RESTLESS LEGS

“Oh sleep! It is a gentle thing” is what the Ancient Mariner thought, and few would argue with that. The trouble is getting enough of it. For those of us blessed with the ability to sleep well and long, one interrupted night comes as a bit of a shock. To imagine what it is like for those whose sleep is frequently interrupted is very difficult. Which is perhaps why a Bandolier reader asked about restless leg syndrome, whether it is real, how common it is, and how to cure it.

Bandolier found no simple answer to the third part of the question, but a good source of information about the first two parts in a large prevalence study that examined both restless leg syndrome (RLS), and the related periodic limb movement disorder (PLMD) [1]. The answer is that about 1 person in 20 has RLS, about 1 in 25 PLMD, and an unlucky 1 in 100 has both.

Study

The study was conducted in five European countries (UK, Germany, Italy, Portugal, and Spain) in the mid-1990s. The target population was adults aged 15 or over living at home. A random selection of telephone numbers was drawn after geographical stratification, and a household member selected by age and sex.

Expert system software was used to administer questionnaires in a formulated and consistent way. The software had been specifically designed and tested to evaluate sleep disorders, and to use key diagnostic criteria administered in an exact way. The software also prompted questions about sociodemographic information, medical history, use of alcohol, tobacco and coffee, medicine use, physical activity, stress, and mental disorder.

Welcome New Zealand

This month it is a pleasure to give a slightly belated welcome to general practitioners and other professionals in New Zealand, who since November 2003 have begun to receive Bandolier every month. Bandolier has many old friends in that beautiful, if distant, country. Readers in New Zealand should feel just as free as readers elsewhere to contact us with suggestions or enquiries.

Bandolier arrives without burning up loads of jet fuel carting the weighty tome over all those miles, but by the simple expedient of sending a computer file to be printed in country. Cheap and effective, roughly what Bandolier sets out to be. For all our other readers around the world, it is worth reminding them that similar arrangements can be made for them. Just contact the Bandolier office.

Electronic stuff

A reminder to those who value a paper copy that the electronic version of Bandolier is always there as a resource, to search back issues and much of the other material that appears only electronically. For instance, a series of essays on looking at evidence are beginning to appear as downloadable PDFs. Bandolier has also been collecting all the stuff it can find on statins, both on efficacy and harm, for this important drug class. Statins will probably have their own page, with the expectation that one or other will soon be available from pharmacists without prescription in the UK.

Paper subscribers do have privileges over electronic users. The contents of the paper version do not appear electronically for at least six weeks, and PDF downloadable copies of Bandolier for at least three months. And it is sometimes so much nicer to have a quiet read in an easy chair with a glass of brain juice.
The definitions used for PLMD and RLS were those of the International Classification of Sleep Disorders.

**Periodic limb movement disorder:**
- A complaint of insomnia or excessive sleepiness.
- Repetitive highly stereotyped limb muscle movements, which in the leg are characterised by extension of the big toe in combination with partial flexion of the ankle, knee, and sometimes hip.

**Restless leg syndrome**
- A complaint of unpleasant sensation in the legs at night or difficulties in initiating sleep.
- Disagreeable sensations of “creeping” inside the calves, often associated with general aches and pains in the legs.
- The discomfort is relieved by movement of the limbs.

**Results**

The sample was 18,980 people, with just over half women, and with an age range of 15 to 100 years. Four participated out of every five people asked. PLMD was higher in women than men, but RLS was higher in men than in women (Figure 1). About one in five people who had one complaint also had the other. Overall, about 1 person in 25 has PLMD, about 1 in 20 RLS, and an unlucky 1 in 100 has both.

PLMD was constant across ages, but RLS increased with age (Figure 2). Compared with the youngest age group, there were statistically increased rates of RLS in people older than 40 years. Associations with medical conditions, demographics and lifestyle were also examined for PLMD and RLS.

**Figure 1: PLMD and RLS in women and men**

![Bar chart showing the percentage of people with PLMD and RLS in women and men.]

**Figure 2: PLMD and RLS by age**

![Bar chart showing the percentage of people with PLMD and RLS by age.]

**PLMD**

People with PLMD were more likely to have musculoskeletal disorders (18%), heart disease (5%), diabetes (2%), or, particularly have a mental disorder (34%). They were more likely to take anxiolytics (5%) or hypnotics (10%). Sleep apnoea syndrome (9%) was also common.

In terms of lifestyle, drinking more than six cups of coffee a day was more frequent (22%) in people with PLMD, and 29% had high life stress.

**RLS**

People with RLS were more likely to have high blood pressure (22%), musculoskeletal disorders (13%), heart disease (7%), diabetes (2%), or a mental disorder (16%). They were more likely to take anxiolytics (5%) or hypnotics (10%).

Coffee drinking was less common in people with RLS, and 41% drank no coffee at all.

**Comment**

A few interesting lessons. First was that for something really quite common, there were few large studies of prevalence based on whole populations and with clearly defined diagnostic criteria. Second is the fact that these conditions are quite common. They affect about 1 in 15 of us.

Whether we can make much of the associations is another matter. One that was interesting was that most of the people with PLMD or RLS had some physical or mental medical condition, roughly 7 out of 10. Whether it is possible to make much of the lifestyle associations is less clear. Some might try to make something out of associations with coffee. But people with RLS tended to drink less coffee. Should they be encouraged to drink more, or have people with RLS found that coffee drinking makes things worse, or have they been told that it does, so have reduced coffee intake?

The next step is treatment. That is less easy. Bandolier found about 20 or so randomised trials, but no systematic reviews, on a quick search. Time for someone to do some literature synthesis, perhaps.

**References:**
HRT and Breast Cancer

Bandolier 24 looked at breast cancer risk from the US Nurses’ study involving about 120,000 women. That concluded that increasing risk of breast cancer was associated with current use of HRT, longer use of HRT, and perhaps was higher with some HRT preparations than others. Use for more than five years was associated with a relative risk of about 1.5. We now have information from over a million women in the UK, which gives much harder evidence on which to base judgements [1].

Study

Over five years to early 2001 NHS breast screening centres participating included a study questionnaire with a letter of invitation sent two to six weeks before routine mammography. The questionnaire contained questions on various factors, including use of HRT (what, when, for how long) and menstrual history.

Participants were flagged on NHS registers so that cancer registrations and deaths could be identified. Women previously on the cancer register were excluded, except for non-melanoma skin cancer.

Table 1: HRT use and breast cancer incidence

<table>
<thead>
<tr>
<th>Use of HRT at baseline</th>
<th>Number per 1,000 women</th>
<th>Relative risk</th>
<th>Number of users for each extra case</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never users</td>
<td>7.4</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Past users</td>
<td>7.0</td>
<td>1.0</td>
<td>not applicable</td>
</tr>
<tr>
<td>All current users</td>
<td>11.2</td>
<td>1.7</td>
<td>260</td>
</tr>
<tr>
<td><strong>Current use of</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestrogen only</td>
<td>8.6</td>
<td>1.3</td>
<td>1600</td>
</tr>
<tr>
<td>Oestrogen-progestagen</td>
<td>13.5</td>
<td>2.0</td>
<td>160</td>
</tr>
<tr>
<td>Tibolone</td>
<td>10.1</td>
<td>1.5</td>
<td>360</td>
</tr>
<tr>
<td>Other</td>
<td>9.7</td>
<td>1.4</td>
<td>420</td>
</tr>
<tr>
<td><strong>Oestrogen use for</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>less than 1 year</td>
<td>5.6</td>
<td>0.8</td>
<td>not applicable</td>
</tr>
<tr>
<td>1-4 years</td>
<td>8.5</td>
<td>1.3</td>
<td>900</td>
</tr>
<tr>
<td>5-9 years</td>
<td>8.8</td>
<td>1.3</td>
<td>700</td>
</tr>
<tr>
<td>10 years or more</td>
<td>8.7</td>
<td>1.4</td>
<td>750</td>
</tr>
<tr>
<td><strong>Oestrogen-progestagen use for</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>less than 1 year</td>
<td>9.9</td>
<td>1.5</td>
<td>390</td>
</tr>
<tr>
<td>1-4 years</td>
<td>11.8</td>
<td>1.7</td>
<td>220</td>
</tr>
<tr>
<td>5-9 years</td>
<td>14.9</td>
<td>2.2</td>
<td>130</td>
</tr>
<tr>
<td>10 years or more</td>
<td>15.3</td>
<td>2.3</td>
<td>125</td>
</tr>
<tr>
<td><strong>Breast cancer deaths</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never users</td>
<td>0.61</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Past users</td>
<td>0.59</td>
<td>1.1</td>
<td>not applicable</td>
</tr>
<tr>
<td>Current users</td>
<td>0.67</td>
<td>1.2</td>
<td>16,000</td>
</tr>
</tbody>
</table>

The relative risk was adjusted for age, time since menopause, parity, age at first birth, family history, BMI, geographical area and deprivation index.

Results

There were 1,084,100 women in the study. At recruitment the average age was 56 years. Follow up was 2.6 years of for breast cancer diagnosis and 4.1 years for breast cancer mortality. There were 9,364 diagnoses of invasive breast cancer and 637 deaths from breast cancer. Most women were postmenopausal, and the main analysis was on 830,000 postmenopausal women.

Table 1 shows the main results, in terms of the number of diagnoses of breast cancer or breast cancer deaths per 1,000 women, the relative risk, and the number of users of HRT needed to generate an extra case of breast cancer diagnosis or breast cancer death.

Current use of HRT, but not past use, was associated with increased numbers of cases and deaths. Past use, even for less than a year, was associated with no increased risk. Over 2.6 years there was one extra diagnosis for every 260 women currently using HRT. Over 4.1 years there was one extra breast cancer death for every 16,000 women currently using HRT.
HRT products containing both oestrogen and progesterone were associated with the highest risk of breast cancer diagnosis, particularly over a longer time. Only 160 women needed to use oestrogen and progesterone HRT for there to be one extra case. Oestrogen-only HRT preparations, and tibolone, and other preparations, were also associated with higher risk of breast cancer diagnosis, but at a lower level than with oestrogen and progesterone (Table 1).

We are also given calculations, of use to individual women and from the societal perspective. For the individual woman, the calculation for use of oestrogen only or oestrogen-progesterone for five or 10 years from age 50 results in about one to 19 additional cases of breast cancer per 1,000 women, depending on preparation and duration of use (Table 2).

For society, the calculation is that on the assumption that 25% of women aged 50-65 years were current users of HRT during the past decade, then that would have resulted in 20,000 additional cancers because of HRT use. Three-quarters would have come from use of oestrogen-progesterone preparations.

**Comment**

This is a marvellous study. It gives all of us information on which we can base advice or decisions. Brief use of some HRT preparations at the menopause results in very low increased risk, but some women will find even that additional low risk more than negligible. Other preparations used for longer will give a higher risk, but that increased risk will be acceptable to some women because of benefits from HRT use.

**Reference:**


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**SPRINGTIME HYPOGLYCAEMIA IN CHILDREN WITH DIABETES**

The suggestion that hypoglycaemia might be more frequent in diabetic children in the Spring has been around for some time [1]. But other than something occasionally discussed, it does not seem to have been much studied. **Bandolier** tried to find out more because of reader enquiry. Two studies [2, 3] have addressed the issue, linking adverse events in intensively treated diabetic children with timing of hypoglycaemia and seasonal variation in glycated haemoglobin levels.

**Studies**

Children aged 0-18 years with diabetes in a geographical area of Sweden constituted the population. They were treated with four or more doses of insulin a day, with self-control from an early age. Fast-acting insulin was combined with slow- or intermediate-acting insulin. Meals were regular in time and content. A multi-disciplinary diabetic team was involved with the care of individuals, with regular contact.

Children or parents were asked to register every severe hypoglycaemic event and hospital admission.

**Results**

The children had an average age of 13 years, with a range of 1-18 years. Most (95%) used at least four insulin injections a day. Average haemoglobin A1c levels were 7%.

The yearly incidence of unconsciousness and severe hypoglycaemia without unconsciousness were recorded during 1994 and 1995 for 126 and 122 children respectively [1]. In each year the incidence of unconsciousness was 0.2 per patient per year, with 12% of children unconscious. The incidence of severe hypoglycaemia without unconsciousness was 1.3 per patient per year, with 34% of children experiencing an event.

There was no difference in glycated haemoglobin or other parameters between those children who experienced unconsciousness and those who did not. Unconsciousness occurred more frequently in Spring than at other times of the year (Figure 1).

A second study [2] examined haemoglobin A1c levels throughout the year, based on 810 blood samples from 114 children aged 2-18 years. Lower values were found in Spring and Summer (Figure 2), despite no change in insulin.

**Comment**

Seasonality of blood glucose, glycated haemoglobin, and
Thiomersal (UK spelling) or thimerosal (US spelling) is an organic compound that contains ethylmercury, and which is frequently used as a preservative in chemistry and biochemistry. It has also been used as a preservative in vaccines.

A consequence has been a concern that giving organic mercury compounds to children might adversely affect their development, because high doses of mercuric compounds affect kidneys and nerves. Methylmercury has particularly been associated with environmental contamination and major human health problems. A study that examines the relationship between use of thiomersal and autism [1] is particularly welcome if it is sufficiently large and of high enough quality to answer the question with some authority.

Study

The study was conducted in Denmark, where, since 1968, people have had a unique identification number. This, together with the use of other specialist registries was used to construct a database of a comprehensive cohort of children born between 1990 and 1996. Information on vaccination could be linked to diagnosis of autism or autistic spectrum disorders, and potential confounders. Autism was diagnosed according to strict diagnostic criteria. All diagnoses up to the end of 2000 were recorded.

From 1970, the only thiomersal-containing vaccine used in Denmark was a whole-cell pertussis vaccine. This was used...
until March 1992 when the last batch was released and used. The vaccine was reformulated without thiomersal, and used until January 1997. The vaccine was administered at five weeks, nine weeks, and 10 months, irrespective of thiomersal content, and had the equivalent of 25 µg ethylmercury in the first dose and 50 µg in succeeding doses, for a maximum dose of 125 µg for each child.

This therefore constituted a population based cohort study of thiomersal use in childhood vaccination.

Results

In the cohort were 467,450 children with just under three million person-years of follow up. There were 440 cases of autism where the mean age at diagnosis was 4.7 years and 878 cases of other autistic spectrum disorders where the mean age at diagnosis was 6.0 years. Information was lost on 5,770 children (1.2%), mainly because of emigration.

Of the cohort, 95.6% were vaccinated at least once, 89% twice, and 63% received all three doses of the whole-cell pertussis vaccine. Only 4.4% did not receive any whole-cell pertussis vaccine.

There was no association between use of thiomersal and the risk of developing autism or autistic spectrum disorder (Table 1). For neither autism nor autistic spectrum disorders was there any increased diagnosis associated with use of thiomersal-containing vaccine. Neither was there any dose-response with increasing exposure to ethylmercury. The relative risks were adjusted for a range of possible confounders, but crude rates were no higher, and even lower, in children exposed to ethylmercury compared with those not exposed.

Comment

What we have here is a superb study of what was, in effect, a real world before-after experiment. The study was huge, and comprehensive, covering almost 99% of children born in Denmark during a period during which a switch was made from use of a vaccine containing thiomersal to one that did not. It was the only vaccine given to children that did contain thiomersal. Moreover, diagnosis of autism or autistic spectrum disorder was according to strict criteria, and comprehensively applied. Follow up was for a minimum of four years, ensuring that almost all cases likely to occur should have occurred during that time.

Of course, Denmark changed to having thiomersal-free vaccines. Even with good evidence of lack of association, that is a good thing. What we have, though, is powerful evidence that autism and autistic spectrum disorders do not arise from use of thiomersal in vaccines.

Reference:
TREATMENT ADHERENCE
IN PSYCHOSIS

Over a quarter of a century ago, David Sackett and Brian Haynes defined compliance (concordance) as the extent to which a person’s behaviour coincides with the medical advice given. Non-adherence can just be about taking the pills, or prematurely ending treatment, or not entering treatment in the first place. Systematic reviews are infrequent, and one about failure of adherence to treatment programmes in people with mental health problems tells us that one in four fails to adhere to treatment [1].

Systematic review

Searching involved two electronic databases, including a specialist mental health database, plus reference lists. Searching was from 1980, but the date of the last search was not given. Any report was included if it included patients with schizophrenia, psychoses, or severe mental disorders, if adherence was the primary outcome and if patients were recruited in a psychiatric setting. Compulsory treatment studies, and those relating to initial appointments were not included.

The definition of non-adherence was either not taking drugs as prescribed, or not keeping appointments as scheduled. Any method of determining these outcomes was allowed.

Results

There were 103 studies found, with data for analysis on just under 24,000 patients in 86 of them. The diagnosis was equally split between patients with schizophrenia, psychoses, or severe mental disorder. Most patients were already on treatment (84%) or were first contacts (14%), with few studies on patients with a history of low adherence. Most studies (85%) were in outpatients or in patients after discharge from hospital. Determination of non-adherence was predominantly made by use of case notes, physician interview or rating scales.

Study sizes ranged from 20 to 2,300 patients, and half the studies had fewer than 100 patients. The bulk of patients (84%) were in studies with more than 151 patients. Duration was as short as two weeks and as long as four years. The median duration was eight months, and 60% lasted longer than six months.

The overall weighted mean rate of non-adherence was 26%, where weighting was by size of study. The unweighted average was 38%. Trial size was a major (and significant) determinant of non-adherence rate (Figure 1), with much lower rates of non-adherence in the bulk of patients in studies with more than 151 patients, whether or not weighting was used. Length of follow up made no difference to non-adherence rates.

Non-adherence was similar whether the definition was not keeping appointments as scheduled (24%) or not taking drugs as prescribed (30%). Similar rates were seen for inpatients, outpatients, and patients after discharge, and for the different diagnoses of schizophrenia, psychosis and severe mental disorder.

Comment

Knowledge is good, methodological insight is better. This study gives us both.

We know from this study that about one in four patients with severe mental illness will fail to adhere to treatment programmes. Neither setting nor diagnosis seems to make much difference.

What we also have is an insight into methodological issues for this type of study, and one that might usefully be applied when looking at similar studies in different settings. This insight is the double one of trial size, and the importance of weighting. There was a clear relationship, with small studies giving much higher non-adherence rates. Weighting by trial size to some extent might obviate the problem, but the implication is perhaps that small studies could have other problems that make them less reliable. What might then have been interesting would have been a sensitivity analysis of different factors only in larger studies.

Reference:
IMPACT AND IMPACT FACTORS

The way in which we think of medical journals depends an awful lot on where you start. Some academics are obsessed with things called “impact factors” that measure how often papers in a journal are cited (Box 1). Other people make sweeping assumptions about quality of journals, based on a range of items like peer review, whether they have heard of it or not, where it is published, or whatever. Bandolier has certainly heard some singular definitions of journal quality in its travels.

Impact factors cover a wide range. Some journals achieve impact factors of 25 or more, anything over 4 is good, most journals have impact factors of 1 or 2, while many have impact factors well under 1. An impact factor of 0.1, for instance, indicates one citation for every 10 articles published. How do impact factors relate with professionals’ attitudes to journals and their quality? A study [1] tells us they are related, but not that closely.

Study

A questionnaire was mailed to 416 randomly-selected physicians (practitioners and researchers) in the US. Physicians were asked to rate the overall quality of general medical journals on a scale of 1 to 10, with 10 being highest. Respondents were also asked whether they subscribed to the journal, and whether they read it regularly.

Results

There were 269 returned questionnaires. Respondents had an average age of 46 years, were mostly men, and 26% were registered in a medical subspecialty. Their average responses, and the journal impact factors, are in Table 1.

None of the journals were rated much less than 5 out of 10, or more than 8 out of 10, with less than a two-fold range of quality between high and low. By contract, there was a 15-fold range in subscription and reading levels, and a 163-fold range in impact factors. There was a correlation between physician rating and impact factor.

Comment

Perhaps these results are not unexpected. All of the journals in Table 1 are good, respectable journals, publishing interesting and high-quality papers. That physicians rated them as they did makes sense. In a US audience, the lower readership for a UK journal (Lancet) and a regional journal (Southern Medical Journal) did not adversely affect judgement of quality.

There are two lessons. Academic pointy-heads should follow the impact factors. The rest of us should seek out good quality and relevant papers to read, wherever they are published, and make more use of our medical librarians (or knowledge managers).

Table 1: Quality rating of journals by physicians and impact factor

<table>
<thead>
<tr>
<th>Journal</th>
<th>Quality rating</th>
<th>Impact factor (in 1997)</th>
<th>Subscribe (%)</th>
<th>Read (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New England Journal of Medicine</td>
<td>8.4</td>
<td>27.8</td>
<td>74</td>
<td>75</td>
</tr>
<tr>
<td>Lancet</td>
<td>7.1</td>
<td>16.1</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Annals of Internal Medicine</td>
<td>8.0</td>
<td>12.1</td>
<td>77</td>
<td>72</td>
</tr>
<tr>
<td>Journal of the American Medical Association</td>
<td>7.4</td>
<td>9.3</td>
<td>71</td>
<td>70</td>
</tr>
<tr>
<td>Archives of Internal Medicine</td>
<td>6.1</td>
<td>4.8</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>American Journal of Medicine</td>
<td>5.9</td>
<td>4.2</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Journal of General Internal Medicine</td>
<td>6.4</td>
<td>2.1</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>Southern Medical Journal</td>
<td>4.8</td>
<td>0.6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hospital Practice</td>
<td>4.9</td>
<td>0.2</td>
<td>31</td>
<td>23</td>
</tr>
</tbody>
</table>

References:


Box 1: Impact factor calculation

An impact factor for a journal attempts to provide a measure of how frequently papers published in a journal are cited in the scientific literature. It is derived by dividing the number of citations in any one year with items published in the journal in the previous two years. The calculation is as follows:

A = total literature citations to substantive items published in a journal in 2003.
B = number of citations in A that refer to articles published in 2001 and 2002.
C = number of substantive articles published in the journal in 2001 and 2002.

The impact factor is then B divided by C, and gives the average number of times an article published in the journal in 2001 and 2002 has been cited in 2003.

Thus if there were 1000 citations in 2003 for 100 articles published in a journal in 2001 and 2002, the impact factor would be 10. Most journals (and there are many, many journals) have impact factors that are below 2. Journals with impact factors above 4 tend to be regarded as having a high impact factor, and those above 10 are stellar.

Reference: