Reaching a century is a chastening experience that could be a trigger for introspection or celebration. Bandolier chooses neither. Life is too short for introspection, and we’re too tired for celebration, so instead another ordinary issue.

There are similarities with issue 1 in 1994. That examined the GRIP project - getting research into practice. Now we are looking at the consequences of getting research evidence into practice in South Derbyshire, with a 30% fall in the chance of dying after a heart attack between 1995 and 1999.

Once getting research results into practice is accepted to be a good thing, the next problem is how to do it well. A randomised trial of coaching from Melbourne shows how simple telephone interventions can help patients achieve a target cholesterol level. And with statin prescribing going through the roof, time to consider rare adverse effects, and look for them.

Electronic Bandolier

The Internet version of Bandolier continues to expand and the PDF download of the 12-page Bandolier Extra on migraine is popular. With the addition of the trial on cannabis and MS, the review of this topic is complete for now. The site on gout continues to expand as more papers are found, and articles on atrial fibrillation and ENT topics have been added. The next task is a brief review of the evidence for Lorenzo’s oil for adrenoleukodystrophy.

Subscribing to Bandolier

The sad thing is that this 100th issue of Bandolier will be the penultimate one under present arrangements. Central funding ends after issue 101. So if you want to continue to have a paper copy after July, you should complete the form on page 8.

Of course, evidence itself is without effect. Putting evidence into action is when we should get the benefits. But do we? Demonstration that use of evidence makes a difference is something that many of us want to see. A report from Derbyshire [1] indicates that for mortality after heart attack, we are beginning to get big gains.

Study

This took place in the health district of South Derbyshire, which has a population of 560,000 with common computerised patient administration and pathology systems. All patients admitted with a coding of acute myocardial infarction over the five years of 1995 to 1999 were obtained, with information from the pathology system about measurements for creatine kinase. Excluded were patients with a coding of myocardial infarction but who had no creatine kinase measured, about 4% of the total. The pathology database was also interrogated for blood lipids in the year after the date of admission.

Results

There were 5,166 admissions over the five years, two thirds men and two thirds under 75 years old. Creatine kinase tests were requested on 4,912 of them, and 3,382 survived at least one year.

Within 30 days 396 died (13%), and within one year 585 died (19%). There was a 9% (95% confidence interval 4 to 13%) per year fall in the 30-day mortality, for men, women, and younger and older patients. For one-year mortality, the
results suggest, though do not specifically state, that there was a 7% a year decline. Mortality was higher in women than men and for patients aged over 75 years compared with those aged between 35 and 74 years.

The proportion of one-year survivors having a blood lipid measurement increased over the five years, especially so in those over 75 years (Figure 1). Among those admitted, and who had a lipid measurement, the proportion whose latest total cholesterol measurement within 12 months of admission was below 5 mmol/L rose dramatically, though was lower for women than men (Figure 2). Similar trends were seen with respect to low density lipoprotein.

Comment

Year-on-year improvements like these are important. In South Derbyshire, the chance of a 50-year old man dying within the first year had fallen by about 30% in 1999 compared with 1995. This big improvement was brought about by many factors, and will probably be better in 2002 than it was in 1999. Over the five years as whole, one year mortality was 19%, and that has to be compared with 28-day mortality of up to about half in Glasgow in the 1980s.

Evidence from major outcome studies, like the 4S study with statins, has helped change practice. More people now have blood tests for lipids after a heart attack, and most meet targets for lowered cholesterol. This is just one factor underlying the improvements, but there will be others, including more use of aspirin, or beta-blockers, or ACE-inhibitors, and better cardiac rehabilitation, and better primary care attention.

It is not just one piece of evidence, but many pieces of good evidence used appropriately that continues to make a difference. We’ve come a long way, but with further to go. Evidence matters!

Reference:
Perhaps what this study shows is that the informed (resourceful?) patient is a powerful being. When patients are encouraged to take more responsibility for their own medical management, linked to a specific goal, they seem to get better results and reduce the gap between the ideal of clinical trials and the real world. Why is this not a surprise?

<table>
<thead>
<tr>
<th>Drug + coaching (67)</th>
<th>4.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug - coaching (67)</td>
<td>5.4</td>
</tr>
<tr>
<td>No drug + coaching (40)</td>
<td>5.4</td>
</tr>
<tr>
<td>No drug - coaching (45)</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Total cholesterol (mmol/L)

Perhaps obesity is a health problem all of us know about, and which concerns many people. A tablet that helped lose weight is something many of us would welcome, and some drug therapies are available. A frequently-asked question is whether anti-obesity drugs work, and how well they work?

We now have two excellent reviews from Health Technology Assessment, which can be downloaded in full from the Internet at no cost [1,2]. Bandolier thought it might be useful to provide a thumbnail of the results to try and answer the frequently-asked questions.

**Orlistat [1]**

This review sought randomised trials of any duration of therapy or length of follow up (with a minimum duration of one year from company submissions to NICE). Participants had to be overweight or obese, or who wished to maintain weight loss having previously been overweight or obese. Trials of people with eating disorders, or with healthy weight were excluded. Orlistat could be combined with other strategies like dietary restriction or behavioural programmes. Controls could be placebo, other anti-obesity agents, or alternative interventions like dietary regimens or physical activity or behavioural modification. Outcomes were obesity or overweight status, like body weight, fat content or fat distribution.

**Results**

Four trials with a one-year outcome had 1274 patients given orlistat 120 mg three times a day and 837 patients given placebo. At baseline BMI was in the range of 28 to over 40 kg/sq metre. The overall weight loss was 2.9 kg (95% confidence interval 2.2 to 3.6 kg).

In four trials, at least 5% reduction in body weight at one year was achieved by 661/1144 (58%) of people on orlistat 120 mg three times a day compared with 225/705 (32%) on placebo (Figure 1). The relative benefit was 1.6 (1.5 to 1.8) and the number needed to treat compared with placebo was 3.9 (3.3 to 4.6) (Table 1).

Reference:
In five trials, at least 10% reduction in body weight at one year was achieved by 460/1388 (33%) of people on orlistat 120 mg three times a day compared with 146/951 (15%) on placebo (Figure 2). The relative benefit was 1.9 (1.6 to 2.3) and the number needed to treat compared with placebo was 5.6 (4.7 to 6.9) (Table 1).

Gastrointestinal adverse effects were mentioned in most trials, but no analysis is given, nor probably was possible. Adverse event withdrawals in four trials at one year were no different for orlistat (97/1178, 8%) or placebo (44/739, 6%). In an economic analysis the report tells us that treating 100 patients with orlistat for two years will cost about £73,000. The cost per quality adjusted life year gained is about £46,000 with a range of £19,000 to £55,000.

**Sibutramine [2]**

The format of the review of sibutramine, including trial inclusion, exclusion, and outcomes was broadly similar to that for orlistat. Many trials were of short duration.

The most useful outcome was that of at least 5% reduction in body weight at six months. In two trials that reported it, this was achieved by 130/205 (63%) of patients on 10 mg sibutramine daily, compared with 52/202 (26%) on placebo. The relative benefit was 2.5 (1.9 to 3.2) and the number needed to treat compared with placebo was 2.7 (2.2 to 3.5) (Table 1). No clear analysis of adverse events seemed possible. Estimates of cost per quality of life gained varied from £5,700 to £35,200, though with reservations.

**Comment**

Obviously there is much, much more in these reports than is abstracted here. The great thing is that those of us with an interest can download them from the HTA Internet site and read them at our leisure and make up our own minds.

On the face of it these are reasonable clinical results. But adverse events have to be weighed against efficacy, and, as usual, this seems to be a bit of a black hole. There are other methodological issues. One, for example, is that of how patients were recruited. This was sometimes through advertisements, sometimes through hospitals, but there is a residue of uncertainty over whether the people in these trials were like our patients. Another involves what to do about withdrawals. Some trials used a method where the last actual measurement was carried forward for missing data. In this situation, this may not be a conservative way of doing things, and may overstate treatment efficacy.

Then there is the uncertainty over cost effectiveness. The imputed costs per quality of life year gain were high. Perhaps there are better ways of spending money to help overweight people who want to lose weight.

**Pointy-head point**

Of interest to all those learning or teaching critical appraisal skills, this concerns calculating NNTs. In both these reports dichotomous outcomes like the number of patients with a particular level of weight loss at a particular time was reported as percentages. The figures were used (X/100 for treatment, Y/100 for placebo for trial 1, A/100, B/100 for trial 2) in RevMan to calculate relative risks.

But the numbers of patients were different from 100, and different trials had different numbers of patients. The weight we give each trial is more or less dependent on the number of patients. So the method used had incorrect weighting.

Actually relative risks are about right, though confidence intervals will not be. NNTs can be wrong, as Table 1 demonstrates by showing the calculations in the right and wrong way. If, as with sibutramine, there is not much difference in total numbers, the effect will be slight. Where the difference is large, and especially where trial sizes are very different, the effect will be greater, as with orlistat.

**Bandolier** doesn’t wish to be picky about two good reports, but there is a lesson for us. We all make mistakes. This mistake was not picked up by the authors, their advisors, their reviewers, or the companies making the products (as best we can tell). Crass mistakes will get through. In the end it is our responsibility to know enough of the basics to pick up mistakes made in good faith.

References:


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**Table 1: Calculating the NNT the right way and the wrong way**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Outcome</th>
<th>Right way</th>
<th>Wrong way</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number/Total (%)</td>
<td>NNT (95%CI)</td>
</tr>
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<td>--------------------</td>
<td>----------------------------------------------</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Orlistat 360 mg</td>
<td>At least 5% weight reduction at one year</td>
<td>661/1144 (58)</td>
<td>3.9 (3.3 to 4.6)</td>
</tr>
<tr>
<td>daily</td>
<td></td>
<td>225/708 (32)</td>
<td></td>
</tr>
<tr>
<td>Orlistat 360 mg</td>
<td>At least 10% weight reduction at one year</td>
<td>460/1388 (33)</td>
<td>5.6 (4.7 to 6.9)</td>
</tr>
<tr>
<td>daily</td>
<td></td>
<td>146/951 (15)</td>
<td></td>
</tr>
<tr>
<td>Sibutramine 10 mg</td>
<td>At least 5% weight reduction at six months</td>
<td>130/205 (63)</td>
<td>2.7 (1.9 to 3.5)</td>
</tr>
<tr>
<td>daily</td>
<td></td>
<td>52/202 (26)</td>
<td></td>
</tr>
</tbody>
</table>

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Bandolier 100
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POLYNEUROPATHY AND STATINS

Myopathy is a recognised risk associated with the use of lipid lowering drugs. In general practice in the UK one estimate is that the incidence of myopathy in users of lipid lowering drugs is 2.3 per 10,000 person years, with a relative risk compared with nonusers of 42 for fibrates and 8 for statins [1]. A new study [2] tells us that polyneuropathy is also likely to be a problem, and that it needs looking at.

Study

This was conducted in a county of Denmark with a population of 465,000. Residents have a civil registration number that is used in discharge prescription registries, so that it is possible to find all residents with a particular disorder, and find out what drugs they have been prescribed.

In a five-year period to the end of 1998, all patients with a discharge of polyneuropathy were examined. Some lived elsewhere, some were diagnosed before the study period, some had predisposing conditions (renal failure, diabetes, thyroid, and others had no proper diagnosis or were wrongly diagnosed. Clinical diagnostic features were distal symmetric sensory symptoms or symmetric motor symptoms and no upper motor neurone signs, or both. Neurophysiological criteria were abnormal conduction in two or more peripheral nerves, with at least one being a leg nerve.

A diagnosis of peripheral neuropathy was only accepted if both clinical and nerve conduction criteria were compatible with the diagnosis. Several levels of confidence were defined for idiopathic polyneuropathy (Table 1).

For each case, all inhabitants of the same sex and age were used to randomly choose 25 control subjects per case.

Results

There were 166 cases (mean age 59 years) of first time diagnosis of polyneuropathy in the five years, of which 35 were definite, 54 probable, and 77 possible. Of these nine (5.4%) had a previous exposure to statins (eight current users), with a median duration of 2.8 years. There were 4,150 controls, of whom 66 (1.6%) had exposure to statins (49 current users).

Table 1: Definition of diagnosis of polyneuropathy

<table>
<thead>
<tr>
<th>Description</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Definite</td>
<td>Adequate work up and tested for exclusion diagnoses and conditions, and no apparent cause of neuropathy established</td>
</tr>
<tr>
<td>Probable</td>
<td>Only sufficient information to rule out alcohol overuse, diabetes and renal insufficiency</td>
</tr>
<tr>
<td>Possible</td>
<td>Information not sufficient to ascertain presence or absence of any exclusion diagnosis</td>
</tr>
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</table>

Table 2: Statin exposure in all cases and definite cases of polyneuropathy

<table>
<thead>
<tr>
<th>Statin exposure</th>
<th>Cases</th>
<th>Controls</th>
<th>Odds ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never use</td>
<td>157</td>
<td>4084</td>
<td>1</td>
</tr>
<tr>
<td>Current use</td>
<td>8</td>
<td>49</td>
<td>4.6 (2.1 to 10)</td>
</tr>
<tr>
<td>Definite cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never use</td>
<td>27</td>
<td>854</td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>7</td>
<td>17</td>
<td>16 (5.7 to 45)</td>
</tr>
</tbody>
</table>

The relative risk of polyneuropathy for current users was 4.6 (2.1 to 10) for all cases with current use, and 16 (5.7 to 45) for definite cases with current use (Table 2). Odds ratios were higher for more than two years of use compared with less than two years, and for larger numbers of doses than smaller numbers.

The number needed to harm (NNH) based on all patients was calculated as 5,500 (2,200 to 18,500). In those over 50 the incidence of polyneuropathy in the background population was 1.7 per 10,000 person years, with an excess rate of 4.5 per 10,000 person years among those exposed to statins. That is roughly one excess case of polyneuropathy for every 2,200 (880 to 7,300) person years of statin use.

Comment

In 1998 about 1% of the Danish population used a statin. It’s probably more now, both in Denmark and elsewhere. If a PCO with 100,000 inhabitants had 1% taking statins, a case of polyneuropathy might be expected every second year. That’s twice as frequent as a case of myopathy.

In primary care in England in 2001 there were about 13 million prescriptions for statins, at a cost of about £420 million. It is not possible to extrapolate too much from that, other than to conclude that with so much statin use, these rare adverse events will occur and should be noticed. Awareness of that may be important in limiting their impact.

This is a powerful and interesting paper, demonstrating how good government information systems can be used for the good of its population. It is important in understanding risk, though not of causation nor mechanism. Papers in the journal Neurology are freely available on the Internet. If you think you want to read this one, then read also an thoughtful accompanying editorial [3].

References:

CANNABIS FOR MULTIPLE SCLEROSIS

The use of cannabis to control spasticity in multiple sclerosis is a hot topic. Bandolier has gathered together all the relevant references in a survey on the Bandolier Internet site. One of the more interesting is a wonderful description of the use of cannabis for treating a variety of conditions in India, by a Dr O’Shaughnessy in 1842. Another acutely observed description comes from a Dr Reynolds, FRS and Physician to Queen Victoria.

But added together, there really is little evidence for efficacy. Small randomised trials show no objective benefit, and most are case reports of one or a few patients. All are self-selected, though occasionally test-retest was usually positive. There is a large trial on cannabis and tetrahydrocannabinol currently ongoing in the UK. In the meantime, a small randomised trial holds out little hope [1].

Trial

This was a randomised crossover trial of placebo, THC and plan extract given orally in sixteen patients with progressive MS and spasticity. Four weeks of treatment with placebo, 2.5-5 mg THC, or plant extract with equivalent THC (identical appearance) was followed by four weeks of washout before the next treatment. A lower dose was used for two weeks, and doubled, if well tolerated, for the second two weeks of treatment.

Muscle tone was measured on a categorical scale (0=normal, 1=slight increase, 2=more marked increase, 3=considerable increase, 4=limb rigidity in flexion or extension) for arms and legs. Patients had to have a score of at least 2 for inclusion. EDSS and several other tests of function and amputation were used.

Results

Six of the 16 patients had primary and 10 secondary progressive MS. The average age was 46 years, with MS for an average of 15 years, and the mean EDSS score was 6.2. All completed all scheduled visits for all three treatments.

Active treatments conferred no benefit. Plant extract, but not THC, had significantly more adverse events. Five patients on plant extract reported subjective increased spasticity and one had an episode of acute psychosis.

Comment

Not much hope of benefit from this trial, and some suggestion of harm. The trial was good, but small, and we still have to wait for the big UK study. Bandolier will continue to add emerging evidence to its Internet site as it appears, and would be grateful if readers could tell us about evidence we may have missed.

References:

BOOK REVIEWS


If you think this book will tell you how to implement evidence-based patient choice, then don’t buy it. It won’t do that, and, if you thought about it for a moment, you would recognise that it never could. There are too many variables before we even get to how we differ as individuals.

No, what this book does is to make you think about the issues that might be important to influence patient choice. Having a cast list that includes the usual suspects gives the book power, and the editors seem to have given them a thoughtful pill before they started writing.

Obviously risk is discussed at some length, and there is a mine of interesting references and perspectives that make one realise that there’s more to this than meets the eye. And what about complex issues like the interaction of health economics and patient choice. It’s covered, and well. But the most gripping chapter is Angela Coulter’s vision of the future, which makes you realise just how much change there is to come. Before the last chapter, evidence-based patient choice could still be an option. After it, there’s simply no argument.


Whatever job Muir Gray does, it’s the wrong one. He should just be given the task of going around talking to people about healthcare, inspiring us with the knowledge not just that things could or should be better, but that we can help make it so. The use of sharp, often painful, little stories reminds us that neither life nor medicine are easy. They also point out that worst impact of the sharpest problems can be ameliorated by good judgement and common sense leveraged with some learning and understanding.

The theme of this offering is the contract between doctor and patient. It looks at the history, at what we are doing now, at our perspectives, what’s right and what’s wrong. And it’s not heavy when it does it, so reading it does not weigh us down with a sense of guilt. Rather it helps us see the vision through the fog of everyday problems.

♦ It can be summarised by the new contract between doctors and patients that he espouses. Both patients and doctors know:
♦ Death, sickness and pain are part of life.
♦ Medicine has limited powers, particularly to solve social problems, and is risky.
♦ Doctors don’t know everything; they need decision making and psychological support.
♦ We’re in this together.
Politicians should refrain from extravagant promises and concentrate on reality.

Doctors should always be open about their limitations.

Patients can’t leave problems to doctors.

Muir Gray is perhaps too gentle with politicians, but it certainly cuts to the chase. And this is a new type of book, and ebook, with associated web site (www.resoucefulpatient.org) where you can buy it, or dip in. You can have the best of both worlds: a paper copy to read in bed or on the train, and a look up when you are wired into your computer.

What makes this publication interesting is that it is continually being updated, and updated versions of the website will also appear in print, instantly. There is no large print run, but "print as required". If you order it from the Internet, your book could be printed with 5, or 10, of 15 others. What you get will be the most up-to-date version.


Some very clever people have written editorials warning us of the tidal wave of older people with arthritis that is set to engulf us over the next two decades. And it is more than pill-pushing this. Bandolier has already looked at the large amount of untreated chronic pain in the community (Bandolier 70), and looked at evidence that musculoskeletal problems like arthritis havbe the largest negative impact on quality of life of any chronic disease (Bandolier 83). Put this together with the demographic changes we know about, and it all adds up to a big heap of trouble, most of it landing in the lap of primary care.

This is already a big job in primary care, with up to 20% of GP time taken up with musculoskeletal problems. So managing osteoarthritis in primary care is a useful title for a book. This one is written by GPs for GPs, and that probably makes it unique, and is one reason that it combines the two important qualities of brevity and relevance.

The language is simple and straightforward. The organisation is logical. The diagrams are super. It is practical, and it uses good evidence. Yet it’s not a cook book, but a "tools, not rules" book.

The section on diagnosis, differential diagnosis and misdiagnosis is just terrific. Can you remember the names and positions of all those hand and wrist bones? Don’t worry, there’s a simple diagram. Taping the knee? There’s a simple diagram. Want to use a “three-pot system” to minimise cost and harm, and maximise efficacy? It is simply explained.

After two years the book could do with a brush up to include more advice on cox-2 inhibitors and brush up internet addresses, but those are tiny quibbles set against masses of good sense. The important thing about this book is its voice - calm, direct, and sensible. What would be even better would be to see this approach evolve in two ways. First to become a ebook, with an accompanying website, and second to expand into other musculoskeletal areas.

Many readers have contacted us with a concern that with the changed arrangements for Bandolier in print, the Internet version would either cease, or become a site for which entry would only be by password and/or subscription. To put minds at rest, neither of these disasters will happen. To make things clear, we’ll tell you how we do it.

Free of charge, not free of cost

The Internet version of Bandolier will be free of charge, as it is now. That means free of charge to you, but not free of cost to us. We cannot do it for nothing. The costs of running an Internet site are minimised because there’s no printing and distribution, and we get a lot of help.

Oxford University Medical School provides the server space and facilities to ensure access for the 150,000 visitors each week to the particular medical school server. That is a big proportion of the total traffic, so the service they provide is not negligible. They also provide the search engine.

The Oxford Pain Relief Trust, a charity, provides the offices in which we work. Pain Research funds pay the rent.

The bulk of the work is in maintaining the site (now with over 3,000 files, and over 100 Mb), and in updating stories already there and writing new ones at the rate of 10-20 a month. Most of that work, plus all the administration, is funded through sponsorship, from charities, industry, and a very, very, small proportion from the NHS.

You can help

We work very hard at getting sponsorship to be able to run and expand Bandolier. You could help by mentioning the possibility of sponsorship to your employing organisations. Bandolier needs a continual stream of sponsorship to cover the costs that keep the Internet service free of charge to you.

It would also help if folks stopped pointing out that there is no need to pay for paper copies because Bandolier is free on the Internet. It may be true, but it doesn’t help our morale. In coming months we will add a section to the site outlining how people using only the Internet version can contribute voluntarily to the cost of running it. That will help us maintain our independence from industry and government.