

## Clinical Biostatistics

### Exercise: Confidence Intervals

The two short papers here appeared together in the British Medical Journal. They are very similar in the question they address and the methods used. Both refer to ‘moxibustion’. In moxibustion, moxa, a preparation of wormwood (*Artemisia moxa*), or another slow-burning substance, is lit and held as near to the point on the skin as possible without causing pain or burning. Both also refer to ‘significant’ events. The word is not used in its statistical sense.

#### Exercise 1:

Read the following paper (*BMJ* 2001;323:485-486 ) and prepare the questions following it.

#### **Adverse events following acupuncture: prospective survey of 32 000 consultations with doctors and physiotherapists**

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Acupuncture is increasingly popular, but it is not free from risk for the patient.<sup>1</sup> Safety is best established with prospective surveys. Our aim was to ascertain the incidence of adverse events related to acupuncture treatment, as currently practised in Britain by doctors and physiotherapists.

#### **Participants, methods, and results**

Volunteer acupuncture practitioners were recruited through journals circulated to members of the British Medical Acupuncture Society and the Acupuncture Association of Chartered Physiotherapists (approximately 2,750 members).<sup>2</sup> A prospective survey was undertaken using forms for intensive event monitoring that had been piloted previously.<sup>3</sup> Minor adverse events were defined as ‘any ill-effect, no matter how small, that is unintended and non-therapeutic, even if not unexpected.’ These events were reported every month, along with the total number of consultations. Minor or serious events that were considered to be ‘significant’—‘unusual, novel, dangerous, significantly inconvenient, or requiring further information’—were reported on separate forms when they occurred. Anonymous reporting was accepted. A sample size of 30,000 consultations was necessary to identify with 95% confidence any adverse event with a frequency of 1 in 10,000 consultations.<sup>4</sup>

[This next paragraph would not be understood by most readers of *BMJ*, but it gave Prof. Bland great pleasure. Take his word for it, it is a correct method.] Estimates of incidences per 10,000 population were calculated with the acupuncturist (not the consultation) as the primary sampling unit. Since the data were skewed, with extreme values present, confidence intervals corrected for bias were calculated using bootstrapping procedure ‘bs’ on estimates from the function ‘svyratio’ in Intercooled Stata version 6.0 [a computer program] with 10,000 replications.

Data were collected from June 1998 to February 2000 from 78 acupuncturists, 13 of whom chose to remain anonymous. The average age of the acupuncturists was 47 (range 27-71) years, 61% were doctors and 39% physiotherapists, and 71% had practised for five years or more. In all, 31,822 (median 318, range 5-1,911) consultations were included.

Table: Significant minor events reported by 78 doctors and physiotherapists in 31,822 acupuncture consultations

Event	Number reported
Administration problems:	
Needle lost or forgotten	5
Patient forgotten in treatment room	2
Application site problems:	
Cellulitis after treatment of oedematous leg *	1
Blister following moxibustion	1
Needle allergy	2
Needle site pain* (one case lasted 2 weeks)	3
Cardiovascular problems:	
Fainting	6
Gastrointestinal problems:	
Nausea †	2
Vomiting	1
General problems:	
Patient fell asleep during treatment	1
Drowsiness* (one case lasted 1 day; one case lasted 1 week)	2
Disorientation (one case lasted 1 hour; one case lasted 1 day)	2
Lethargy*	2
Neurological and psychiatric problems:	
Anxiety and panic (one episode lasted 60 hours) †	2
Euphoria	1
Headache for 3 days	2
Hyperaesthesiae with numbness for 3 days*	1
Seizure shortly after insertion of needles (probably reflex anoxic)*	1
Slurred speech	1
Exacerbation of symptoms:	
Back pain, fibromyalgia,* shoulder pain,* vomiting,* migraine*	5

\* Event led to reduction in daily activities in one patient.  
† Event led to reduction in daily activities in two patients.

Altogether, 43 'significant' events were reported (table), giving a rate of 14 per 10,000 (95% confidence interval 8/10,000 to 20/10,000). In addition, 48 apparently similar events were reported on the monthly forms, presumably due to different interpretations of 'significant'. All adverse events had cleared within one week, except for one incident of pain that lasted two weeks and one of sensory symptoms that lasted several weeks. According to accepted criteria,<sup>3</sup> none (0/10,000 to 1.2/10,000) of these events was serious.

A total of 2,135 minor events was reported, giving an incidence of 671 per 10,000 (42/10,000 to 1,013/10,000) consultations. The most common events were bleeding (310 (160 to 590) per 10,000 consultations) and needling pain (110 (49-247) per 10,000 consultations). Aggravation of symptoms occurred in 96 (43-178) per 10,000 consultations; in 70% of these cases, there was a subsequent improvement in the presenting complaint. The highest rates reported by individual acupuncturists, expressed as a percentage of consultations, were 53% for bleeding, 24% for pain, and 11% for aggravation of symptoms.

### Comment

Doctors and physiotherapists who performed acupuncture reported no serious adverse events and 671 minor adverse events per 10,000 acupuncture consultations. These rates are classified as minimal<sup>5</sup>;

however, 14 per 10,000 of these minor events were reported as significant. These event rates are per consultation, and they do not give the risk per individual patient.

Demographic data suggest that the acupuncturist volunteers were reasonably representative of the members of the two societies, but over-reporting and under-reporting are inherently possible in such studies. High individual rates may be due to a low personal threshold for reporting, or they may indicate the need for further training of the acupuncturist. Some avoidable adverse events occurred, and acupuncturists might consider modifying their practice to reduce the incidence of such events.

## Acknowledgements

We thank members of the British Medical Acupuncture Society and the Acupuncture Association of Chartered Physiotherapists for collecting data, Mike Fitter and Hugh MacPherson for advice in designing the questionnaire, and Val Hopwood for help in recruiting volunteers.

Contributors: EE, SH, and AW planned the study, which was supervised by AW. The data were collected by members of the British Medical Acupuncture Society and the Acupuncture Association of Chartered Physiotherapists. The results were collated by AW, and AH performed the statistical analysis. The final report was written by AW, SH, AH, and EE. AW and EE will act as guarantors.

## Footnotes

Funding: The posts of AW and EE are funded by the Maurice Laing Foundation.

Competing interests: AW has received fees for lecturing at scientific and educational meetings arranged by the British Medical Acupuncture Society and the Acupuncture Association of Chartered Physiotherapists. SH has received fees for lecturing and for acting as editor of the professional journal of the British Medical Acupuncture Society, *Acupuncture in Medicine*.

## References

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4. Eypasch E, Lefering R, Kum CK, Troild H. Probability of adverse events that have not yet occurred: a statistical reminder. *BMJ* 1995; 311: 619-620.
5. British Medical Association Ethics. *Medical ethics today. Its practice and philosophy*. London: BMA Professional Division Publications, 1993.

## Questions about this report

- (a) Are there any problems with the sampling method? What alternative methods might have been used? Would they solve the problem?
- (b) Are there any problems with the data collection methods? What alternatives might have been used? Would they solve the problem?
- (c) The average age of the acupuncturists was 47 (range 27-71) years. The median number of consultations for a practitioner was 318, range 5-1,911. What does this tell us about the shapes of the distributions of age and number of consultations?
- (d) Altogether, 43 'significant' events were reported, giving a rate of 14 per 10,000 (95% confidence interval 8/10,000 to 20/10,000). What does this mean?
- (e) According to accepted criteria, none (0/10,000 to 1.2/10,000) of these events was serious. Can we conclude that there is no risk of serious events?
- (f) The authors say '14 per 10,000 of these minor events were reported as significant. These event rates are per consultation, and they do not give the risk per individual patient'. Why do they not give the risk per individual patient?

- (g) The authors do not appear to draw any explicit conclusions. What would you conclude from this study?

## Exercise 2:

Read the following paper (*BMJ* 2001;323:486-487 ) and prepare the questions following it.

### **The York acupuncture safety study: prospective survey of 34 000 treatments by traditional acupuncturists**

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Recent reports have highlighted the importance of having good evidence on the safety of acupuncture.<sup>1,2</sup> Sound evidence on the risks associated with acupuncture is, however, scarce.<sup>3</sup> Our primary aim, therefore, was to describe the type and frequency of adverse events after acupuncture. A secondary aim was to examine mild transient reactions associated with acupuncture, some of which may indicate a positive response to treatment.

#### **Participants, methods, and results**

The study involved a prospective postal audit of treatments undertaken during a four week period in 2000. All 1,848 professional acupuncturists who were members of the British Acupuncture Council and were practising in the United Kingdom were invited to record details of adverse events and mild transient reactions after treatment. Standardised self report forms were used. Participating practitioners also provided information on themselves, including age, sex, length of training, and years of practice. To have a 95% probability that no serious event occurs in  $n$  treatments, a survey sample size needs to be three times  $n$ .<sup>4</sup> On this basis, a sample of 30,000 treatments was sought. Piloting indicated that a four week period was needed.

A total of 574 practitioners participated, 31% of the total population. The mean age of participants was 44.8 years (range 23-79 years), 65% were female, and 62% had been practising acupuncture for more than five years. Information on sex, training college, and length of practice was available from the British Acupuncture Council's database. Participants were sufficiently representative of the population of practitioners for a re-weighting of the primary data to be unnecessary. Participating practitioners reported on 34,407 treatments.

Practitioners were asked to give details of any adverse events they considered to be 'significant,' including any event that was 'unusual, novel, dangerous, significantly inconvenient, or requiring further information.' There were no reports of serious adverse events, defined as events requiring hospital admission, leading to permanent disability, or resulting in death (95% confidence interval 0 to 1.1 per 10,000 treatments). Practitioners did, however, report 43 minor adverse events, a rate of 1.3 (0.9 to 1.7) per 1,000 treatments. The most common events were severe nausea and fainting (table). Three avoidable events—two patients had needles left in, and one patient had moxibustion burns to the skin—were caused by practitioners' errors.

**Table: Details of 43 minor adverse events associated with 34 407 acupuncture treatments, all reported as ‘significant’ by practitioners**

<b>Minor adverse events</b>	<b>Number of occurrences</b>	<b>Descriptions</b>
Severe nausea, actual fainting, severe dizziness, heavy sweating, and vomiting	12	5 cases of severe nausea (2 with feeling faint, sweating, and dizziness; 1 started next day and lasted several days; 1 started 4 days later with angina and nose bleeds); 4 fainted (2 with nausea and dizziness); 1 severe dizziness and feeling faint; 1 heavy sweating and slight needle shock; 1 vomiting after treatment
Unexpected, severe, and prolonged aggravation of existing symptoms	7	1 difficulty walking the next day because of stiff, painful legs; 1 increase in shoulder pain for 20 minutes; 1 neck and shoulder pain increase for 1 week; 1 morning sickness worsened; 1 diarrhoea in patient with colitis; 1 constipation in patient with irritable bowel; 1 temporary aggravation of neck pain
Prolonged and unacceptable pain and bruising	5	3 local pain at site of needling; 2 heavy bruising
Psychological and emotional reactions	4	1 emotional outburst and anger at practitioner; 1 feeling of panic with sensation of heat and sweatiness; 1 intense emotional release, feeling manic, relaxed, rage, and confusion; 1 depression with anxiety
Avoidable errors	3	2 forgotten needles; 1 moxibustion burns at 2 points
Miscellaneous symptoms	10	1 haematuria next day; 1 headache next day; 1 unwell, tired, sore throat, breathless, and achy; 1 knee went weak and patient could not stand on it; 1 very tired next day; 1 felt sick and exhausted; 1 severe drowsiness; 1 tiredness next day with 10 hours of diarrhoea; 1 rash after taking herbs; 1 rash developed on abdomen a few days after treatment
Unspecified	2	

Participating practitioners recorded 10,920 mild transient reactions occurring in 5,136 treatments, 15% (14.6% to 15.3%) of the 34,407 total. Some local reactions at the site of needling were reported—mild bruising in 587 (1.7%) cases, pain in 422 (1.2%) cases, and bleeding in 126 (0.4%) cases. Patients experienced an aggravation of existing symptoms after 966 (2.8%) treatments, 830 (86%) of which were followed by an improvement, possibly indicating a positive ‘healing crisis.’ The most commonly reported mild transient reactions were ‘feeling relaxed’ in 4,098 (11.9%) cases and ‘feeling energised’ in 2,267 (6.6%) cases, symptoms that often indicate an encouraging response to treatment.<sup>3</sup>

## Comment

In this prospective survey, no serious adverse events were reported after 34,407 acupuncture treatments. This is consistent, with 95% confidence, with an underlying serious adverse event rate of between 0 and 1.1 per 10,000 treatments. This conclusion was based on data collected over a four week period by one in three of the members of the British Acupuncture Council. Even given the potential bias of self reporting, this is important evidence on public health and safety as professional acupuncturists deliver approximately two million treatments per year in the United Kingdom. Comparison of this adverse event rate for acupuncture with those of drugs routinely prescribed in primary care suggests that acupuncture is a relatively safe form of treatment.<sup>5</sup> Further research measuring patients' experience of adverse events is merited.

## Acknowledgements

Contributors: HMacP initiated the project, co-ordinated the study, and is the guarantor. KT and MF contributed to the study design, interpretation of results, and drafting of the manuscript. SW analysed the data and assisted with the interpretation of results. The study was adapted from a survey design developed by Adrian White and colleagues. Alan Bensoussan, Stephen Birch, Alan Breen, Roy Carr-Hill, and Adrian White provided valuable comments on a draft protocol.

## Footnotes

Funding: The study was supported by a grant from the British Acupuncture Council.

Competing interests: None declared.

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5. Tranmer MR, Moore RA, Reynolds DJM, McQuay HJ. Quantitative estimation of rare adverse events, which follow a biological progression: a new model applied to chronic NSAID use. *Pain* 2000; 85: 169-182.

## Questions about this report

- (a) Are there any problems with the sampling method?
- (b) What problems might the low response rate from the acupuncturists lead to?
- (c) Are there any problems with the data collection methods? What alternatives could be used? Would they solve the problem?
- (d) The mean age of participants was 44.8 years (range 23-79 years), What does this tell us about the shape of the distribution of age? Would we expect the median age to be less than or greater than 44.8 years?

- (e) Practitioners reported 43 minor adverse events, a rate of '1.3 (0.9 to 1.7) per 1,000 treatments'. What is '(0.9 to 1.7)' and what does it tell us?
- (f) The authors conclude that their data are consistent with an underlying serious adverse event rate of between 0 and 1.1 per 10,000 treatments. Is this a reasonable interpretation?
- (g) The authors say that further research measuring patients' experience of adverse events is merited. What would this tell us that these papers do not?