

## UPDATE ISSUES

This issue of *Bandolier* is mostly about updating stories from previous months and years. Why update? For a number of reasons, but these boil down to quantity and quality.

### Quantity and quality

Quantity may be just a reflection of time. Over even a few years trials may be completed and published which just weren't available earlier. Newer trials may be larger, or done to higher standards, or may concentrate more on important outcomes. An example is the review in this issue on outcomes after epidural analgesia for labour compared with parenteral opioids. A review from 1994 suggested that a higher Caesarean section rate was associated with epidural analgesia. A new review, with more than 10 times as many patients, says that there is no difference.

Quality may reflect other factors, some as simple as search strategies. An example is a new review on the effect of exercise on bone mass in women. The new review found many more studies than a similar review published less than a year ago.

### Getting better

The point is that our knowledge base continues to strengthen as more and better systematic reviews appear. Reviews are also beginning to concentrate more on outcomes that are important to patients and practitioners, rather than just on outcomes that are measurable. We feature a review looking at definitions of a cure for fungal toenail infections as an update on a story in *Bandolier* several years ago.

### eBandolier

The divergence between what appears in the paper version of *Bandolier* each month, and what appears on our Internet site will continue to grow. Many of you like the Oxford Pain Internet Site. Plans are being laid to extend the idea of concentrating and summarising knowledge in various areas. About 14 target areas have been identified for similar treatment, including evidence-based healthy living, palliative care, and possibly diagnostic testing. It all depends on getting the resources to do the work, but expect major changes over the next year. The aim is to provide accessibility to all with Internet access, free, and understandable. Ideas and comments welcome.

## BONE MASS AND EXERCISE IN WOMEN

*Bandolier* 62 examined a systematic review [1] of how exercise affects bone mass in postmenopausal women. It was disappointing, with only six studies and only two of those randomised. Another, better, review has now been published, with many more studies, much more data, and with comprehensible and useful results [2].

### Searching

The new review had a comprehensive search strategy to identify randomised and non-randomised controlled trials looking at the effects of training programmes on bone mass. Journals were also hand searched.

Included studies had to meet several criteria:

- ◆ Length of training programme at least 16 weeks.
- ◆ Relevant outcome was bone mineral density measured by established techniques.
- ◆ Lumbar spine or femoral neck measurements because these are at risk of osteoporotic fracture.
- ◆ Separate analyses for pre and postmenopausal women.
- ◆ Separate analyses for women and men.
- ◆ Good data presentation to allow calculation of treatment effect and variance.

### Outcome

A study treatment effect was calculated, which was the difference between the percentage change in bone mass in one year in the training group minus the percentage change in bone mass in one year in the control group. A positive figure indicates a protective effect of exercise.

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*The views expressed in Bandolier are those of the authors, and are not necessarily those of the NHSE*

## Results

There were 34 randomised comparisons and 19 non-randomised, beautifully laid out in tables in the paper, in training programmes ranging from six to 24 months.

The effects of training on bone mass at the lumbar spine in 552 postmenopausal women are shown in Figure 1. The overall treatment effect was a one-year percentage difference due to training of 0.79% for endurance and strength training programmes. For 204 premenopausal women there was a 0.91% benefit.

The effects of training on bone mass at the femoral neck in 409 postmenopausal women are shown in Figure 2. The overall treatment effect was a one-year percentage difference due to training of 0.89% for endurance and strength training programmes. For 174 premenopausal women there was a 0.90% benefit.

In both cases, non-randomised studies produced an estimate that was roughly twice as large as for randomised studies. Data from non-random studies are not included here.

## Comment

The bottom line from the new review is that exercise training programmes prevented or reversed bone loss of almost 1% per year compared with the controls. The effects were consistent for the lumbar spine and the femoral neck. The variability in the results was seen mostly in the smaller trials, and the larger trials showed results consistent with the overall effect (Figures 1 and 2).

The notable feature is that two systematic reviews published within about a year of each other had such a different clutch of randomised trials. In part this reflects the later cutoff point for searching, with several studies published in the mid-1990s that were likely to have been missed by the earlier review. In part it reflects a much more comprehensive search strategy.

The result is important – yet another benefit of exercise for womens' health. Most of the exercises were somewhat more vigorous than a brisk walk and included treadmill walking and running, and some resistance and back strengthening exercise or aerobics, for instance. Taken together, these are also a useful teaching aid for critical appraisal.

There is also a cautionary tale here for reading systematic reviews. If the amount of information found is small, perhaps with a few trials and tiny numbers, then the chances of the review being correct is diminished.

### References:

- 1 GA Kelley. Aerobic exercise and bone density at the hip in postmenopausal women: a meta-analysis. *Preventive Medicine* 1998 27: 798-807.
- 2 I Wolff et al. The effect of exercise training programs on bone mass: a meta-analysis of published controlled trials in pre- and postmenopausal women. *Osteoporosis International* 1999 9: 1-12.

Figure 1: Lumbar spine - postmenopausal

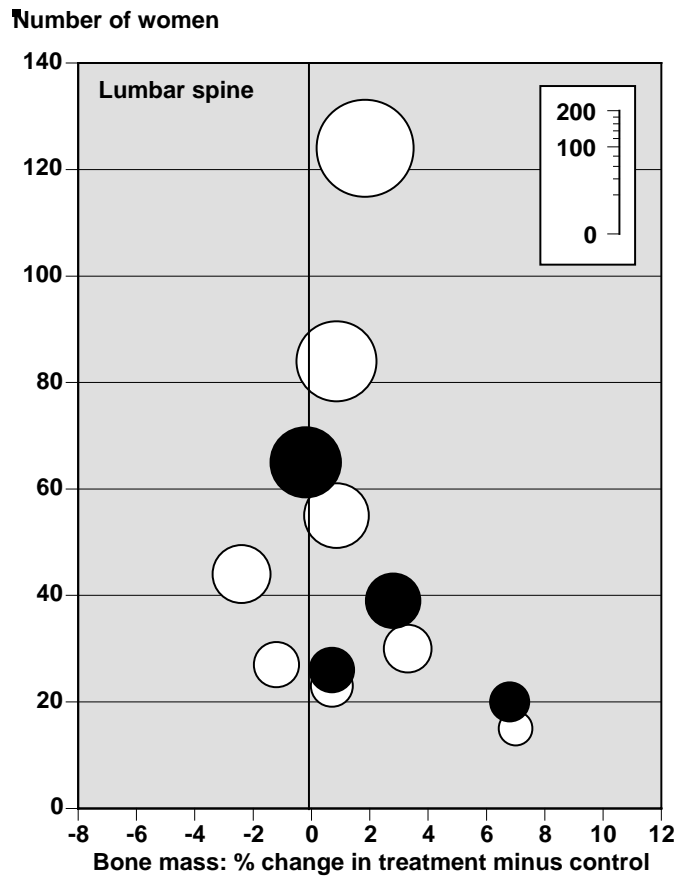
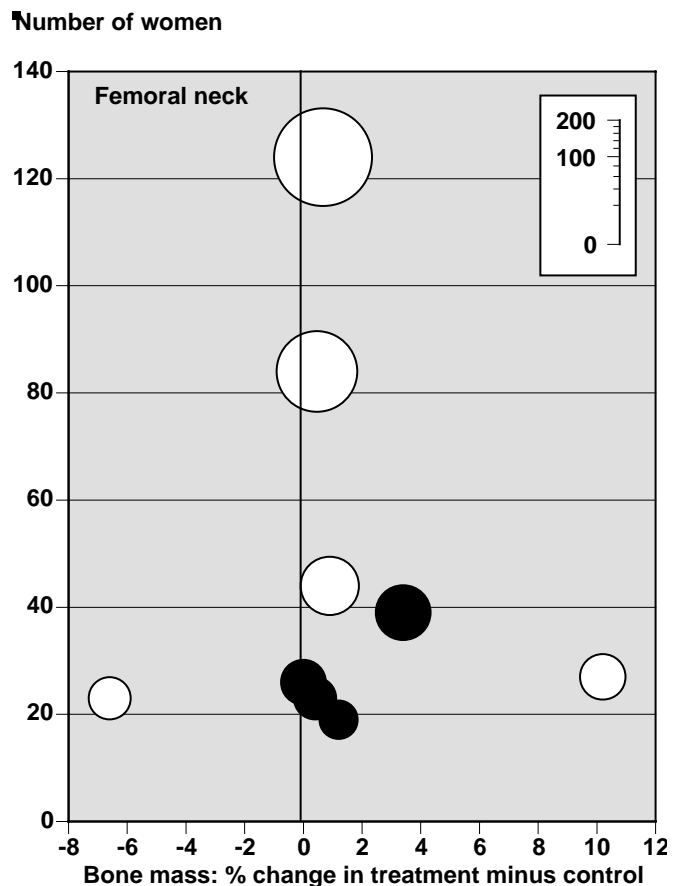


Figure 2: Femoral neck - postmenopausal



Legend: Difference between the percentage change in bone mass in one year in training group minus the percentage change in bone mass in one year in control group. Open circles endurance training, filled circles strength training.

# WOMEN SHOULD WALK

*Bandolier* is keen on evidence on healthy living. One of the excellent sources of evidence is the US nurses' health study, started in 1976, when about 122,000 female nurses in the 30 to 55 age group were enrolled. Questionnaires were filled in then, and other information was collected in 1980, '82, '86, '88 and 1992. This information showed the relationship between folate and multivitamin use and reduced colon cancer incidence (*Bandolier* 60).

A new analysis [1] sought to pin down the relationship between coronary heart disease and exercise in women. In Japanese men, a study showed that regular walking decreased mortality (*Bandolier* 50).

## Study

Detailed information on physical activity was first collected in 1986 and updated in 1988 and 1992. This included various forms of vigorous and non-vigorous exercise, plus a walking history that included their walking pace: easy or casual (less than 2 mph), average (2.0 to 2.9 mph) or brisk (more than 3 mph) [note that 1 mph = 1.6 kph]. A weekly metabolic-equivalent (MET) was calculated for the various forms of activity. Total MET hours per week was then calculated.

| Activity    | MET per hour                  |
|-------------|-------------------------------|
| Vigorous    | more than 6                   |
| Nonvigorous | less than 6                   |
| Walking     | 2.5 to 4.5, depending on pace |

A MET is the caloric need per Kg per hour of activity divided by the caloric need per Kg at rest

## Outcomes

The primary endpoint was coronary events defined as nonfatal myocardial infarction or death due to coronary disease occurring after 1986 and before mid-1994. There were 645 coronary events. The physical activity assessed in 1986 was used as the baseline.

## Results

Information was grouped into quintiles of MET hours per week, with about 14,000 to 15,000 women in each quintile. The distribution of physical activity between the quintiles is shown in Figure 1. The mean of 15 MET hours per week in quintile 4, for instance, implies that a woman would walk briskly for about four hours per week. Women in the high MET quintiles were less likely to smoke, were leaner and had lower prevalences of diabetes, hypertension and hypercholesterolaemia than those in the lowest quintiles.

Figure 1: MET hours per week for each quintile

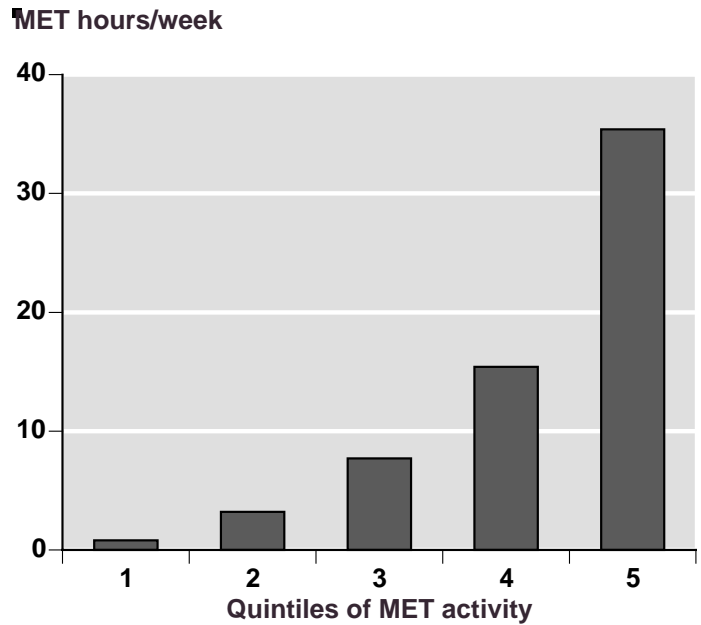
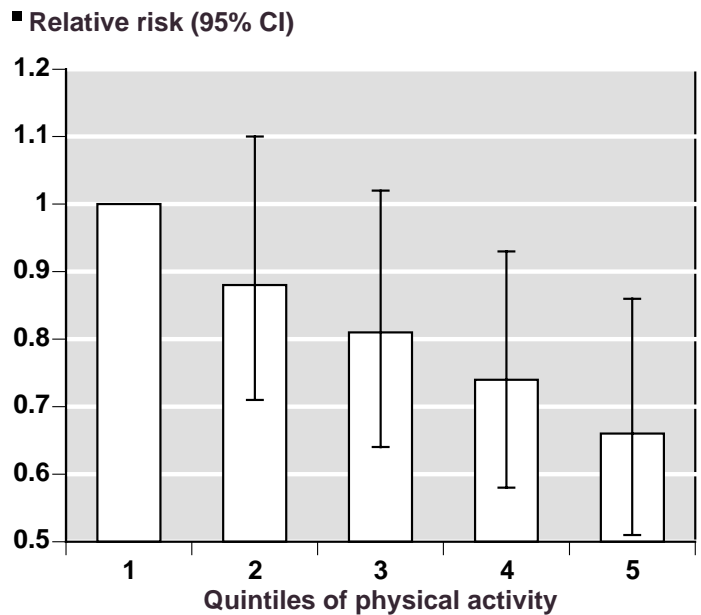


Figure 2: Relative risk of coronary event for each quintile. Significant reduction in quintiles 4 and 5.

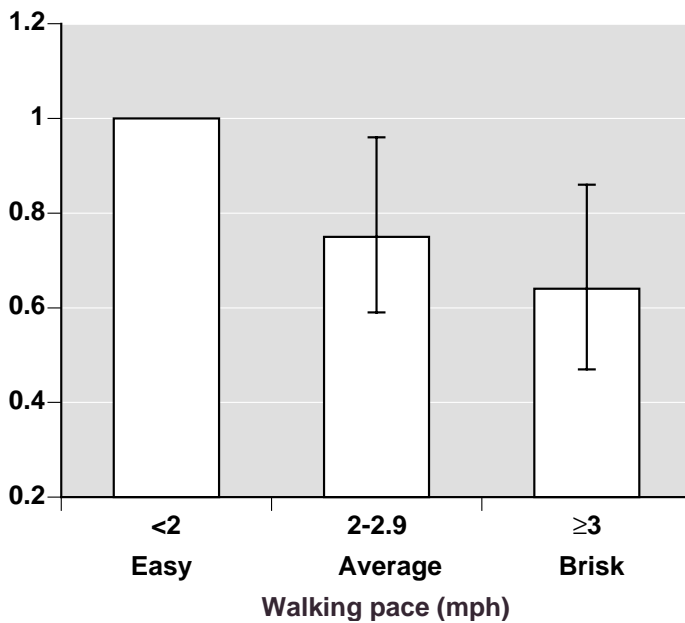


When adjustment was made for these factors there remained a significant association between higher levels of total physical activity and reduced risk of a coronary event (Figure 2). There was a 34% reduced risk for the highest total activity quintile.

In women who took no vigorous exercise, brisk walking had a similar effect on reducing the risk of a coronary event (Figure 3). Using women who walked at a casual or easy pace as a baseline, women who walked briskly reduced their risk by 36%. Compared with sedentary women, women who walked briskly for 1 to 3 hours a week had a risk reduced by 30% (95% CI 5 to 49%) after allowing for other factors.

**Figure 3: Relative risk of coronary event by walking pace for women who did not take vigorous exercise**

■Relative risk (95%CI)



## Comment

This is another study linking increased physical activity to better health. Importantly this study is one of the biggest to examine the effects of exercise in women. The bottom line is that women who walk briskly or exercise vigorously for three hours a week or more can reduce their risk of heart disease. *ImpAct 3* examined a visionary scheme for prescribing walking exercise.

*Bandolier 50* had reports of walking reducing coronary and all cause mortality in retired Japanese men in Hawaii, and of exercise reducing death rates in a Finnish twin study. The benefits of moderate exercise have been known for some time, and the evidence continues to accumulate. The size of the effects continues to impress, and just shows that evidence-based healthy living is something upon which we should concentrate more.

Reference:

- 1 JE Manson et al. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. *New England Journal of Medicine* 1999 341: 650-8.

## HARM FROM ACUPUNCTURE

It is rare to find a systematic review devoted to adverse effects. Examining acupuncture for life-threatening adverse reactions [1] shows a number of potential problems, not all of which are recognised commonly. Fifty-six articles were identified, examining two main areas.

### Infections

Infections linked to acupuncture and the improper handling of needles or their reuse without adequate sterilisation included hepatitis B and C, HIV, bacterial endocarditis and staphylococcal septicaemia. These studies included overviews, epidemiological surveys and case reports.

### Trauma

There are apparently over 60 cases of pneumothorax caused by acupuncture reported. Other traumatic events include cardiac tamponade and punctured heart, including at least one actual death.

## Comment

This refreshing little review points out that the seemingly innocuous, if done improperly or without care, can result in serious harm. The numbers of patients harmed by acupuncture in this literature review is difficult to assess, but runs into the hundreds. Choosing acupuncture because it is deemed harmless may be a poor choice.

Reference:

- 1 E Ernst, A White. Life-threatening adverse reactions after acupuncture? A systematic review. *Pain* 1997 71: 123-6.

## CONSTIPATION IN CHILDREN

In *Bandolier 65* we featured an audit on laxative use in Shropshire which identified 12 children under 16 years (seven per 100,000 population) who had used stimulant laxatives for a mean of 3.8 years. A Greek study [1] links childhood constipation with low fibre in the diet.

### Study

A randomised sample of children aged two to 14 years in three Greek counties. There were 291 children with constipation and 1602 controls. Nutritional data were obtained from a three-day dietary record and a dietary history.

### Results

Children with constipation had a lower caloric intake than controls, and 28% were reported to be anorexic by parents compared with 5% of controls. Only fibre intake was independently associated with constipation. There was a strong association with family history. The prevalence of constipation was only 3% if neither parent was constipated, was 10% if one was constipated, and was 49% if both parents were constipated.

## Comment

This detailed account strongly links childhood constipation to low fibre intake and family history of constipation.

Reference:

- 1 E Roma et al. Diet and chronic constipation in children: the role of fiber. *Journal of Pediatric Gastroenterology and Nutrition* 1999 28: 169-74.

# SELF-ADMINISTERED EMERGENCY CONTRACEPTION

Emergency postcoital contraception is thought to be underused because it must be prescribed by a doctor and used within 72 hours of intercourse. Getting an appointment in time may be difficult, and there may be a degree of embarrassment. One of the concerns about making emergency contraception more easily available, for instance through pharmacists without a prescription or by having it available at home, is that it may be misused. A randomised study from Scotland suggests that is not the case [1].

## Study

Women aged 16 to 44 years were recruited at a follow-up consultation following use of emergency contraception or after a termination. Women agreeing to participate in the study were randomised on the basis of even/odd birth dates to receive one packet of emergency hormonal contraceptive tablets to keep at home, or were simply informed of emergency contraception availability and use. The emergency contraception used was tablets containing 50 µg ethinyl oestradiol and 0.25 mg levonorgestryl.

Women were given a notification to mail to the study centre if they used emergency contraception. Those with emergency contraception at home could obtain a replacement package. After one year, all the women were sent a questionnaire asking about use of contraception, pregnancies and terminations. This was followed up on two occasions, and if it was not returned, information was sought from family doctor or Scottish Health Department with registers of births and terminations.

## Results

There were 549 women in the treatment and 522 in the control group. The final questionnaire was returned by about 65% of women, and information on births or terminations was available on about 93%.

Women who were given emergency contraception to be kept at home were significantly more likely to use it once than those who had to obtain it from a doctor (Figure). There was no difference in the proportion of women using emergency contraception twice or more over the year. Emergency contraception was almost always used correctly.

Emergency contraception was used on 387 occasions (248 times in treatment group and 139 times by controls). Twelve pregnancies began in a cycle in which emergency contraception had been used, representing a failure rate of about 3%.

The total number of unintended pregnancies was 18 (3%) in those with emergency contraception at home, compared with 25 (5%) in those who had to get it from a doctor. This was not statistically different. During the year, in both groups, the predominant form of contraception changed from condoms to oral contraception.

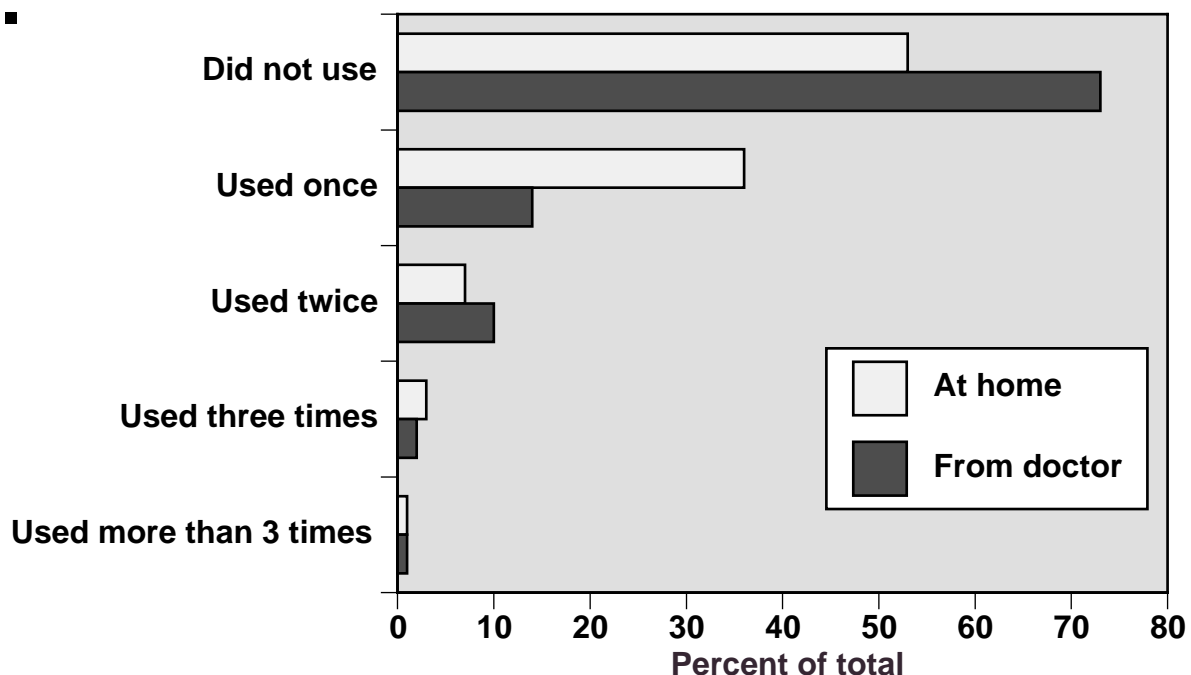
## Comment

The fear that emergency contraception kept by women at home would be misused has been dispelled by this trial. *Bandolier* could not find any other similar trials published.

Reference:

- 1 A Glasier, D Baird. The effects of self-administered emergency contraception. *New England Journal of Medicine* 1998 339: 1-4.

Figure: Use of emergency postcoital contraception



# EPIDURALS AND LABOUR

A review on the effect of epidural analgesia and the Caesarean section rate featured in *Bandolier* 34 concluded, from two randomised and four non-randomised studies, that epidurals increased the rate of section. A new review [1], with much more data from larger randomised studies, not only comes to a sensible conclusion that Caesarean section rates are unaffected, compared with parenteral opioids, but also has much useful secondary data on maternal and neonatal outcomes.

## Review

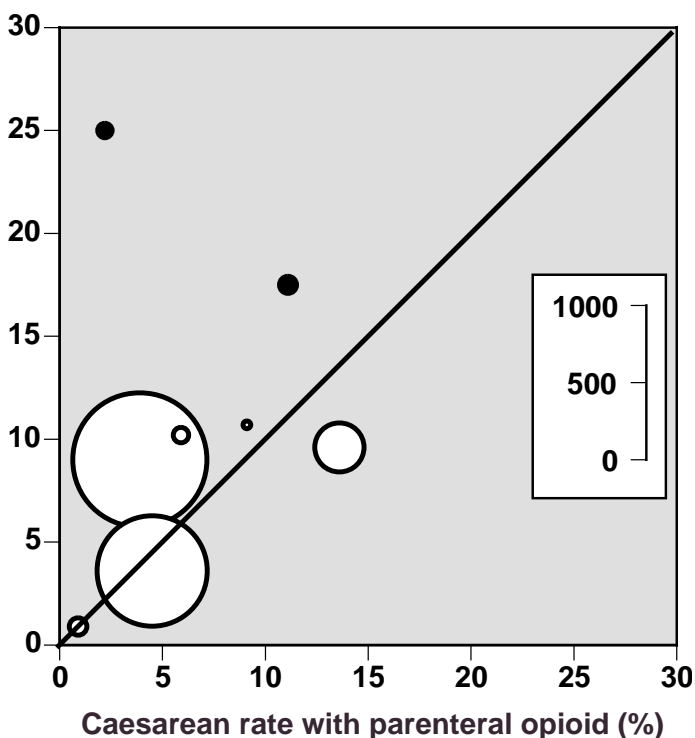
The review had a thorough search strategy for randomised studies comparing epidural analgesia with parenteral opioids. It used MEDLINE, the Cochrane Library, and hand searched non-abstracted journals and meeting abstracts. It obtained information from authors of abstracts and papers where needed. The primary outcome measure was the Caesarean section rate. There were many secondary outcomes sought.

## Results

Ten studies met the inclusion criteria, with 1614 nulliparous and 755 multiparous patients randomised. All but one study provided information on an intention-to-treat basis. The parenteral opioid was predominantly pethidine (meperidine) given by intramuscular or intravenous injection; one study used intravenous fentanyl and another intravenous butorphanol.

**Figure: Caesarean section rates with epidural and parenteral opioid analgesia. Each point is one trial (filled circles are trials in original review).**

■ Caesarean rate with epidural (%)



The Caesarean section rate was 8.2% with epidural and 5.6% with parenteral opioid (Figure). They found no significant difference using a random-effects model for odds ratios. The implication is that there may be one additional Caesarean section for every 40 women given an epidural rather than parenteral opioid. Caesarean section rates were no different with epidural or parenteral opioid for nulliparous women (about 8%) or multiparous women (about 2.5%).

There were a number of secondary outcomes for mothers and babies (Table). For mothers, epidurals resulted in much less pain in the first and second stages of labour, and much less dissatisfaction. However, the cost was a higher rate of instrumental delivery, longer labours, more use of oxytocin and more episodes of hypotension and elevated temperature. For newborns, epidurals resulted in fewer babies with low APGAR scores or low umbilical pH, and fewer needing naloxone.

## Comment

The bulk of the information in this review was published after that featured in *Bandolier* 34 (and published in 1994) was completed. There is now information on over 10 times as many randomised patients than in the earlier review. It shows clearly that the earlier trials overestimated any increased Caesarean section rate with epidural analgesia in labour.

Reference:

- 1 SH Helpert et al. Effect of epidural vs parenteral opioid analgesia on the progress of labour. *JAMA* 1998 280: 2105-10.

## EB OPPORTUNITY

### JB Medical

An opportunity exists for someone with good critical appraisal skills, a firm grasp of medical statistics and an understanding of the clinical context into which EBM must fit. JB Medical provides high quality, evidence-based, medical educational materials, principally for the pharmaceutical industry. A new, full time author with the enthusiasm to get involved in the sharp end of clinical and economic data analysis and able to write clearly and coherently is needed to work in our head office near Colchester.

Salary will depend on the skills and experience, but is likely to be around £30k. Contact:

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| <b>Maternal outcome</b>                                     | <b>Studies/<br/>Patients</b> | <b>Result: NNT or NNH (95%CI)</b>  |
|---|------------------------------|--|
| <b>Better outcomes with epidural</b>                        |                              |  |
| First stage labour pain                                     | 6/<br>2031                   | Average 40 mm lower with epidural (95%CI 38 to 42 mm) on 100 mm scale    |
| Second stage labour pain                                    | 5/<br>1062                   | Average 29 mm lower with epidural (95%CI 21 to 38 mm) on 100 mm scale    |
| Dissatisfaction   | 5/<br>1581                   | 15% with epidural, 43% with parenteral opioid. NNT 3.6 (3.1 to 4.3)      |
| <b>Worse outcomes with epidural</b>                         |                              |  |
| Instrumental delivery                                       | 9/<br>2319                   | 15% with epidural, 9% with parenteral opioid. NNH 15 (11 to 26)          |
| First stage labour duration                                 | 5/<br>1079                   | Average 42 minutes longer with epidural (95%CI 17-68 minutes)            |
| Second stage labour duration                                | 6/<br>1190                   | Average 14 minutes longer with epidural (95%CI 5-23 minutes)             |
| Use of oxytocin after analgesia                             | 4/<br>1001                   | 45% with epidural, 32% with parenteral opioid. NNH 7.9 (5.4 to 15)       |
| Temperature >38°C   | 2/<br>1371                   | 23% with epidural, 5% with parenteral opioid. NNH 5.6 (4.7 to 7.0)       |
| Hypotension   | 3/<br>1684                   | 37% with epidural, 0% with parenteral opioid. NNH 2.7 (2.5 to 3.0)       |
| <b>No difference between epidural and parenteral opioid</b> |                              |  |
| Nausea  | 5/<br>835                    | 7% with epidural, 6% with parenteral opioid. No significant difference   |
| Instrumental delivery for dystocia                          | 2/<br>211                    | 12% with epidural, 17% with parenteral opioid. No significant difference |
| <b>Neonatal outcome</b>                                     | <b>Studies/<br/>Patients</b> | <b>Result: NNT (95%CI)</b>   |
| <b>Better outcomes with epidural</b>                        |                              |  |
| APGAR <7 at 1 minute  | 6/<br>2015                   | 1% with epidural, 2% with parenteral opioid. NNT 68 (40 to 231)          |
| APGAR <7 at 5 minutes                                       | 7/<br>2176                   | 4% with epidural, 7% with parenteral opioid. NNT 35 (21 to 112)          |
| Low umbilical artery pH                                     | 6/<br>2034                   | 14% with epidural, 17% with parenteral opioid. NNT 27 (15 to 220)        |
| Need for naloxone in the newborn                            | 2/<br>815                    | 1% with epidural, 3% with parenteral opioid. NNT 37 (22 to 135)          |
| <b>No difference between epidural and parenteral opioid</b> |                              |  |
| abnormal, or intrapartum meconium                           | 3/<br>1126                   | 19% with epidural, 20% with parenteral opioid. No significant difference |
| Severe asphyxia (umbilical artery pH <6.99)                 | 5/<br>1715                   | <1% on both. No significant difference                                   |

# FUNGAL TOENAIL INFECTIONS

## DEFINITIONS AND RESULTS

Fungal infections of the toenails are difficult to cure. But one of the most vexing questions is what constitutes a cure. Nails may look normal, but still harbour the fungus that caused the problem, with the result that some time after the end of treatment the infection recurs, and the cycle of treatment has to start again.

### Study

A new review of terbinafine, itraconazole and fluconazole [1] sought the answer by looking for evidence of disease-free nails one year or longer after the start of treatment. A disease-free nail was defined as one that both looked normal and had negative results from potassium hydroxide microscopy and culture. The search strategy was reasonably comprehensive, and found seven studies, only some of which appeared to be randomised. Studies had to describe results in toenails (distinct from fingernails), use both culture and microscopy and include a clinical evaluation. Case reports, series of fewer than 15 patients, those combining finger and toenails, and those reporting on nails rather than patients were excluded.

### Results

There were no data for fluconazole. The results for terbinafine and itraconazole are shown in the Figure. For terbinafine, 217 of 491 patients (44%) had a disease-free nail at one year. Most studies used terbinafine 250 mg daily for longer than the recommended 12 weeks. For itraconazole, 99 of 291 patients (34%) had a disease-free nail at one year. These results were obtained whether 200 mg daily was given, or as 400 mg daily for one week each month.

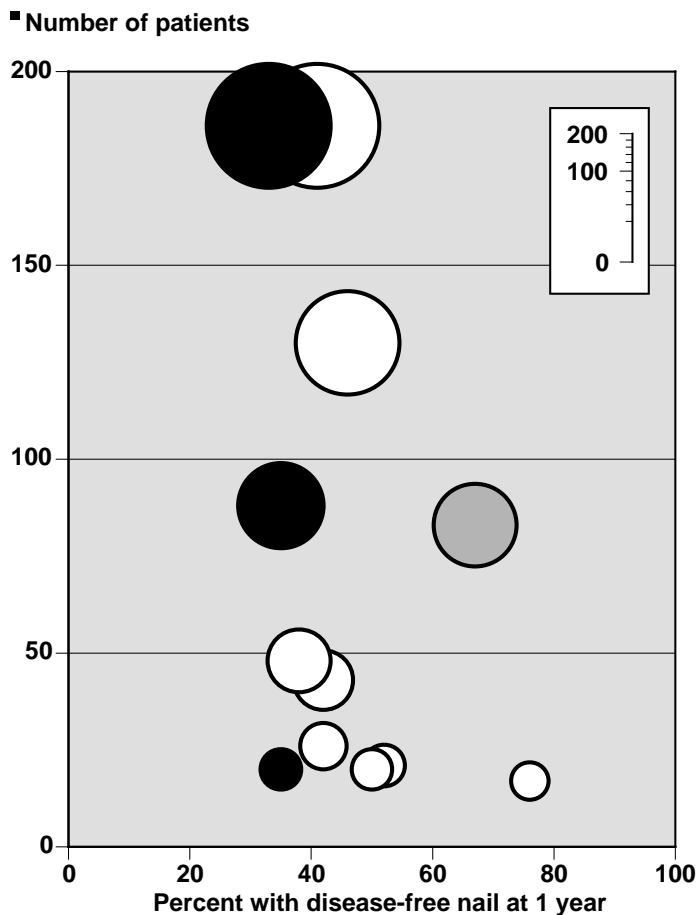
### Comment

Fungal nail infection is one of those seemingly innocuous subjects that seems to get people vexed whenever it is raised. This interesting little paper poses an important question for patient and practitioner – when is a cure not a cure? Epstein points out the deficiencies in the definition – or lack of definition – of a cure.

*Bandolier* 26 examined this subject, and found two randomised trials comparing terbinafine with griseofulvin in toenails. One is in this review, but the other had 48-week outcomes that might have been included by Epstein, but perhaps were omitted because 48 weeks is less than one year (though one also had longer outcomes). Disease-free nails at 48 weeks occurred in 67% of patients receiving terbinafine. Including these trials (half-tone fill in the Figure) would increase the one-year result for disease-free nails with terbinafine to 48%

These are expensive treatments for a condition that is not uncommon, and more attention would seem to be needed. The concentration on suitable end-point is pertinent, but the execution may be flawed. Is it time to have a good sys-

Figure 1: Disease free nails at one year with terbinafine (open circles and half-tone fill) and itraconazole (filled circles)



tematic review, as we have for topical treatments from the Cochrane Library [2], and especially as more randomised studies are being published?

#### Reference:

- 1 E Epstein. How often does oral treatment of toenail onychomycosis produce a disease-free nail? Archives of Dermatology 1998 134: 1551-4.
- 2 F Crawford et al. Topical treatments for fungal infections of the skin and nails of the foot. Cochrane Library 1999, 3.

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