Most of us use computers these days, and most of those computers have software to allow us to fiddle with words or numbers. Bandolier learns how to use software by the old-fashioned technique of trying it, getting advice from our friends, and, when that doesn’t work, shouting a lot. Occasionally we’ll open a book that tells us how we should be doing it. In a last desperate attempt to use one programme (Photoshop) we turned to a most useful book (Photoshop 6 for Dummies by Deke McCelland) because it claimed that, though Photoshop was difficult, just holding the book up to the screen made it 50% easier.

That’s exactly the relationship we would like for Bandolier and the use of evidence. In this issue several stories try to help in this regard. For instance, a meta-analysis of the use of probiotics for antibiotic-associated diarrhoea gives us almost useless statistical outputs. We show how a bit of surfing can lead us to a more useful result.

Then there’s a reminder from hyperbaric oxygen for multiple sclerosis that randomised trials give different (negative) results from case series (positive). And, using the example of stress reduction interventions for blood pressure reduction, a reminder that smaller, shorter trials can claim a treatment works when larger, longer trials tell us that it does not.

It’s not rocket science, but re-learning the lessons stops us being tripped up when the next fantastic claims are made based on inadequate evidence.

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Subscription rates are £36 in the UK and £72 overseas, and there are big discounts for bulk orders. Internet users are now able to make a contribution using a special donation form.
Results

There were seven studies with 881 patients. No information was given on reporting quality, allocation concealment, or blinding. Two studies were in children, and the rest in adults, with one limited to elderly patients. Three studies showed a significant reduction in diarrhoea, and the overall relative risk was 0.4 (0.3 to 0.6).

We were not told what proportion of patients had diarrhoea with placebo, or with probiotic, neither overall nor for individual studies.

Finding more information

Bandolier used PubMed to obtain the abstract of each paper in the meta-analysis. One was available in full text. A brief search was conducted, again using PubMed, for any other papers that may have been published subsequently.

Two were found, one (full text) from the Italian group publishing the meta-analysis on Helicobacter eradication, and one (abstract) from the USA on patients in hospital given antibiotics. All abstracts and papers had information directly or implicitly giving the numbers of patients with diarrhoea, and in total.

New results

The rates of diarrhoea with probiotic and with placebo for nine individual trials are shown in Figure 1, where open circles represent Lactobacillus and filled circles Saccharomyces.

The overall rates and NNTs for the original and extended meta-analyses, and for Lactobacillus and Saccharomyces only are shown in Table 1. The relative risk for diarrhoea with probiotic was 0.4 (0.3 to 0.6) for the original meta-analysis and 0.6 (0.4 to 0.7) for the extended analysis with nine trials.

Using all the information, antibiotic-associated diarrhoea occurred in 23% of patients without probiotic and in 13% of patients with probiotic. For every 10 patients using daily probiotic with antibiotics, one fewer will have diarrhoea.

Comment

Most people find this an interesting topic. Hardly anyone found a relative risk useful or illuminating. Tell them that the incidence of diarrhoea falls from 23% to 13%, or the NNT is 10, or preferably both, and everyone knows what the results are. Rocket science this is not, but reporting results without utility is not clever and is without value. The good news is that an IT strategy embracing a cheap computer and web browser software can remedy all that.

Reference:

Table 1: Results of meta-analysis for all studies, those in the original meta-analysis, and with Lactobacillus or Saccharomyces only

<table>
<thead>
<tr>
<th>Studies</th>
<th>Number</th>
<th>Diarrhoea/total (%) with Probiotic</th>
<th>Placebo</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>9</td>
<td>60/636 (13)</td>
<td>144/639 (23)</td>
<td>10 (7.1 to 17)</td>
</tr>
<tr>
<td>Studies in meta-analysis</td>
<td>7</td>
<td>37/443 (8)</td>
<td>90/445 (20)</td>
<td>8.4 (6.1 to 14)</td>
</tr>
<tr>
<td>Lactobacillus only</td>
<td>6</td>
<td>57/414 (14)</td>
<td>105/419 (25)</td>
<td>8.9 (6.0 to 17)</td>
</tr>
<tr>
<td>Saccharomyces only</td>
<td>3</td>
<td>23/222 (10)</td>
<td>39/220 (18)</td>
<td>14 (7 to 108)</td>
</tr>
</tbody>
</table>

Figure 1: Antibiotic-associated diarrhoea with and without probiotics. Open circles used Lactobacillus and filled circles used Saccharomyces.
RHEUMATOID ARTHRITIS TREATMENTS IN THE REAL WORLD

The real world is sceptical about clinical trials, and whether the results of trials transfer into clinical practice. Complaints vary. One complaint is that randomised trials do not recruit patients like ours, and exclude too many patients, making patients in trials unlike those in the real world. Another is that patients in trials are somehow coerced into remaining on treatments when in real life adverse events or lack of efficacy make them discontinue treatment. Or trials are not long enough when patients may have daily treatment for many years. The real cynics think that clinical trials are a stitch up between industry and government.

Whatever the reason, cynicism and caution are justified. A new treatment may have been used by only a few thousand patients (typically about 1,500, though that is rising). That is too few to be confident of safety, especially if older, or sicker patients, or those on other medicines are being treated than those included in clinical trials.

A way forward?

Take new treatments for rheumatoid arthritis as an example. A NICE review (Bandolier 99) had information on about 1,000 patients given etanercept, and about 630 given infliximab. The treatments were effective within the limits of the trials, but only a small proportion used the licensed doses, and those for only 24-30 weeks, not long when the treatment may be used for years. And these biological treatments are innovative. We have no experience of treating patients with monoclonal antibodies for many years.

So what would you do? A guess at a way forward would be to create strict treatment protocols, defining who should be treated, and how, but leaving the clinical decision of who to treat with what to the doctor and patient. Without exception every patient treated would be monitored, at set times, and with defined criteria of what to measure. Adverse events would be recorded, and reasons for stopping treatment.

That, of course, is similar to what the British Society for Rheumatologists and other bodies have proposed. But in Sweden they already have the results [1], and describe how an academic unit can work with non-teaching institutions to do good real world research.

Study

In the University Hospital of Lund in southern Sweden, a clinical treatment protocol was adapted to monitor new treatments in rheumatoid arthritis. Six non-teaching hospitals also used the protocol, so that coverage of patients with rheumatoid arthritis in southern Sweden was complete.

There were strict eligibility criteria, including a proper diagnosis of rheumatoid arthritis, failure to respond to or tolerate at least two disease-modifying drugs including methotrexate. Though not approved by the European Medicines Agency at the time (1999-2000), Swedish law allowed use of several treatments on an individual patient basis.

For etanercept, infliximab and leflunomide initial doses were according to licence, with changes as necessary. Assessments were mandated before treatment started, and at 3, 6 and 12 months, and 3-6 months thereafter.

Results

Of 369 patients treated, 166 were on etanercept, 135 on infliximab and 103 on leflunomide. Some (33) tried two treatments and one all three. Patients on the TNF-antagonists etanercept and infliximab were similar, but those on leflunomide were older, had more severe joint damage, were more often treated with monotherapy and had somewhat lower inflammatory activity as judged by ESR values.

After 12 months of treatment with etanercept, about 60% of patients had an ACR20 response, 40% an ACR50 response and about 18% an ACR70 response (as judged from graphs in the paper). Figure 1 shows that these results were similar to those of a trial of the licensed dose at six months. After 20 months, 79% of patients who began treatment were still using it.

After 12 months of treatment with infliximab, about 60% of patients had an ACR20 response, 40% an ACR50 response and about 18% an ACR70 response (as judged from graphs in the paper). Figure 2 shows that these results were similar to those of trials of similar doses and dose intervals at about six months. After 20 months, 75% of patients who began treatment were still using it.

After 12 months of treatment with leflunomide, about 20% of patients had an ACR20 response, 20% an ACR50 response and about 10% an ACR70 response (as judged from graphs in the paper). After 20 months, 22% of patients who began treatment were still using it.

Adverse events were well reported, especially deaths, life-threatening, and serious adverse events. For the TNF-antagonists five myocardial infarctions occurred, there were some episodes of serious bacterial infection, and there were three lymphomas and one case of acute myeloid leukaemia.

Figure 1: Etanercept results from RCT and protocol

<table>
<thead>
<tr>
<th>Percent with ACR criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Etanercept (RCT)</th>
<th>Etanercept (Protocol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
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<td>0</td>
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</table>

www.ebandolier.com
This real-world study provided significant information about treating patients with rheumatoid arthritis using new therapies. The amount of information in terms of patient numbers multiplied by duration of treatment was, for the TNF-antagonists, about equal or more than that from clinical trials. Results on efficacy were similar to clinical trials. The adverse events recorded confirmed those seen in clinical trials, and reminded us that they could be serious.

Most important was the model. It shows that high-quality monitoring of new treatments can be done without the intervention of manufacturers, who may be biased. There was no industrial sponsorship for this study. There’s no reason why similar schemes could not be put in place for most new introductions. It requires some thinking in advance about what is required, cooperation of doctors, and some good information technology.

Reference:

**Hyperbaric oxygen for MS: update**

*Bandolier* 62 explored evidence about the effectiveness of hyperbaric oxygen therapy for multiple sclerosis, and found it to be profoundly negative. A new review [1] examines the subject in a wider context and comes to a similar conclusion, but adds an economic assessment suggesting that even if it were effective, the cost for one successfully treated patient would be over £600,000.

**Review**

The formal search for this review included five electronic databases, including a specialised multiple sclerosis registry from the Cochrane Collaboration and a specialised register for hyperbaric medicine, as well as manual searches of hyperbaric journals, proceedings and texts since 1980. In assessing the evidence, it examined reviews, randomised trials, non-randomised studies and case series.

**Results**

The main findings of the new review can be summarised thus:

- There were three systematic reviews, each examining 14 trials, concluding that there was no net benefit.
- There were 12 randomised, double blind trials, four of which showed some benefit, if benefit included any minor improvement or improvements like transient sphincter improvement, in subgroup analysis. Nine of these studies enrolled fewer than 50 patients.
- There was one non-randomised comparative study showing minor benefit.
- There were four case series, all of which showed benefits.

The authors of the review make the point that all of these studies are likely to have some degree of bias in favour of hyperbaric oxygen. The only patients with long-term assessments were those who continued treatments over several years, and many of those dropping out of the trials were likely to be patients finding no improvement.

The impact of hyperbaric oxygen is unlikely to be great. While there is no statistically significant improvement in either symptom improvement or improvement of sphincter function, the best estimates for numbers needed to treat were 42 and 25 respectively, with confidence intervals that include infinity.

Based on the need for 68 treatments in the first year, and a cost of US$300 per treatment, the best estimate for the cost of one patient benefiting from improved symptoms would be US$860,000 (or Euros), or £612,000, but with a range of about $300,000 to infinite cost.

**Comment**

This will be a most useful position paper for purchasers because it puts hyperbaric oxygen therapy into a perspective including other treatments and their costs. It is also the official position of the Undersea and Hyperbaric Medical Society.

The methodological take-home message, again, is that observational studies show benefit while proper randomised studies do not. We must not forget this lesson.

Reference:
There is quite a lot of evidence relating exercise to improved cardiovascular disease, but few include women, and few of those have examined the effect of the most popular exercise for women, walking. A new study from the USA in a large number of older women rights that wrong, and shows that walking is a good thing [1].

Study

There were 73,700 women in a women’s health observational study involving women aged 50 to 79 years at entry. Of these about 62,000 were white, 5,600 black, 2,800 hispanic, 2,300 asian, and 1,300 American Indian or other racial background. They were enrolled between 1994 and 1998, with observation up to mid-2000. Women were free of cardiovascular disease and cancer at baseline.

There was a clinic visit at enrolment, during which self-administered questionnaires were completed about personal and family medical history, smoking, diet, physical activity and other lifestyle factors. Height, weight, hip and waist circumference, and blood pressure, were measured. The questionnaire on recreational physical activity was detailed, and used to calculate a weekly energy expenditure score in metabolic equivalents (MET-score). A sample of 1,092 women entered a reliability study to demonstrate the reproducibility of the assessment questionnaires.

The primary endpoints were newly diagnosed coronary heart disease (nonfatal myocardial infarction and death with a coronary cause) and total cardiovascular events (myocardial infarction, death from coronary cause, coronary or carotid revascularisation, angina, congestive heart failure, stroke). All endpoints were confirmed from medical records by blinded observers.

The age- and multivariate-adjusted risk of both coronary heart disease and total cardiovascular disease fell as the amount of exercise rose (Figure 1). The mean number of MET-hours per week in each quintile was 0, 4.2, 10, 18 and 33 respectively for quintiles 1-5. Similar reductions were seen for walking (0-17 MET-hours per week) and for vigorous exercise (0-210 minutes strenuous exercise a week). Trends for reduced risk with increased total physical activity and for walking was important. The multivariate relative risk and age and walking time adjusted relative risks both showed a significantly lower risk of cardiovascular disease when women walked at more than a casual pace (Figure 2).

Comment

Cardiovascular disease is not insignificant in older women. There were 1,551 first cardiovascular events (including 345 fatal and nonfatal heart attacks and 309 strokes) over 3.2 years among 73,743 women aged 50-79 years. That’s one event in 50 women over three years on average. Cardiovascular disease in women who exercised and walked the most occurred at about half the rate of in those who did not exercise or walk at all. This was true irrespective of race, age or body mass index.

The strengths of this study were its size, being prospective, the racial and ethnic diversity of the women included, the detailed assessment of physical activity at baseline, and the uniform criteria for the end points. It makes a powerful case to find ways to make it easier for women to walk, because walking is beneficial in other ways too. It reinforces similar evidence for men. Joined up government could do no better than to establish ways to ensure that more of us walk longer, and faster, and more often. It would be more beneficial than most tablets.

Reference:
Homocysteine Lowering After Percutaneous Coronary Intervention

The influence of homocysteine levels in blood on heart disease was visited in Bandolier 57. The evidence that lowering homocysteine levels by increasing folic acid and B vitamin intake is still a matter of debate, at least for those of us not known to have very high homocysteine levels.

But what of secondary prevention? Is there any benefit of lowering homocysteine levels in people with high cardiovascular risk, like after heart surgery? No answers yet on that either, but a randomised trial tells us that folate and B vitamins improve outcomes after percutaneous interventions [1].

Study

Patients undergoing percutaneous angioplasty of at least one significant coronary stenosis greater than 50% were randomised to receive folic acid (1 mg/day), vitamin B12 (400 µg/day) and vitamin B6 (10 mg/day) or placebo for six months. Not included were patients with unstable angina, subacute myocardial infarction, renal insufficiency or patients taking vitamin supplements. Follow up was performed at six months and one year. Adverse clinical events were:

- Death
- Cardiac death
- Nonfatal myocardial infarction
- Need for repeat vascularisation (target vessel or any vessel)
- A composite of these

Results

There were 272 patients given folate and vitamins and 281 given placebo. They were well matched at baseline, but at six months those in the folate plus vitamin group had mean plasma homocysteine levels that were 26% lower (at 1.0 mg/L; 7.5 µmol/L) than in those given placebo.

All the adverse clinical events occurred less frequently with folate and vitamins than with placebo (Figure 1). This was statistically significant for target vessel and any revascularisation, and for any event. An adverse clinical event occurred in 15% of patients with folate and vitamins, compared with 23% with placebo. The adjusted relative risk was 0.7 (0.47 to 0.94), and the NNT was 14 (7 to 122).

For every 14 patients undergoing percutaneous cardiac interventions and treated with folate and vitamins for six months, one fewer will experience an adverse clinical event at one year than if they had been treated with placebo.

The only adverse events were two patients taking vitamins and folate who discontinued because of pruritus.

Comment

This is a lovely trial from Switzerland that takes epidemiology into the clinic, and adds to the store of positive messages about the use of folate. As many as five other acronymed studies are presently underway in heart disease and stroke, so evidence will build as these trials report over the next few years.

The exact place of B vitamin and folate supplements in people with cardiovascular disease still needs to be defined. There seems to be little downside, with few and mild adverse events reported here.

For those of us who want to join the bandwagon, though, the message still remains that eating fruit and vegetables is not enough. You’d need several plates of broccoli to even approach the 400 µg a day that seems to be needed. A multivitamin with at least 200 µg is easier.

Reference:


Figure 1: Effects of placebo and vitamin supplementation to reduce blood homocysteine on adverse clinical outcomes after percutaneous coronary interventions

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Vitamin treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any revascularisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target lesion revascularisation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0 5 10 15 20 25

Percent
STRESS MANAGEMENT INTERVENTIONS AND BLOOD PRESSURE

Bandolier has been told that it may have a “type A” personality, whatever that means. Worse than being branded something you can’t understand is the punch line, that “type A” personalities will have raised blood pressure. Even worse again is the accusation that if we have hypertension it’s our fault, and worse of all is the exhortation to relax and manage our stress, because then everything will be all right.

So Bandolier thought a look at the evidence that stress management helps would be fun. Can stress management interventions help reduce blood pressure in people who are mildly hypertensive? Current published trials suggest not.

Search

PubMed was searched for randomised controlled trials published from 1990 to mid-2002 using the terms ‘stress’, ‘hypertension’ and ‘blood pressure’. Studies included compared a stress management intervention comprised of several components with a control intervention. Excluded were studies that assessed a single component alone, such as transcendental meditation or progressive muscle relaxation.

Results

Duplicate publications and subset analyses were excluded, leaving four trials for inclusion [1-4], and details of these will be found in a Table on the Bandolier Internet site. There were 762 patients in the four studies. Before study entry patients in all the trials had diastolic blood pressure greater than 80 mmHg, and in two systolic blood pressure was greater than 125 or 140 mmHg. Trials were diverse in terms of duration, which varied between eight weeks and 18 months, and stress management intervention, though all incorporated a relaxation component. Quality was not high, all four trials scoring 2 out of 5 on a much-used system.

Other components of the stress management interventions included education about blood pressure and stress, psychological or behavioural components (anger and anxiety response), and problem solving. Controls received no intervention in three studies, and undertook mild non-aerobic exercise in another. Compliance with the interventions was reported in one trial only and relied on self-reports by patients, but was good.

Absolute changes in systolic and diastolic blood pressure were small. Figure 1 shows the results for the change in systolic blood pressure over the period of the study for each trial, with larger symbols indicating larger trials. The two largest trials were on the line of equality, and intervention made no difference over six and 18 months.

Changes reached statistical significance compared with control in the two smaller trials over eight and twelve weeks. In one of these post-treatment reduction in diastolic blood pressure was maintained at six months follow-up, but systolic blood pressure had increased to baseline levels.

The weighted mean systolic blood pressure reduction was 4 mmHg with stress management interventions and 3 mmHg with control. Weighted mean diastolic reductions were 5 mmHg and 4 mmHg respectively.

Comment

There is no evidence for using stress management interventions alone since the studies showed no long-term reduction in blood pressure of clinical significance. There may be a place for using these interventions, to help individuals relax, in addition to advising the usual lifestyle changes such as reduction in salt intake, increased aerobic exercise, and weight reduction.

What is interesting is that small, short trials had the capacity to mislead, showing bigger reductions for treatment over control over short periods. Larger, longer studies demonstrated no difference between treatment and control, and there was no difference overall.

References:

ADULTERATED CHINESE HERBAL MEDICINES

Chinese herbal medicines are becoming more popular, and there is even evidence that they might work. *Bandolier* 60 reported on positive results from a randomised trial in irritable bowel disease, and there are suggestions of efficacy in respiratory tract infection, eczema and even hepatitis B from systematic reviews of, admittedly, generally poor studies.

One of the problems, though, is that these herbal medicines are not standardised, and usually contain many ingredients. A review [1] tells us that some of those ingredients can be synthetic drugs, responsible both for good effects, and for serious harm.

Review

At least six databases were searched up to December 2001 for studies that might report on the adulteration of Chinese herbal medicines. Electronic searching was supplemented by other forms of searching, including personal databases, and letters to experts and manufacturers.

Studies of any architecture were accepted, case reports and series, and analytical investigations. Studies had to specify the medicine in sufficient detail to identify it as a recognised Chinese herbal medicine.

Results

There were 22 relevant articles, 15 case reports, two case series and six articles about analysis of Chinese herbal medicines. Most reports originated in Western countries, but there was one each from China, Taiwan and Japan.

The range of adulterants found is shown in Table 1, and included steroids, NSAIDs, anticonvulsants, benzodiazepines, hypoglycaemic agents and drugs used for treating erectile dysfunction. The problems they caused are also shown in Table 1, and included a number of serious adverse effects possibly or probably related to adulterants.

What proportion of Chinese herbal remedies contain adulterants is not clear. Analysis of 2,600 samples in Taiwan showed that 24% were adulterated with at least one synthetic medicine. In the USA it was 7%. The case reports showed that two or more adulterants were present in 14 of 15 Chinese herbal medicines.

Comment

There was one death reported in these reports, and at least six potentially life threatening events. Suspicion of adulteration was based not only on adverse effects, but suspiciously good efficacy. Chinese herbal medicines may work because of the adulterants.

Most people consider alternative therapies to be safe, and often do not mention that they are using them. Given that multiple adulteration of Chinese herbal medicines seems to be common, there is potential for problems, especially when other treatments are being prescribed. Imagine an older patient on NSAID and aspirin additionally taking a Chinese medicine containing indomethacin or phenylbutazone!

We simply do not know what the rate of adulteration is. One UK study of 11 herbal creams showed that eight contained dexamethasone at concentrations up to 1.5 mg/gram of cream. In the absence of better information, we should assume that Chinese medicines are adulterated.

Biochemistry laboratories in our hospitals have the capacity to look for adulterants using techniques as standard as thin layer chromatography to gas chromatography with mass spectrometry. There are a few papers and theses to be gained in this area, while helping protect patients and public from a dangerous fraud.

Reference:


Table 1: A list of adulterants found in Chinese herbal medicines, and problems caused by adulterants (note that problems and adulterants are not linked in these lists)

<table>
<thead>
<tr>
<th>Adulterants found</th>
<th>Problems caused</th>
</tr>
</thead>
<tbody>
<tr>
<td>aminopyrine</td>
<td>agranulocytosis</td>
</tr>
<tr>
<td>caffeine</td>
<td>arrhythmia</td>
</tr>
<tr>
<td>chlorzoxazone</td>
<td>coma</td>
</tr>
<tr>
<td>clobetasol propionate</td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>diazepam</td>
<td>diabetes</td>
</tr>
<tr>
<td>diclofenac</td>
<td>increased INR</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>hypertension</td>
</tr>
<tr>
<td>ethoxybenzamide</td>
<td>hypoglycaemia</td>
</tr>
<tr>
<td>fluocinolone acetonide</td>
<td>gastrointestinal bleeding</td>
</tr>
<tr>
<td>glibenclamide</td>
<td>septic shock</td>
</tr>
<tr>
<td>hydrochlorothiazide</td>
<td></td>
</tr>
<tr>
<td>hydrocortisone</td>
<td></td>
</tr>
<tr>
<td>indomethacin</td>
<td></td>
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<tr>
<td>mefenamic acid</td>
<td></td>
</tr>
<tr>
<td>methylsalicylate</td>
<td></td>
</tr>
<tr>
<td>paracetamol (acetaminophen)</td>
<td></td>
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<tr>
<td>phenacetin</td>
<td></td>
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<tr>
<td>phenytoin</td>
<td></td>
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<tr>
<td>prednisolone</td>
<td></td>
</tr>
<tr>
<td>sildenafil</td>
<td></td>
</tr>
</tbody>
</table>

Table: A list of adulterants found in Chinese herbal medicines, and problems caused by adulterants (note that problems and adulterants are not linked in these lists)