

- 1 Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C. Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. *Lancet* 1999; 353: 93-97.
- 2 Gillespie LD, Gillespie WJ, Cumming R, Lamb SE, Rowe BH. Interventions for preventing falls in the elderly (Cochrane Review). In *Cochrane Library* (CDROM and online). Cochrane Collaboration; issue 1, Oxford: Update Software, 1999.

## 5-HT<sub>2A</sub> gene promoter polymorphism and anorexia nervosa

Sir—David Collier and colleagues reported<sup>1</sup> a putative allelic association between the -1438A/G promoter polymorphism of the 5-HT<sub>2A</sub> gene and anorexia nervosa (AN). The genotype frequencies, however, are not compatible with the reported allele frequencies for the control group: 75 and 117 of their controls are homozygous for the -1438A/A genotype and heterozygous for the -1438A/G genotype, respectively, resulting in 267 -1438A alleles within this group. However, the investigators give a number of 184. In addition, the total number of alleles in controls should be 452 (not 450) because 226 individuals were considered as controls. Furthermore, the percentages of the genotypes do not coincide with the genotype frequencies.

All  $\chi^2$ -statistics and p values presented in the report are based on these clearly incorrect frequencies. If the allele frequencies are calculated from the provided genotype frequencies, the p value for the allelic association is 0.084, not 0.022. This means that this result is not significant at the 5% test level. Furthermore, the reported test for differences in genotypes between patients with AN (nominal  $p=0.026$ ) fails to detect association in this situation after Bonferroni correction (corrected  $p=0.052$ ). Hence, there seems to be no association between the 5-HT<sub>2A</sub> gene promoter polymorphism and anorexia

nervosa from Collier and colleagues' data.

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- 1 Collier DA, Arranz MJ, Li T, et al. Association between 5-HT<sub>2A</sub> gene promoter polymorphism and anorexia nervosa. *Lancet* 1997; 350: 412.

### Authors' reply

Sir—The table in our original report contained an error because the numbers of genotypes for "all controls -1438AA" and "all controls -1438GG" were transposed, whereas the genotype frequencies for these cells were shown correctly. Andreas Zeigler and Tilman Gorg have also spotted a second error, in which the control alleles were shown as -1438A: 184 and -1438G: 266. These figures should have been 185 and 267, respectively (total number of patients 226). The table below shows the correct figures and legend, with recalculated and corrected p values, which have been checked by an independent statistician. We have also suggested a two-fold p value (Bonferroni correction).

David A Collier, on behalf of all authors

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### Multicentre clinical trials

Sir—C Cornu and colleagues (Jan 2, p 63)<sup>1</sup> describe the difficulties and administrative hurdles of implementing a multicentre clinical trial in Europe. We fully agree that implementation of such trials is probably the utmost priority in European clinical research.

An inappropriately small number of patients is one of our most frequent criticisms of non-industry-sponsored clinical trial applications at the Ethics Committee of the Vienna University

Medical Faculty. Applicants are often advised to increase sample size by cooperating with other European centres to enhance recruitment capability. The concomitant increase in the administrative burden, however, often leads to long delays, sometimes to the point of aborting the trial, as was vividly illustrated by the example of Cornu and colleagues.<sup>1</sup>

These delays are surprising, since in an age of rapid electronic communication European clinical trials should be easier to implement than ever before. What then stands in the way of a pan-European clinical research initiative? We propose that the resistance to harmonisation of research regulations and administrative procedures is largely found in the self-serving interests of national bureaucrats, ethics committees and other dignitaries for whom regional and national parochialism creates a cherished sphere of influence. These notables have little to gain and much to lose from pan-European harmonisation that would transfer powers to a supranational body. The frequently invoked "cultural differences" across Europe, purported to justify national differences in clinical trial regulations, is little more than a thinly veiled pretext for protection of group interests.

How should academic clinical medicine respond? Foremost, by using influence and prestige to help dispel the myth that national differences in European research (and drug) regulations in a way benefit patients or society at large. At present, a European Directive<sup>2</sup> on clinical trial conduct is being considered by the European Parliament and the Council of Ministers, which proposes pan-European harmonisation of various aspects of drug research. Surprisingly, the initiative originates from Directorate General (DG) III within the European Commission, which is responsible for industrial affairs, rather than DG XII, which deals with research. In any case, this effort deserves the full support of academic medicine. However, at present, lobbying for this document has been largely left to the pharmaceutical industry. Although we recognise that big pharmacological interests are not always congruent with those of the academic medical community, academia would be well advised to support the idea of this proposal, even against the interests of local dignitaries.

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	Genotype-wise			Allele-wise	
	-1438A/A	-1438A/G	-1438G/G	-1438A	-1438G
Anorexia nervosa (n=81)	25 (0.31)	33 (0.41)	23 (0.28)	83 (0.51)	79 (0.49)
All controls (n=226)	34 (0.15)	117 (0.52)	75 (0.33)	185 (0.41)	267 (0.59)
Female controls (n=88)	11 (0.125)	51 (0.58)	26 (0.295)	73 (0.41)	103 (0.59)

#### Allele-wise:

Anorexia nervosa (AN) vs all controls:  $\chi^2=5.15$ , 1 df,  $p=0.023$  [0.046] OR 1.52 (95% CI 1.04-2.21).

AN vs female controls:  $\chi^2=3.23$ , 1 df,  $p=0.07$  [0.14], 1.48 (0.96-2.28).

#### Genotype-wise:

AN vs all controls:  $\chi^2=9.68$ , 2 df,  $p=0.008$  [0.016].

AN vs female controls:  $\chi^2=9.21$ , 2 df,  $p=0.01$  [0.02].

#### Recessive model:

AN vs all controls:  $\chi^2=9.61$ , 2 df,  $p=0.002$  [0.004], 2.52 (1.33-4.77).

AN vs female controls:  $\chi^2=8.48$ , 2 df,  $p=0.004$  [0.008], 3.13 (1.34-7.42).

p values corrected for multiple testing by two-fold shown in square brackets.

### Frequencies of -1438G/A polymorphism in 5-HT<sub>2A</sub> gene promoter region in anorexia nervosa

- 1 Cornu C, Cano A, Pernel B, Melis GB, Boissel JP. Could institutional trials exist in Europe? *Lancet* 1999; 353: 63-64.
- 2 European Commission, Proposal for a European Parliament and Council directive on the approximation of provisions laid down by law, regulation or administrative action relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. COM(97) 369 final. Brussels: EC, Sept 3, 1997.

Sir—We endorse C Cornu and colleagues' call,<sup>1</sup> on behalf of the EUTERP Pilot Study Group, for institutional promotion of independent clinical research in the European Union (EU). Their consideration about the difficulties induced in checking the effectiveness of marketed drugs can be extended to other important public-health issues such as the development of drugs for rare diseases.

As is the case with trials that can limit the extension of indications and use of products already on the market,<sup>1</sup> pharmaceutical companies are not interested in developing drugs for a limited market. Among the 100 products granted positive opinion by the European Agency for the Evaluation of Medicinal Products (EMA) by the end of 1998 only ten are aimed at rare diseases. Sometimes companies have developed products that are potentially useful for this area of major interest in terms of public health, but often those companies cannot see any advantage in developing the products according to acceptable standards. Of the 32 applications withdrawn from the EMA, no fewer than seven (21.9%) were drugs for rare diseases. Difficulties arising from a non-remunerative market at low cost apparently lead to disaffection. Indeed, only two (6.1%) of 33 authorisation procedures now under evaluation are products for rare diseases.

A dedicated EU agency is required to identify public needs and therapeutic issues, and promote cooperation between industry and independent institutions to develop drugs that are useful to public health. This agency should also fund the resumption of independent research and development of drugs abandoned by companies. The agency could also buy the patent for the drugs concerned, at a reasonable price, and put them on the market as generic medicinal products.

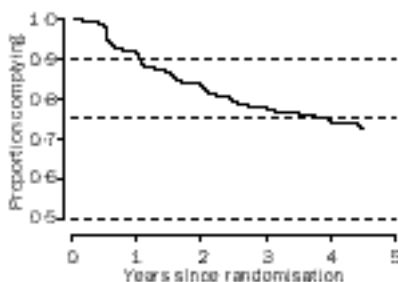
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- 1 Cornu C, Cano A, Pernel B, Melis GB, Boissel JP, on behalf of the EUTERP Pilot Study Group. Could institutional clinical trials exist in Europe? *Lancet* 1999; 353: 63-64.

## Drop-outs in tamoxifen prevention trials

Sir—U Veronesi and colleagues (Jan 16, p 244) raise the question of drop-out rates in tamoxifen prevention trials.<sup>1</sup> In the International Breast Cancer Intervention Study, compliance has generally been good and is running at 90% after 1 year, 83% after 2 years, and 74% after 4 years, on the basis of the first 4303 entries of those with follow-up. We also have 61 women who are on a temporary treatment holiday. Non-compliance is greater in the first year with a clearly visible dip at the 6-month follow-up and a smaller dip at 1 year (figure). These rates have changed little over time.



Kaplan-Meier estimate of compliance

The results of the trial remain blinded and entry is ongoing. As of Jan 1, 1999, we have recruited 5084 women, 66 of whom have developed breast cancer, leading to an overall incidence of 6 per 1000 women years of follow-up. We expect the trial to make an important contribution to the value of tamoxifen prophylaxis for breast cancer.

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- 1 Veronesi U, Maisonneuve P, Costa A, Rotmensz N, Boyle P. Drop-outs in tamoxifen prevention trials. *Lancet* 1999; 353: 244

## Needle-exchange programmes are not the answer

Sir—I chuckle when I read papers that praise programmes that give clean needles to addicts in an attempt to prevent the spread of HIV. It defies common sense that a person high on drugs will scoot across town to exchange a dirty needle for a clean one. Isn't it rather like asking a drunk to stop drinking and go get a clean shot glass to prevent the spread of germs?

I shuddered when I read Kelly Morris's Jan 2 news piece "US drug project abandons needle exchange"

(p 49)<sup>1</sup> I have always considered *The Lancet* to be a prestigious journal, not a forum for prodrug policies.

Needle-exchange programmes began in 1984 in Amsterdam, started by a drug-user advocacy group called the Junkie Union, and have become one of the priorities for those who lobby for permissive drug policies and programmes. Provision of needles with which to inject illegal drugs is in violation of US Federal drug paraphernalia laws. Those like Diana McCague who break the law should expect to be punished by the courts.

Perhaps you are unaware that the Drug Reform Coordination Network (DRCNet) is well known for its support of liberal drug policies and opposition to punishment of drug users by the law. The DRCNet does not encourage use of the word legalisation because of public reaction, but rather use of drug reform. DRCNet is associated with drug "reform" organisations such as the Drug Policy Foundation (DPF), Marijuana Policy Project, Families Against Mandatory Minimums, Netherlands Institute on Human Rights and Drugs, and National Organization for the Reform of Marijuana Laws. At one time, DRCNet worked out of the headquarters of DPF and encouraged tax free donations funnelled through DPF. Perhaps they still do.

However, I find it difficult to believe that you are unaware of the McGill and Montreal universities study of about 1600 injection-drug users. This study, which was reported in a news item in *The Lancet*,<sup>2</sup> showed those who took part in Montreal needle-exchange programmes were two times more (not less) likely to become infected with HIV than those who did not.

Programmes that give away clean needles facilitate drug use, endanger children, and put whole communities at risk. Have you ever thought about those discarded needles in the gutters just waiting to prick an inquisitive child's fingers? Or about the behaviour of addicts desperate for a fix? Talk to those who live in neighbourhoods near needle-distribution programmes. It is not compassion to write off drug users who desperately need treatment, not needles! The most compassionate and humanitarian approach for the drug user and society is prevention, intervention, and treatment, not the distribution of free needles.

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- 1 Morris K. US drug project abandons needle exchange. *Lancet* 1999; 353: 49.
- 2 Anon. Montreal needle-exchange surprise. *Lancet* 1996; 348: 324.