase in L/min.

Results

The main results are shown in the Figure, where results for each study are given together with the weighted mean value. There were improvements across the board, with only an occasional study failing to find benefit from inhaled steroids. As well as improvements in symptoms, there was also a reduction in concomitant \(\beta\)-agonist use, and 10 of 12 studies showed a reduction in the use of oral steroids by a weighted mean of 68%.

Twenty-three studies reported adverse effects, and six of these said that no adverse effects were found. Those reported were minor with no child stopping treatment because of them. No evidence of adrenal suppression was found in 12 studies that studied it. Nor was there any evidence of reduction in height velocity in eight studies, nor of cataracts in four studies.

Adding theophylline to inhaled steroid

A randomised, placebo-controlled and double-blind trial examined the effectiveness of 400 \(\mu\)g of inhaled budesonide together with 250 mg or 375 mg oral sustained release theophylline, or 800 \(\mu\)g inhaled budesonide [2]. All doses were twice daily for three months. The entry criterion for the 62 adult patients in the study was that they continued to have cough, wheeze or breathlessness despite inhaled steroid at a daily dose equivalent to 800 \(\mu\)g or 1000 \(\mu\)g budesonide.

Results

Treatment with the lower dose of budesonide plus theophylline resulted in greater improvements in lung function, but with no difference in daily symptom scores or use of \(\beta\)-agonists. A steroid-sparing effect was thought to be useful.
**Long-acting inhaled β-agonists**

A large randomised and double-blind trial in 852 adult patients examined the effects of the long acting inhaled β-agonist formoterol over one year [3]. The entry requirement was stable asthma assessed over a four week period. So 1114 patients were initially recruited, 852 randomised, and 694 completed a full one year of treatment.

There were four treatments, with each dose given twice daily and inhaled by means of a multidose turbohaler:

- 100 µg budesonide
- 100 µg budesonide plus 12 µg formoterol
- 400 µg budesonide
- 400 µg budesonide plus 12 µg formoterol

The main outcome measure was the number of severe and mild exacerbations of asthma per patient per year. Severe exacerbation was defined as one needing treatment with oral glucocorticoid, or a decrease in PEFR to more than 30% below baseline for two consecutive days. Mild exacerbations were defined as PEFR more than 20% below baseline, use of more than three additional uses of inhaled therapy a day, or waking at night because of asthma.

**Results**

There were fewer exacerbations, mild or severe, with higher doses of steroids and with the addition of formoterol (Table). The effects of higher steroid and formoterol appeared to be additive. The proportion of patients with episode free days (no symptoms, no use of medications, and a PEFR of more than 80% of baseline) were higher with higher doses of steroid and with addition of formoterol.

For patients without severe exacerbations a similar trend was seen. But because absolute numbers could be calculated from the data, numbers needed to treat can be derived. Thus increasing the dose of budesonide from 200 µg to 800 µg a day gave an NNT of 9.5 (95% CI 6 to 22) for a patient to be free of severe exacerbation of asthma for one year. Adding formoterol 24 µg per day to budesonide at whatever dose used gave an NNT of 11 (6.6 to 34) for a patient to be free of severe exacerbation of asthma for one year. Adverse effects seemed to be mild and evenly distributed throughout the groups.

**Comment**

There are a number of national and international guidelines on asthma management and prevention, and those are the obvious places for prescribers to go for advice. A recent MeReC bulletin gives information on the updated British Thoracic Society’s guidelines [4].

The systematic review on inhaled steroids in children underpins some of the recommendations. The other two trials contain information which may form part of future guidelines, and both typify some of the high-quality clinical research that is ongoing.

**References:**

1. C Calpin, C Macarthur, D Stephens, W Feldman, PC Parkin. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systematic review of the literature. Journal of Allergy and Clinical Immunology 1997 100; 452-7.
2. DJ Evans, BA Taylor, O Zetterstrom et al. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide more moderate asthma. New England Journal of Medicine 1997 337; 1412-8.
3. RA Pauwels, C-G Löfdahl, DS Postma et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. New England Journal of Medicine 1997 337; 1405-11.
4. New guidelines for the treatment of asthma. MeReC Bulletin 1997 8: number 4.
DIAGNOSIS OF ACUTE SINUS INFECTIONS

There are times when papers are so good that one wants to jump for joy, or weep because one hasn’t done it oneself. Bandolier felt this way about a beautiful demonstration of how to sort out diagnosis, in this case diagnosis of acute sinus infections in primary care [1].

Study

It was a prospective study of 357 patients intended to examine a range of symptoms and signs, and simple blood tests against computed tomography in the diagnosis of acute sinus infection. Some people couldn’t be included (pregnant women, for example), some didn’t want a scan, and pressure on scan time meant that not all could be scanned. Information was therefore available on 201 people.

They had all received a diagnosis of acute sinus infection and were considered to be in need of antibiotic therapy. A host of symptoms and signs were recorded, and within two days of the clinical diagnosis they had a CT scan which included the entire nasal cavity and the paranasal sinuses. The scans were interpreted independently by two radiologists, with re-evaluation and consensus in case of disagreement. Sinusitis was defined as total opacification or fluid level in an ethmoid, sphenoid, frontal or maxillary sinus.

Altogether 17 symptoms and 10 signs were examined, together with results of ESR, C-reactive protein and white blood counts.

Results

In the 201 patients who underwent a CT scan, 127 (63%) had acute sinus infection diagnosed by the CT scan. When the signs, symptoms and blood tests were subjected to logistic regression analysis, it was found that only four were significantly associated with presence of infection. They were:

1. Purulent secretion in cavum nasi
2. Purulent rhinorrhoea
3. Double sickening
4. ESR >10 mm/hr

“Double sickening” was defined as the presence of two phases in the illness history.

The likelihood ratios calculated for the presence of 0, 1, 2, 3 or 4 of these signs and symptoms in 199 of the 201 patients are shown in the Table.

Comment

The implication of these findings are that acute sinusitis is over-diagnosed in primary care (though that has been shown before). For Norwegian GPs, a putative diagnosis of acute sinusitis is likely to be correct 63% of the time. If a patient has the four relevant signs and symptoms, that post-test probability increases to over 95%, with 3 of the four to about 80%. But if there are none, there is only a 15% chance that the patient has sinusitis.

Can this be applied generally? There is no obvious reason why not (Norwegian GPs usually have ESR and other testing available on site). In any event, this award-winning paper shows “how to do it” in sinusitis and in any other area. A pleasure and privilege to read, and a “must have” for anyone seriously interested in making evidence count in diagnosis.

References:
1 M Lindbøk, P Hjortdahl, U Johnsen. Use of symptoms, signs, and blood tests to diagnose acute sinus infections in primary care: comparison with computed tomography. Family Practice 1996 28: 183-8.

| Number of signs and symptoms | Sinusitis present | Sinusitis absent | Likelihood ratio |
|-----------------------------|-------------------|------------------|-----------------|
| 4                           | 43                | 1                | 25.2            |
| 3                           | 41                | 13               | 1.8             |
| 2                           | 32                | 23               | 0.8             |
| 1                           | 8                 | 22               | 0.2             |
| 0                           | 2                 | 14               | 0.1             |
| Total                       | 126               | 73               | ---             |
INTENSIVE INSULIN TREATMENT AND HEART ATTACK

Diabetic patients are more likely to die after a heart attack than those without diabetes. A randomised trial of intensive insulin therapy (DIGAMI trial from Sweden) compared with usual treatment demonstrates that death rates can be reduced by 33% in the three and a half years after a heart attack.

Patients

Included patients were those with an acute myocardial infarction and a blood glucose of more than 11 mmol/L. In the treatment group they were given an insulin-glucose infusion for at least 24 hours (according to a defined protocol), followed by subcutaneous insulin for at least three months.

Results

In the first year after their heart attack, 58/306 treated patients died, compared with 82/314 controls. Cause of death was cardiovascular in 97% of cases in this first year. Over a mean follow up of 3.4 years there were 138 deaths (44%) in the control group and 102 (33%) in the treated group. The 95% confidence interval around the mean reduction in death rate of 28% was 5% to 45%.

The main results (as NNTs) are in the Table. The one-year NNT was 14 and the 3.4 year NNT was 9. This means that nine patients with heart attack and blood glucose >11 mmol/L have to be treated with insulin therapy for one of them to be alive 3.4 years later, who would not have been if they had been given usual care.

There was a pre-defined low-risk group (younger, no history of heart disease) with no previous insulin treatment, to which 44% of the enrolled patients belonged. For them, the NNT was 7.

Comment

Here is an excellent study from a good stable (Karolinska) and with a background of biological plausibility. The trial isn’t enormous, and the confidence interval around the outcome is wider than we may like. But an NNT of 7 is a worthwhile figure, because it refers to mortality rather than some minor outcome, and because the intervention - getting control of hyperglycaemia - is one we might want to do anyway.

Reference:

1 K Malmberg. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. British Medical Journal 1997 314: 1512-5.

HTA PUBLICATIONS

There is now a steady output from the NHS R&D Direc-
torates Health Technology Assessment Programme. Ban-
dolier has reviewed some of these, but they are exhaus-
tive and we are finding it hard to keep up. A list of publi-
cations follows:-

1 Home parenteral nutrition
2 Diagnosis, management and screening of early localised prostate cancer.
3 The diagnosis, management, treatment and costs of prostate cancer in England & Wales.
4 Screening for fragile-X syndrome
5 A review of near patient testing in primary care.
6 Systematic review of outpatient services for chronic pain control.
7 Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
8 Preschool vision screening.
9 Implications of socio-cultural contexts for the ethics of clinical trials.
10 A critical review of neonatal hearing screening in the detection of congenital hearing impairment.
11 Neonatal screening for inborn errors of metabolism: a systematic review.
12 Routine preoperative testing: a systematic review of the evidence.
13 Systematic review of the effect of laxatives in the elderly.

Details about the reports and how to obtain them can be obtained from NCCHTA in Southampton. Their fax number is +44 (0) 1703 595639 and email on hta@soton.ac.uk. They can be also found on the Internet at http://www.soton.ac.uk/~wi/hta.

Main results of DIGAMI study: effect of intensive insulin treatment on mortality

| Patient group          | Mortality at year | NNT (95% CI) |
|------------------------|-------------------|--------------|
| All patients           | 1                 | 14 (7.3 to 164) |
| All patients           | 3.4               | 9.4 (5.5 to 33) |
| Low risk, no insulin   | 3.4               | 7.2 (4.1 to 27) |
A STRANGER TO THE LAVATORY

Laxatives are big business. Over 11 million GP prescriptions were dispensed in England in 1996, apart from over-the-counter sales. Many people have a real or imagined problem with their bowels. So when two linked systematic reviews recently landed on Bandolier’s desk they were eagerly grasped for some answers. Alas - all is not as clear as it might be.

The first [1] review of 36 trials wasprecised in Bandolier 46. The authors chose mean bowel movement frequency per week. Overall findings showed that laxatives and fibre consistently increased bowel movements compared with placebo (an extra 1.5 bowel movements per week) although there was no conclusion as to the relative merits of laxative or fibre. One of the possible criticisms was that most of the studies were conducted in populations in which the control groups had more than 3 bowel movements a week when one definition of constipation is fewer than three movements a week.

A second review from the Health Technology Assessment stable [2] starts with the epidemiology of constipation (which is really interesting) and definitions of constipation, followed by methods of clinical management. The search was based on the Tramonte article, widened to include a number of other databases and also non-English language papers. It evaluated treatment in the elderly and excluded papers for participants under the age of 55. Without information that elderly patients respond differently, this may not have much logic. The meta-analysis doesn’t add a lot, and there are a few errors, which is a pity. In direct comparison treatments, a comparison of magnesium hydroxide versus laxamucil reports laxamucil as more effective but the text reports magnesium hydroxide as being more effective than laxamucil.

Where does this leave things? There is evidence that laxatives and fibre increase bowel movements but we still do not know how well they work. In spite of the paucity of evidence some £45M of laxatives are dispensed in England every year. Money down the drain?

References:
1. SM Tramonte, MB Brand, CD Mulrow, et al. The Treatment of Chronic Constipation in Adults - A systematic review. Journal of General Internal Medicine, 1997 12: 15-24.
2. M Petticrew, I Watt, T Sheldon. Systematic review of the effectiveness of laxatives in the elderly. Health Technology Assessment 1997 1: No 13.

NTRAG

The North Thames Research Appraisal Group (NTRAG) offers a wide range of critical appraisal skills training for healthcare professionals. Tutored by experts in the field, our 1998 Improving Clinical Effectiveness programme will improve your ability to assess a wide range of medical evidence in terms of its validity and relevance to clinical and management decisions.

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SOUND AND FURY

Routine preoperative testing is big business. Many, perhaps most patients coming for surgery have a range of preoperative tests done, including biochemistry, haematology, ECGs and X-ray, and others. Are they necessary?

A great review of the evidence [1] suggest that for the most part they are not. The authors provide all the evidence necessary for test providers to sit down with consumers to discuss what makes sense to do, and what can be dispensed with. Rational choice could save much money and make things less complicated. And more important, there are important hints about where doing tests does make sense.

This HTA review is a must for laboratories and surgical teams.

Reference:
1. J Munro, A Booth, J Nicholl. Routine preoperative testing: a systematic review of the evidence. Health Technology Assessment 1997 1: No 12.