OF CABBAGES AND KINGS

Bandolier as you all know has occasional panic attacks (Bandolier 11). This month’s has three components, risk management, reading in bed and déjà vu.

Risk management

Risk management is understandably big business for Trusts, who can buy in to a pool insurance policy but must look after the shop if claims are to be paid. The spectre, reality rather than vision, is that it is risk managers who will decide that certain interventions will be withdrawn from the menu. The reason for withdrawing services will be the prospect of major harm leading to a major claim and a major payout.

This may have most impact on ‘discretionary’ interventions, that is where the clinician provides what she or he sees as a Rolls-Royce quality service which has a (small) risk of causing major harm. There are alternatives, which do not provide as high quality benefit but do carry a lower risk of harm. An example is providing epidural local anaesthetic for pain relief after major surgery. This carries a 1 in 5000 risk of neurological sequelae [1], a big or a small risk depending on how you look at it. You could just have intramuscular injections of morphine, although these too carry some risk. The risk of neurological sequelae is too low for clinicians to have to mention it to patients, because the usual rule is that if the risk is less than 1% then it does not have to be mentioned in consent procedures. Clearly it is a setting in which many clinicians feel that the benefit, high quality pain relief, is well worth this 1 in 5000 risk. Risk management may dictate otherwise.

Reading in bed

Reading in bed may be one of life’s great pleasures but Bandolier believes that technological advance is required. How can you lie on your side to read comfortably while wearing reading glasses? Is there a market here for lorgnettes, with right or left -armed versions for those who read on their right or left side respectively? What about bookrests which swivel from the bedside or bedhead? Thank goodness Bandolier does not come with heavy bindings. A copy of the bound Bandolier for the best suggestions.

Evidence-based Kings

The déjà vu comes from the intriguing book on George III by Macalpine and Hunter [2]. The Reverend Thomas Willis handled the coercion and restraint of the King. Appearing before a parliamentary committee he made the claim, which he couldn’t substantiate by retrospective audit, that he could cure 9 out of 10 of his patients. Along came Philippe Pinel, founder of the French school of psychiatry, and the man who symbolically and literally took the chains of his patients at the Bicêtre in 1793, to check out this English wizard. Pinel was systematic - “I have for the last 15 years ... consulted all the works which have appeared on it in the English language” - but (as Bandolier often finds) “I have found no secret although all attest their success”. He was also aware that self-limited disorders can lead to claims of magic cures - he had lost “faith in pharmaceutical preparations”, because “I saw with wonder, the resources of nature when left to herself, or skilfully assisted in her efforts”. The book also has a picture of what is claimed to be the first histogram in medicine, Dr Richard Powell’s chart of 1810, showing the number of lunatics by lustrum, or 5 year period; it was used to demonstrate the ‘fashionable’ increase in mental illness after King George’s little trouble. Recommended reading.

References:
1 Kane RE. Neurologic deficits following epidural or spinal anesthesia. Anesthesia and Analgesia 1981;60:150-161.

Exhibiting the whole Number of Lunatics returned under the Act both from the London & Country Districts for seven successive Lustra

Lustra

<table>
<thead>
<tr>
<th>1775-9</th>
<th>1780-4</th>
<th>1785-9</th>
<th>1790-4</th>
<th>1795-9</th>
<th>1800-4</th>
<th>1805-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1700</td>
<td>1800</td>
<td>1900</td>
<td>2000</td>
<td>2100</td>
<td>2200</td>
<td>2300</td>
</tr>
</tbody>
</table>

Number
Patients with cardiac disease, and especially those who have already had an infarct, often believe that sexual activity can bring on a heart attack. Portrayal of such events on TV and in films serves to reinforce this commonly held belief.

So it is good to see some high quality evidence which allows us to put figures on the risks, and to be able to use these in advising patients. A study from Harvard [1] gives us the numbers.

**Study**

Between 1989 and 1993 1774 patients were interviewed soon after an MI (median 4 days, range 0 - 30 days). For inclusion the patients had to have elevated cardiac enzymes, pain or other symptoms of MI and ability to complete a structured interview.

The interviews were conducted by trained personnel, and about a third of the interviews were audiotaped and checked for quality control. The interview identified issues surrounding the MI, including sexual intercourse immediately before, and during the year before the MI. Patients who reported sexual intercourse within 26 hours of the MI were asked about all sexual activity in the previous 26 hours. Undertaking regular physical exercise, the amount of heavy exertion and its frequency also formed part of the interview.

**Design**

A new design was used for this study in which control information for each patient was based on his or her past exposure.

The two-hour period immediately before MI onset was compared with two types of control: their usual frequency of sexual activity during the past year and their sexual activity in the comparable two-hour period at the same time the day before the MI.

A number of potential modifiers of the risks were examined, including age, sex, clinical history, smoking, drugs and exertion. Only frequent moderate exercise was shown to modify the risk. The risk of an MI in the two hours after sexual activity decreased from 3.0 to 1.9 to 1.2 for patients who engaged in heavy physical exercise once or not at all, twice, and three or more times respectively.

**Results**

1774 patients were interviewed. 141 chose not to answer questions about sexual activity. Of the remaining 1633 (643 of whom had angina or a previous MI), 858 (48%) reported sexually activity in the year before their MI.

The frequency of sexual activity in the 858 active patients (mean age 55 years, 82% men) is shown in the figure. Of these, 9% reported sexual activity in the 24 hours before their MI and 3% in the two hours before their MI.

The relationship between the relative risk of onset of MI and sexual activity in the four hours immediately preceding it is shown in the second figure. The relative risk was increased only during the first two hours after sexual activity in the first two hours after sexual activity the risk that an MI would occur was 2.5 (95% CI 1.7 - 3.7).
One in a million

Only 27 of the 1774 patients reported sexual activity in the two hours before their MI. After correcting chance occurrence, sexual activity was a likely contributor in only about 0.9% of the cases in this study.

Data from the Framingham Heart Study indicates that the baseline risk that a 50-year old, nonsmoking, nondiabetic man will experience an MI is about 1% per year, or 1 chance in a million in any hour. Since the relative risk of MI is about 2, engaging in sexual activity increases his risk to 2 in a million, and only for a two-hour period.

A baseline yearly risk of reinfarction or death for an individual with a prior MI is about 10%, but less than 3% if the individual can exercise without symptoms on an exercise test. For individuals in the higher risk category, sexual activity would double the risk of MI from 10 in a million per hour to only 20 in a million per hour and then only for about two hours.

Perspective and risk

The effect of sexual activity on annual risk is negligible because the absolute risk difference is small, the risk is transient, and the activity is relatively infrequent. Not exercising, smoking and getting angry are all more likely to pose bigger risks, at the trivial level because we get angry more frequently than we have sex (at least in the Bandolier office).

It is also interesting to compare the risk from sexual activity with risks of travel, sport, or even walking highlighted elsewhere in this issue. It is good to know there are things we can do without particular risk, like drinking moderately (Bandolier 27) and eating vegetables (Bandolier 20).

Reference:

Failed meta-analysis

David Naylor has written an interesting paper [1] in which he argues “the case for failed meta-analysis”. He defines a failed meta-analysis not as one that fails to meet accepted standards, nor even one that may have been misleading (as was the case with the magnesium sulphate meta-analysis described in Bandolier 7). He defines a failed meta-analysis as a systematic review that “for various reasons other than poor methodology on the part of the analysts does not allow data aggregation that permits a definitive quantitative conclusion about the merits or demerits of a particular health care intervention”.

Why meta-analysis can fail

He lists a number of ways that meta-analysis of good methodological design can fail to yield definitive quantitative results:

1 Aggregation feasible, but results inconclusive.
2 Aggregation not feasible owing to inconsistencies in design, study quality endpoint reportage, or data availability
3 Aggregation not feasible owing to variability in populations.
4 Aggregation not feasible owing to variability in interventions.

He cites the landmark publication of Effective Care in Pregnancy and Childbirth as one of the first steps to promote failed meta-analysis. That wonderful publication, which led to the Cochrane Collaboration, was the first comprehensive collection of systematic reviews, of which “about one third” were “unapologetically inconclusive”.

Benefits from failure

Perhaps Naylor is being over-dramatic in calling these meta-analyses “failed meta-analyses”; but who are we in Bandolier to criticise the use of racy titles?

The point is that any such review has systematically collected the known work on a particular topic - a worthwhile end in itself. It will have pointed out deficiencies in study design or quality which cause the meta-analysis to fail. It will have pointed out any confusion over outcomes or end-points which needs to be addressed before more studies are conducted. It will prevent (hopefully) further pointless studies being conducted whose ethical status will be compromised unless design or outcome problems are addressed.

So long live negative meta-analysis - but only until they become positive - and long live editors with the intestinal fortitude to publish them.

Reference:
Knowing what to do for the best

Ankylosing spondylitis is an inflammation of the spine involving the lower back and sometimes peripheral joints. It predominantly affects young men, usually before age 30. It has a prevalence of about 0.1% (1 in 1,000) and a strong association with HLA B27 histocompatibility group (95% of patients).

Physical therapy

Treatment often includes exercise and physiotherapy, regarded as being important in slowing the deterioration in spinal mobility and maintaining quality of life. How these treatments are best delivered is not known with any certainty. A randomised trial of three different physiotherapy regimens in ankylosing spondylitis demonstrates the real problems in research to determine what to do for the best.

Randomised trial

The study [1] at Leeds randomised 44 patients to receive either:-

1 intensive in-patient physiotherapy
   - a three-week admission which involved daily intensive exercise, stretching, aerobics, hydrotherapy and other treatments as needed.

2 out-patient hydrotherapy and home exercises
   - a six-week period of twice-weekly out-patient hydrotherapy

3 home exercise alone
   - patients were instructed in the home exercise regime and given diary cards to complete, with review at six weeks. They could have further diaries if wanted.

All patients were advised to continue exercising after completing the study.

Assessments

A number of measurements were made immediately before starting treatment, after completing treatment, and two, four and six months afterwards. Cervical rotation, chest expansion, lumbar movement and a visual analogue scale for both pain and stiffness were measured.

Results

Despite some initial differences, at six months there were no differences in outcomes between the groups. The bottom line was that there was no bottom line.

Problems

The authors were frank about the problems they encountered while doing this research, and it is instructive to look at some of the issues which makes a negative result suspect.

1 Poor recruitment rate. Many patients refused to enter; if they were employed they were not willing to commit to in-patient treatment, and if unemployed they preferred to have in-patient treatment.

2 High drop out rate. At six months 87%, 60% and 57% in each group attended for assessment. Some patients who were randomised to groups other than those they preferred, and when thwarted, defaulted.

3 Measurements were not blinded. There was insufficient funding for measurements to be made by a physiotherapist who did not know what treatments had been given.

4 Measurements were imprecise given the magnitude of changes expected. In a pilot study the repeatability of measurements was studied over three days. For cervical rotation, for example, the mean difference between measurements was 1°, with a standard deviation of 8.5° (95% confidence range is four times a standard deviation, in this case 34°). The mean change seen with treatment was 20° at most.

Comment

Doctors and physiotherapists have to take a pragmatic approach to treatment, and making changes is difficult where patients have chronic disorders and when they think they know what works for them. Knowing what to do for the best where good evidence is lacking will never be easy.

Nor is it easy for researchers, as this paper shows. Studies like this take an enormous amount of enthusiasm, time and dedication. The failure to generate a definite answer may be a disappointment, but highlighting these important practical problems in getting good quality answers is very important.

Reference


Physiotherapy Effectiveness

A series of references and short reviews on physiotherapy effectiveness are available from Tracy Bury, Chartered Society of Physiotherapy, 14 Bedford Row, London WC1R 4ED. The cost is £1 each or £5 the set. They cover:-

- back pain
- evidence-based health care
- cardio-pulmonary rehabilitation
- electrophysical agents
- incontinence
- neurology
- orthopaedics/rheumatology
- paediatrics
MAD COWS AND ECSTASY

Chance and choice in an evidence-based society

The headline of this article could well have been written by the Bandolier editorial team, combining as it does elements of science and showbiz. It is, however, the title of a major paper in that most respectable of journals, the Journal of the Royal Statistical Society.

The title was chosen by Adrian Smith for his Presidential address [1] and provides an excellent overview of all the issues about which Bandolier cares so dearly.

Professor Smith laments the image of statistics as mere number-crunching and prefers to say that statistics is “the science of doing science”. It will be encouraging to doctors, frequently criticised for not practising evidence-based health care, to learn that medicine stands out like a shining beacon in a world of evidence-based decision-making. Doctors will regard with some relish Professor Smith’s lambasting of the legal profession and he quotes a depressing comment from the Bench of the Court of Appeal:

“Evidence of the Bayes Theorem or any similar statistical method of analysis in a criminal trial plunged the jury into inappropriate and unnecessary realms of theory and complexity, deflecting them from their proper task...Their Lordships....had very grave doubts as to whether that evidence was properly admissible because it trespassed on an area peculiarly and exclusively within the jury’s province, namely the way in which they evaluated the relationship between one piece of evidence and another. The Bayes Theorem might be an appropriate and useful tool for statisticians, but it was not appropriate for us in jury trials or as a means to assist the jury in its task “[2].

So there we have it, as Professor Smith says. To hell with rationality as we know it - their Lordships have pronounced!

Showing just how broad the view of a statistician actually is, the author presents fascinating issues about chance and choice, looking at sociological obstacles to evidence-based health care, principally the problems of translating decisions about groups (the basis of epidemiology) to decisions about individuals (the core business of clinical practice). Psychological obstacles and issues are also discussed and his section on risk shows just how illogical we are in assessing risks - as the table shows.

To prevent these problems he advocates better education but emphasises the size of the task that faces us. He also challenges statisticians to play a bigger part in debates dominated by opinion, prejudice, and sometimes hysteria, most recently the debates on mad cows and ecstasy. He finishes with a wonderful quote about Florence Nightingale (at a time when she was injecting morphine for her back pain - Bandolier ed):

“Florence Nightingale believed - and in all the actions of her life acted on that belief - that the administrator could only be successful if he (she) were guided by statistical knowledge. The legislator - to say nothing of the politician - too often failed for want of this knowledge. Nay, she went further: she held that the universe - including human communities - was evolved in accordance with a divine plan....But to understand God’s thoughts, she held we must study statistics, for these are the measures of His purpose. Thus the study of statistics was for her a religious duty”.

Karl Pearson

Request this article from your library: it is a classic, and great reading for the beach at Blackpool or a cafe in the Dordogne.

References:


2 The Times. Juries not to apply mathematical formulae. May 9 1996.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Period</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Travel:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Bus or coach</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Rail</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Car or taxi</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Bicycle</td>
<td>50.0</td>
<td></td>
</tr>
<tr>
<td>Pedestrians</td>
<td>70.0</td>
<td></td>
</tr>
<tr>
<td>Motorcycle</td>
<td>104.0</td>
<td></td>
</tr>
<tr>
<td><strong>Sport:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amateur boxing, UK</td>
<td>1946-62</td>
<td>0.5</td>
</tr>
<tr>
<td>Canoeing, UK</td>
<td>1960-62</td>
<td>10.0</td>
</tr>
<tr>
<td>Rock-climbing, UK</td>
<td>1961</td>
<td>40.0</td>
</tr>
<tr>
<td>Scuba diving, UK</td>
<td>1970-80</td>
<td>220.0</td>
</tr>
<tr>
<td>Hang-gliding</td>
<td>1977-79</td>
<td>1500.0</td>
</tr>
<tr>
<td><strong>Medical procedures:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>1986</td>
<td>5.0</td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>1970-73</td>
<td>40.0</td>
</tr>
<tr>
<td>Childbearing</td>
<td>1987-89</td>
<td>69.0</td>
</tr>
<tr>
<td>Childbearing</td>
<td>1974-76</td>
<td>100.0</td>
</tr>
<tr>
<td>Needle biopsy of the liver</td>
<td></td>
<td>200.0</td>
</tr>
</tbody>
</table>
ISSUES IN TRIAL REPORTING

Reports of randomised controlled trials, and systematic reviews of them, are the way in which we make decisions about whether treatments work, and whether we should use them. Quality issues surrounding trial methods and reports are important - because we are likely to give greater weight to trials of high quality and less weight to those of lower quality.

Ken Schulz and his colleagues have demonstrated that trials which are not randomised exaggerate the estimate of effectiveness by about 40%, and those which are not double-blind exaggerate the estimate of effectiveness by about 17% (Bandolier 17).

In a new analysis, Schulz and colleagues have examined how well randomised trials of parallel group studies in obstetrics and gynaecology handle issues of blinding, and what happens to patients who are excluded or who ‘drop-out’ after randomisation [1].

Study

They chose reports from four major obstetrics and gynaecology journals in the 1990 and 1991 issues - 206 of them. Of these 110 were identified for evaluation. Most of the trials were pharmaceutical interventions (72/110).

Blinding

Of the 110 trials, 31 were reported as double-blind, 15 had blinded outcome assessments, one having blinded participants or caregivers, and 63 as not having any form of blinding.

Double-blinding was judged to be feasible in 65 trials, so only about half of the trials that could have been double-blinded were double blinded.

Double-blinding may not always be appropriate or possible. In trials with objective end points (death, for instance), any anticipated gain in blinding may not be worth the additional difficulty or expense. Where outcomes are subjective, or where observers’ knowledge of treatment allocation may produce bias, if possible it should be mandatory. Blinding may not be possible - in surgical trials, for instance. Despite this, blinding of assessments is possible and advisable.

Reports which call themselves double blind may not be. An example given is of a report that assigned patients by hospital number and gave two tablets to one group and only one to another. Compromised blinding should always be examined when reading reports.

Protecting treatment allocation

Of the 31 double-blind reports, only eight provided information on the protection of allocation schedule (keeping the randomisation code in a secure place, or not breaking the code until the end of the study). Only five trials reported that blinding had been implemented successfully, and only two tested the efficacy of their blinding - and both found substantial unblinding of the treatment assignments.

<table>
<thead>
<tr>
<th>Numbers of papers reporting on blinding and exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of trials</td>
</tr>
<tr>
<td>Double blinding possible</td>
</tr>
<tr>
<td>Double blinding stated</td>
</tr>
<tr>
<td>Protected treatment allocation</td>
</tr>
<tr>
<td>Successful blinding stated</td>
</tr>
<tr>
<td>Blinding tested</td>
</tr>
<tr>
<td>Excluded at least one patient</td>
</tr>
<tr>
<td>Insufficient information on exclusion</td>
</tr>
<tr>
<td>No exclusions</td>
</tr>
<tr>
<td>Explicit statement that none excluded</td>
</tr>
</tbody>
</table>

Exclusions

It is rare for all patients randomised to fulfil all the criteria established at the beginning. These become drop outs, or exclusions. Reports sometimes tell us about what happens to these patients, and then do an analysis of the results on what happened to all patients who fulfilled the trial protocol - a ‘per protocol’ analysis.

The most rigorous way of dealing with results, the most valid and unbiased way, is to analyse all patients randomised to the originally assigned groups, regardless of compliance with the protocol - the ‘intention-to-treat’ analysis.

In the Schulz analysis, 52/110 reports had at least one patient excluded. Of these, 29 indicated that more than 10% of patients randomised had been excluded and only 34 said which treatment groups excluded patients had been allocated to. Insufficient information was presented in nine reports to make any judgement. 49/110 trials reported no apparent exclusions. Yet only 11 of these explicitly stated that no exclusions had taken place.

Intention to treat uniquely preserves the ability of randomisation to reduce bias. Bandolier’s own experience is that intention to treat has different meanings for different authors, so for safety the rule is to trust most those analyses where all patients randomised are analysed, though per protocol analysis may provide additional useful information.

Guidelines on blinding

Schulz and colleagues suggest that authors should provide the following information on blinding:-

1. Mechanism - tablets, capsules, tablets.

2. Similarity of characteristics of treatment - appearance, taste, administration.
3 Control of allocation schedule - location of allocation schedule during the trial, when the code was broken after the trial, circumstances in which code could be broken for individual patient.

4 Statement on perceived success or failure of the double blinding efforts.

If these guidelines were followed by authors, it would make the work of the reader and reviewer a great deal easier, and help us get closer to the truth about treatment efficacy and effectiveness.

Reference:

UNBIASED COST-EFFECTIVENESS: AN OXYMORON?

Oxymoron:

“a rhetorical figure by which contradictory terms are conjoined so as to give point to the statement or expression (now often loosely = a contradiction in terms)” - Shorter Oxford English Dictionary.

Have you noticed how the arguments of the pharmaceutical companies have changed recently? No longer do they talk simply about a new drug being more effective; they emphasise that the drug is much more cost-effective for the health service, the argument being that even though the cost of prescribed medication is more expensive, savings are made elsewhere in the health care system.

With typical clarity and colour Robert Evans, one of the world’s leading health economists, responds trenchantly to two letters in the Annals of Internal Medicine [1] which criticised a Leader he wrote nine months previously.

His leading article [2] is well worth reading for anyone who receives information about the cost-effectiveness of new drugs (and that must apply to all of us these days). It was written as a commentary and critique of a major ten-page report in the Annals of Internal Medicine on the principles of “Economic Analysis of Health Care Technology” [3].

Bob Evans’ thrust was that this Taskforce was funded entirely by the pharmaceutical industry and that it was giving a verisimilitude of objectivity to a technique which should be assumed to be biased. His criticisms are typically forthright, for example saying that “a pseudodiscipline, pharmaco-economics, has been conjured into existence by the magic of money with its own practitioners’ conferences and journals. There are a lot of drugs and there is a lot of money so the ‘field’ is booming.”

References:

CORRESPONDENCE

Adverse drug reactions

We received our copies of Bandolier 28 recently and thought that a local perspective on adverse drug reactions might be of interest to you.

The prospective cohort study reported by Bates et al that you featured in that issue reiterated the message that adverse reactions to drugs are common, and identified 247 adverse drug “events” in a study population of 4031 admissions (6.1%). This compares with an Oxford study (Br J Clin Pharmacol in press), in which we collected adverse drug reaction data on 20,695 consecutive acute general medical admissions to seven general medical wards at the John Radcliffe Hospital between April 1990 and March 1993.
This was a spontaneous reporting scheme in which nurses, pharmacists, doctors, and medical students were invited to report adverse drug reactions occurring in patients during hospital admission. Deliberate or accidental overdoses were not included; nor were patients who were not admitted overnight to hospital. There were 1420 reports to the Oxford scheme, a rate of 6.9%.

In a parallel study in the John Radcliffe Hospital, 1071 acute medical admissions were systematically reviewed by an experienced adverse drug reaction pharmacist, and this study indicated that the spontaneous reporting scheme was effective in identifying 60% of all adverse drug reactions occurring on the general medical wards. This suggests that the true incidence of adverse drug reactions is nearer 10%.

In 25% of these cases the adverse drug reaction was the main cause of admission to hospital, and the remaining 75% arose after admission; i.e. on average each year 172 medical admissions to the medical wards at the John Radcliffe Hospital are due to adverse drug reactions, and a further 516 patients suffer an adverse reaction during their stay in hospital. In the 3 years covered by the study 2 patients died as a direct result of their adverse drug reactions.

The Boston group chose to use the term adverse drug event, which we believe causes confusion. This term is well established in another context, namely that of pre-marketing clinical trials, in which it is used to mean any adverse event that occurs during the trial; this is important, because the use of the term “event” rather than “reaction” avoids the need to make a judgement on causality at a time when little is known about the unwanted effects of the investigational drug. This use can also be extended to large post-marketing trials. For example, the increases in violent and accidental deaths seen in trials of lipid-lowering drugs were correctly classified as adverse events, and although they may have proved a lucrative field for those writing grants for studies on cholesterol and serotonin, in all likelihood they were not adverse reactions to the drug therapy.

However the Boston group have extended the use of this term to other types of adverse drug reaction, including errors in prescribing, misuse or malfunction of infusion pumps, and potential adverse reactions (e.g. potential drug interactions). Of course, these events do not come within the definition offered by the WHO, as they and you correctly pointed out, but it is also confusing to label them as adverse events. They are often in fact toxic reactions arising from poor prescribing.

The Bandolier article incorrectly states that ADRs are “idiiosyncratic and rare”, whereas in fact, as we and many others have shown, they are very common and are usually dose-related. In our view the WHO definition is a poor one. Any event that is attributable to a drug should be called an adverse reaction; dose-related adverse reactions can then be subdivided according to whether they are toxic reactions or side effects.

JK Aronson DJM Reynolds
Department of Clinical Pharmacology
Radcliffe Infirmary Oxford OX2 6HE

<table>
<thead>
<tr>
<th>Mode of transport</th>
<th>journeys</th>
<th>hours</th>
<th>km</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motorbike</td>
<td>100.0</td>
<td>300.0</td>
<td>9.70</td>
</tr>
<tr>
<td>Air</td>
<td>55.0</td>
<td>15.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Water</td>
<td>25.0</td>
<td>12.0</td>
<td>0.60</td>
</tr>
<tr>
<td>Bicycle</td>
<td>12.0</td>
<td>60.0</td>
<td>4.30</td>
</tr>
<tr>
<td>Foot</td>
<td>5.1</td>
<td>20.0</td>
<td>5.30</td>
</tr>
<tr>
<td>Car</td>
<td>4.5</td>
<td>15.0</td>
<td>0.40</td>
</tr>
<tr>
<td>Van</td>
<td>2.7</td>
<td>6.6</td>
<td>0.20</td>
</tr>
<tr>
<td>Rail</td>
<td>2.7</td>
<td>4.8</td>
<td>0.10</td>
</tr>
<tr>
<td>Bus/Coach</td>
<td>0.3</td>
<td>0.1</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data from Royal Society of Prevention of Accidents