Improving the debate on cannabis: "The effects of cannabis on driving are difficult to evaluate"

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Publication Details
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Abstract
In their article on the cannabis debate, Strang et al raise the issue of cannabis and its effects on driving, suggesting that “a clearer understanding will be required of the extent to which a particular concentration of the drug (or its metabolites) can reliably be taken as evidence that an individual's driving ability was consequently impaired.” A review of the literature, however, suggests that defining an acceptable level of cannabis consumption for driving is unlikely to be possible for several reasons.

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Length of penicillin treatment of streptococcal infections

Is seven days of treatment as effective as 10 days?

Editor—Zwart et al recommend seven days of treatment for streptococcal infections as opposed to three days.1 For several decades we were educated to continue penicillin for such cases for no fewer than 10 days.2 The rationale was that streptococci must be eradicated to prevent rheumatic fever and that this was achievable only after 10 days of treatment. This was based on bacteriological, epidemiological, and clinical observations. The cost of oral penicillin is almost negligible, and I think we need more assurance to be persuaded to cut treatment to only seven days. Is there any study that will prove that treatment for seven days is as effective as treatment for 10 days for preventing rheumatic fever?

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2 Christie AB. Strephtococcal infections—scarlet fever. In: Christie AB. Infections: epidemiology and clinical prac-

Antibiotics should not be used for self limiting illnesses

Editor—I have two concerns about Zwart et al’s article: firstly, the methodology, and, secondly and more importantly, that it was conceived at all, in view of the issue of antibiotic use.

The study had an unusually high number of exclusions (36.7%), and 26.6% of the patients were not randomised. The secret code of treatment was broken at the request of the doctor or the patient. There was a faster resolution in the patients in the seven day treatment arm at two days than in the three day treatment arm at two days, despite identical treatment, and I am not convinced by the authors’ explanation. A possibility concerning all the above points is that the randomisation was not successful, and therefore the results of the trial may not be secure.

However, these doubts are minor compared with the real issue, which is how we use the precious resource of antibiotics. Resistance to commonly used antibiotics is rising fast.3 The increasing use of antibiotics do not prevent complications.4,5 Finally, antibiotics have at best mild to modest benefit in pharyngitis.

If we continue to prescribe antibiotics for self limiting illnesses where there is small benefit at most, we will see an increase in the incidence of serious resistant infections such as pneumonia and meningitis, and in the mortality inevitably associated with these infections. Our resolution for the new millennium should be to stop prescribing antibiotics for minor self limiting conditions, to allow nature to heal these, and to save antibiotics for what they were designed for in the first place—serious and life threaten-
ing disease.

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The data do not support the conclusions

Editor—Zwart et al conclude from a placebo controlled randomised clinical trial that seven days of penicillin treatment for symptoms of acute sore throat is better than three days of treatment.1 In the accompanying editorial, one of the authors of the Cochrane review on antibiotics for sore throats (8 hours’ benefit) is puzzled by the anomalous trial data that are presented.2

As shown in figures 1 and 2 in Zwart et al’s paper, the two primary outcome measures, resolution of symptoms and resolu-
tion of impaired daily activities, do not support those conclusions. The Kaplan-
Meier plots show that at day 3 the resolution of symptoms in group 1 (seven days of penicil-
lin) and group 2 (three days of penicillin) was significantly different, although both groups had received identical treatment.

This unexplained twofold difference between the two penicillin groups carries over to misleading conclusions at day 7. Importantly, outcomes in group 2 were almost identical with those for group 3 (placebo) for the entire study period.

The following results emerge by simply reformulating the research question as: what is the benefit of an additional four days of penicillin treatment, after the initial three days? From figure 1, in the seven day and three day groups, patients who were free of symptoms from day 3 through to day 7 were 37% v 15%; 50% v 25%; 70% v 43%; 80% v 55%; and 88% v 63% (thus differences in rates of cure are 22%, 25%, 27%, 25%, and 25%, respectively). As additional treatment in group 1 starts after day 3, when this point is taken as the baseline reference the relative benefits are 3%, 5%, 3%, and 3% for days 4 through 7. Similarly, the other primary outcome measure, resolution of impaired activity (figure 2), shows relative benefits of −2%, −3%, −1%, and 3%, indicating no cumulative benefits from the extra four days of penicillin.

The authors need to explain the anomalous cure rate advantages for patients in group 1 at the day 3 baseline. My prime sus-
pect is the unaccounted differences in prognostic factors such as “sore throat days” at entry among the three treatment groups, perhaps inadvertently favouring the seven day group. Also, use of well defined disease duration (onset, entry, and resolution) in life

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table analyses may clarify these puzzling results. Because the findings show equivalence of placebo to three days of penicillin in treating symptoms of acute sore throats, I see no reason for the Cochrane review of Del Mar and colleagues to be revised.1  

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3 Del Mar C, Glasziou PP. Do antibiotics shorten the illness should be used with caution for data of this groups.
4 Del Mar C, Glasziou P. Antibiotics for the symptoms and criteria, fever, and quinsy (1:60 untreated) in Zwart et al's study is almost unavoidable.1  

Imagine two patients—Bob in the seven day group and Paul in the three day group. Both get better after 24 hours, but Paul relapses on day 5 and recovers on day 7. On the life table Bob seems to have recovered in the crucial first three days whereas Paul does not. Moreover the early takeoff of the recovery curve in the seven day group. It does not in any way indicate allocation bias between the groups.

The severity of symptoms is not pre-

resulted double blind trial of seven days versus three days treatment or placebo in adults. BMJ 2000;320:150-4. (15 January)
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resulted double blind trial of seven days versus three days treatment or placebo in adults. BMJ 2000;320:150-4. (15 January)
3 Del Mar C, Glasziou PP. Do antibiotics shorten the illness should be used with caution for data of this groups.
We agree with Little et al that the population studied should be taken into account when the findings are generalised. However, because we found important and relevant effects of penicillin, we feel free to reverse the association between result and population. To incite further discussion on the management of sore throat in adults we therefore recommend for other routine settings, such as the primary care setting in the United Kingdom, the selection criteria that we used in our study and that are also used in Dutch daily practice.

Fleetcroft and Little et al fear that penicillin will be used as a routine drug in a routine setting, thus leading to medicalised patients and resistant strains. We share their fear, but believe that doctors and patients can make a well balanced decision only when they are informed not only about the costs and adverse effects of antimicrobial treatment, but also about the benefits.1

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2 Del Mar C. Sore throats and antibiotics. BMJ 2000;320:130-1. (15 January.)


Treating children with sleep disorders

Children with breathing difficulties are being overlooked

*Editor—*I was disappointed to see that once again children with sleep disorders are being lumped into a homogeneous group of children with “behavioural” problems, then “studied” without using polysomnography. I think it’s presumptuous and dangerous to think that a child who has trouble sleeping has a behavioural problem. Few physicians are aware that breathing difficulty can cause night waking and bedtime resistance, and it is because of studies like that of Ramchandani et al1 that doctors don’t look for sleep disorders properly, don’t know much about them, and are told repeatedly that behavioural treatments are the appropriate treatment. This is wrong unless we can guarantee that the children have behavioural problems. A study looking at obese children using polysomnography diagnosed unsuspected obstructive sleep apnoea in 75% of the children studied—meaning the physicians examining the children picked up only 1 in 4 cases. It therefore seems a big leap of faith not to be doing polysomnography more often. Some of the children waking at night could have upper airways resistance syndrome, which can also cause sleep problems. Most doctors can barely take a proper history for sleep disorders, let alone diagnose a subtle case of upper airways resistance syndrome causing repeated night waking or bedtime resistance. Studies like that of Ramchandani et al certainly don’t help because they take the emphasis away from finding a “real physiological” problem and on to stress behavioural modification.

Before we continue to send physicians out to behaviourally modify breathing difficulties or other subtle causes of sleep disorders that can mimic behavioural problems, we need to do polysomnography on these children.

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Night waking is natural behaviour

*Editor—*The basic assumption of the study of Ramchandani et al that very young children should settle down to sleep away from their parents and not be seen or heard from again until morning is flawed. In many non-Western societies this type of sleep pattern would be seen as an aberration.

Anthropologist Carol Wortham of Emory University in Atlanta uncovered a variety of sleep patterns in 10 traditional hunter-gatherer societies, none of which coincide with our society’s current ideal of sleeping alone without waking alone for the entire night. Parents must estimate the amount of night waking in children and their desire for comfort by parents are both natural and healthy. Our difficulty in combating this behaviour may arise because we are struggling against nature and basic human biology. We must be careful not to confuse that which is desirable for human health with that which is merely a current preference and expectation of our society.

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Early intervention increases sleep times in young babies

*Editor—*Ramchandani et al’s systematic review of treatments for established infant sleep problems shows that behavioural interventions improve sleep problems. The authors reference the frequency of sleep disorders as 20% in children aged 1-3 years, the tendency for these problems to be persistent, and their associations with behavioural difficulties and family disharmony. Other authors quote the frequency of sleep disturbance to be as high as 35%. Armstrong reported that 60% of parents were getting up at night when their child was 12 months old, and half of them were rising three times a night or more.3

We tested the impact of a short behavioural intervention in normal neonates in a randomised trial (submitted for publication). In all, 265 families with normal newborn singleton babies were recruited within the first three weeks of life and were randomly allocated to intervention or control groups. Families in the intervention group received a single 45 minute tutorial from a research nurse. The tutorial emphasised that in children who were healthy and gaining weight satisfactorily sleep achievement should be regarded as a ‘learned skill’ influenced by environmental factors or “cues of sleep.” Parents were encouraged to avoid fatigue in their infants by not overhandling and to establish cues of sleep independent of the parent. Outcomes were measured through a sleep diary at 6 weeks of age.

All aspects of sleep performance were significantly improved in the intervention group. Total sleep increased by almost nine hours a week at 6 weeks (P<0.0001). The proportion of infants sleeping 15 hours a day was 61% in the intervention group and 28% among controls (P<0.0001). 78% of sleep cycles among infants in the intervention group included over eight hours of night sleep, compared with 61% of cycles among controls (P<0.0001).

Although the technique emphasised minimising parental handling at sleep time, there was no difference in the amount of crying between the groups. Follow up at 3 months of age showed that improvements were maintained. Our findings therefore support, and add to, those reported in the systematic review.

Although Ramchandani et al did a well designed systematic review, our unpublished work was not identified, and it would be unreasonable to expect it to have been. This experience therefore supports the calls for a register of planned and ongoing randomised trials,4 and also shows the importance of regularly updating systematic reviews through the Cochrane Collaboration as new evidence becomes available.

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Treatment of child sleeping problems and the quality of trials are important

Editor—Ramchandani et al’s finding that behavioural treatments are effective in treating sleep problems will inform practice but omitted three important issues.

Firstly, two of the nine identified treatment studies included infants as young as 1 month. Infants are not born with the ability to sleep through the night, but sleep patterns are entrained by environmental cues. Waking at night in the early months of life is an adaptive behaviour to secure frequent feeding and to allow for rapid weight gain and brain growth. Sleeping through the night in the early weeks of life and a lack of waking for feeds is likely to put vulnerable infants (such as preterm infants or poor feeders) at risk of poor and suboptimal development and growth. Behavioural treatments for night waking should thus not start before 6 months of age.

Secondly, infants who are breast fed do sleep less during 24 hours and are more likely to wake at night than bottle fed infants. Parents should be informed that breast feeding does not impede infants from learning to sleep through the night. Early routines, avoidance of feeding the infant into “sleep submission,” and the use of focal feeds can, however, help to reduce the stress of night time feeding breast. Thirdly, sleeping problems often coexist with excessive crying or feeding difficulties. Parents with infants with multiple difficulties are more likely to seek help. Studies are still required to establish that behavioural interventions are effective in infants with multiple problems.

Finally, quality criteria developed for drug trials were used to judge the quality of the behavioural treatments. These include double blinding to guard against performance bias and randomisation to exclude selection bias. Double blinding is not possible in behavioural studies. Therapists have to know what they are doing and why. Randomisation in small samples (less than 30) is often not effective as the effect sizes may become inflated because of outliers and there may be pretreatment differences. Quality ratings are there to judge the internal validity of a trial—that is, the confidence that the cause of any observed differences is due to the treatment conditions. The increasing use of “off the shelf” criteria for judging the quality of behavioural treatments is of doubtful validity. There are specific methods to guard against performance bias in behavioural trials such as the investigation of generalised placebo effects. Checking and controlling for a range of pretreatment differences may be as important as randomisation itself.

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References


Authors’ reply

Editor—We are aware of Fay’s general point that it is the underlying sleep disorder rather than the presenting complaint at which treatment should be directed. She suggests that polysomnography is indicated for all children presenting with a sleep problem. We consider it more important that careful clinical inquiry is made to identify children with wide ranging physical conditions or other sleep disorders associated with sleep disturbance rather than to focus on the few conditions that can be identified by polysomnography. Furthermore, the appropriate diagnostic criteria for paediatric sleep related breathing disorders are being frequently refined (adult criteria, which have been used in the past, are not appropriate), and polysomnography is just one of the clinical investigations that may be required to diagnose these conditions.

All but one of the studies in our review (one study did not explicitly state screening procedures) included a broad assessment of the children’s overall sleep pattern and medical history, including careful screening for symptoms suggestive of other sleep disorders and medical conditions. In the absence of any clinical signs of sleep related breathing disorders, and with clear indication of behavioural aspects maintaining the child’s sleep problem, it would be difficult to justify (both to parents and to healthcare providers) the need for potentially unhelpful polysomnographic assessment.

Fay suggests that waking at night and bedtime resistance may themselves be a clinical sign of a sleep related breathing disorder, arguing that a large proportion of children with obstructive sleep apnoea also have such problems. This link is contentious and disputed, and, even if it is accepted it does not follow that a large proportion of children with night waking and bedtime resistance also have obstructive sleep apnoea. The prevalence figures make it more likely that children with obstructive sleep apnoea form a small subset of those with behavioural sleeplessness. Research suggests that a detailed sleep history would alert clinicians to which patients are likely to fall into this group. A phased approach to both assessment and treatment is needed to ensure maximum diagnostic accuracy and to minimise unnecessary procedures.

Buckner is right that assumptions about children’s sleep are culturally determined. However, the reality that parents and health-care professionals face within a Western society is that it is often considered desirable for children to sleep independently. In this context continuing sleep disturbance in a young child has many adverse effects on both the child and his or her parents or carers. Given this, seeking the best ways of helping such parents or carers find solutions to their difficulty seems a reasonable pursuit.

We agree with Symon et al that a register of planned and ongoing trials, and the updating of systematic reviews through the Cochrane Collaboration are important. We have had discussions with the Cochrane Collaboration to that end. Nevertheless, their study would not have been included in our review as we focused specifically on an established sleep problem. Another systematic review has dealt with studies similar to theirs.

We agree with the first three points made by Wolke. His fourth, about the choice of quality criteria, identifies a dilemma facing anyone conducting a systematic review: should they describe each study and its strengths and weaknesses in detail or use a quality rating scale as a form of shorthand? Within a journal it is rarely possible to describe each study in detail, and it can also make for difficult reading. The use of quality criteria makes comparison of trials easier to understand, but at the cost of inevitable loss of accuracy. We would welcome the development of quality criteria more appropriate for psychological treatment trials. Until that time use of well standardised quality ratings represents the best compromise.

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Recent advances in intensive care

Percutaneous tracheostomy may not be more effective than open technique

Editor—In his review of recent advances in intensive care Stott emphasised the efficacy of percutaneous tracheostomy in comparison with the conventional open surgical approach. We agree that percutaneous tracheostomy may indeed be the preferred method in selected cases,
but it is invariably not used in patients who present anatomical challenges such as a short, thick neck; goitre; a history of neck surgery; or a concurrent coagulopathy. Such difficult cases probably represent about a quarter of an average population requiring tracheostomy.

We disagree with Stott’s assertion that the incidence of complications has been shown to be lower with percutaneous tracheostomy than with open surgical techniques. The paper quoted in support of this statement—by Hill et al—describes the results of 356 percutaneous procedures performed in a single unit over four years. No direct comparison is made with open tracheostomies, and the authors do not report the numbers and type of patients deemed unsuitable for percutaneous tracheostomy and referred for open procedures. The six previous independent series quoted that detailed complication rates for open tracheostomy were published on average nearly 20 years earlier, and a conclusion was reached by comparison with these older studies.

Stott fails to mention Dulguerov et al’s meta-analysis reported in 1999, which showed that percutaneous tracheostomy is associated with a higher prevalence of certain complications.5 Their comparison of recent surgical tracheostomy trials (n = 21; 3512 patients) and percutaneous tracheostomy trials (n = 27; 1817 patients) shows that perioperative complications are more common with the surgical technique (10% vs 3%), whereas postoperative complications occur more often with the surgical technique (10% vs 7%). The bulk of the differences is in minor complications, except perioperative death (0.14% vs 0.03%) and serious cardiorespiratory events (0.33% vs 0.06%), which were much higher with the percutaneous technique. This, coupled with the reduced cost, avoidance of moving critically ill patients, and low long term complication rates, means that I can still conclude that percutaneous tracheostomy is a significant recent advance.

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Genetic factors and osteoporotic fractures in elderly people

Twin data support genetic contribution to risk of fracture

Entror—Kannus et al suggest from prospective data collected on Finnish twins that genetic factors are of only minor importance in explaining the population occurrence of osteoporotic fracture, particularly in women.1

The evidence given to support this is the relatively small excess in concordance in monozygotic twins compared with dizygotic twins. But it is well recognised that twin concordances may be misleading unless the underlying prevalence of a disease is taken into account. For example, a small absolute difference in monozygotic compared with dizygotic twins is more suggestive of a genetic effect for a trait that is relatively rare (such as fracture) than for one that is common. The data thus warrant closer scrutiny.

We have estimated the relative contribution of genetic, shared environmental, and unique environmental components to the variation in susceptibility to fracture in these twins from the data provided. The analysis was conducted using a variance components approach with the statistical software MX.3

The method assumes that risk of fracture is determined by a continuous underlying liability and is a plausible assumption for this trait.4

Author’s reply

Errror—Brookes and Howard’s point that not all patients are suitable for a percutaneous tracheostomy is well made, but the

figure quoted of 25% is conjecture and not referenced. As I cannot find any data to produce a figure of my own I will not, but I do question their final paragraph when they state that because of this figure a double blind trial would be unethical. This is curious as nowhere in my article did I suggest that one should be performed.

The meta-analysis referenced looks only at studies published up to 1996 and compares four different percutaneous techniques with surgical tracheostomies performed in two different eras.6 As most of the deaths occurring with percutaneous tracheostomy occur with a non-dilatational technique it would seem prudent to exclude these from the analysis.

There have been three published prospective trials comparing dilatational percutaneous tracheostomy with open surgical techniques.7 8 9 These show complication rates for percutaneous tracheostomy to be as low or even lower than for the surgical technique. This, coupled with the reduced cost, avoidance of moving critically ill patients, and low long term complication rates, means that I can still conclude that percutaneous tracheostomy is a significant recent advance.


More still needs to be known about immunonutrition

Errror—I have concerns over one section in Stott’s article on recent advances in intensive care.1 These concerns relate to the paragraphs on nutrition, and particularly the key points box on page 358; there it is stated that recent work has shown that omega 3 polyunsaturated fatty acids improve mortality in critical illness.

The question of immunonutrition is complex, and the different nutrients used in clinical trials can have different, and opposing, effects on the immune system. For example, L-arginine and glutamine stimulate a variety of immune functions.3 In contrast, omega 3 and omega 6 fatty acids inhibit a variety of immune functions.2 3 4

The timing of administration of these nutrients may therefore be critically important: although it is generally believed that stimulation of the immune system is beneficial in critically ill patients, this may not always be the case. For example, in certain patients (those with adult respiratory distress syndrome or multiorgan failure) in whom the cytokine cascade and production of inflammatory mediators has been suggested to be excessive, administration of omega 3 and omega 6 fatty acids would be beneficial in reducing production of these mediators.

In terms of immunonutrition affecting clinical outcome in critical illness, a recent critical analysis of all the randomised controlled trials in which L-glutamine was given found little evidence to support its routine clinical use.7 A recent meta-analysis found that giving combinations of immunomodulatory nutrients reduced infectious complications but not mortality.9

When the use of nutrition in critically ill patients is being considered, these considerations must be taken into account. It is still not clear which patients will benefit from being fed these immunomodulatory nutrients and which may not.

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Notes

1 Stott S. Recent advances in intensive care. BMJ 2000;320:538-41. (5 February)
As expected, the results show significant evidence of familial resemblance in the risk of fracture in both male and female twins. In female twins, despite the nationwide sampling frame, there is insufficient statistical power in this study to distinguish between models containing components in which this clustering is attributed to genetic factors alone, shared family environment of the twins, or the combination of the two. In a model in which the only contribution is from genetic and unique environmental factors, genetic factors account for 36% of the variance in the liability to fracture at any body site.

In male twins the familial resemblance is explained by a significant contribution from genetic factors but not by the shared family environment, with genetic factors accounting for 35% of the variation in liability to fracture. A greater genetic contribution is also suggested at the spine in a study in Kanners et al's study (bjm.com/cgi/content/full/319/7221/1354/DC1), although influence is limited by the small numbers of same-sex pairs and the lack of data on differences between the sexes in rate of fracture. In contrast to the conclusion reached by the authors, these data show that genetic factors contribute to a third of the liability to osteoporotic fracture in men and are entirely compatible with the hypothesis that genetic factors contribute to a similar extent in women. The data suggest that there may be differences in the nature of the genetic risk in men and women and at different body sites that merit further study.

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Study supports possibility of differences in development of osteoporotic fractures between sexes

Editor—Kanners et al report their large, long term prospective study analysing the genetic predisposition of osteoporotic fractures in elderly Finnish twins. It is important to note that whereas the concordance rate for fractures was indeed not strongly different between monozygotic and dizygotic twin pairs in women, there was a fourfold difference in men.

In their electronic response to the article [published here in the paper journal, above] MacGregor et al have estimated the relative contribution of genetic components on the basis of the data provided; they found that a strong role for genetic factors in men but not women. Previous studies have pointed to possible differences in the main regulatory factors in the development of low bone mineral density and osteoporotic fractures between the sexes. We suggest that the data presented by Kanners et al could be interpreted as further evidence supporting this hypothesis.

Bone density is suggested to be multifactorially regulated and polygenically determined. Underlying diseases such as inflammatory bowel disease and several drugs such as glucocorticosteroids can modulate and enhance the effect of genetic factors on the development of osteoporotic fractures. For example, our studies have shown that the allele 2 at the Avo polymorphism in the interleukin-1β gene—related to a higher production of the cytokine—is associated with a subgroup of patients (those with the non-familial form of Crohn’s disease). Additionally, we have found a strong correlation between this polymorphism and bone mineral density in patients with inflammatory bowel diseases but not in healthy controls. We also found a difference between the two sexes: the association at the lumbar spine was present only in men.

Bone loss at the cortical and trabecular bones seems to be influenced by several physiological and other elements such as the menopause or use of corticosteroids. Therefore, analysing data after screening for the often “silent” vertebral fractures could further modify Kanners et al’s results concerning the importance of the genetic background.

Bone mineral density is a key predictor of osteoporotic fractures. To judge the weight of genetic influence it would be important to compare concordance rates in the groups with low and high Z score values. We suggest that studies in well defined subgroups of patients may help to define those conditions in which genetic background has a high prognostic value for the risk of osteoporotic fractures.

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Amaud Salvador Pena professor of gastrointestinal immunology Free University Hospital, Amsterdam, The Netherlands aas.pena@aes.nl

Model fitting for data on osteoporotic fractures among monozygotic and dizygotic twin pairs of Finnish twin cohort

<table>
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<th>Non-additive genetic effects (D)</th>
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<th>Unique environmental effects (E)</th>
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*Combines information on statistics of goodness of fit (the lower the χ² value the better the fit) and simplicity of model (the best model usually being the one with the lowest value).


Authors’ reply

Editor—On the basis of our published data MacGregor et al computed estimates of genetic variance in liability to osteoporotic fractures. Our original manuscript had the same modelling analysis (table), but after a recommendation by a reviewer and the BMJ’s editorial committee we omitted the modelling part of the study from the paper. MacGregor et al’s interpretation of the results of the modelling differs from ours. We emphasise three points. Firstly, no matter what model is used to examine our data, the liability to osteoporotic fracture has a large environmental component (always ≥60%) in both sexes. This is not clearly pointed out by MacGregor et al.

Secondly, we do not want to say that “genetic factors are of only minor importance in explaining the population occurrence of osteoporotic fracture”; we want to say that they are not strongly related to it. We thus want to draw attention to the fact that although genetic factors have a dominant role in explaining individual variation in bone density, the result is quite different (that is, unshared environmental effects become dominant) when the end point is changed from bone tissue to fractures, the true end point of the entire osteoporosis problem.

Thirdly, in women MacGregor et al highlight the AE model (the only contribution to risk of fracture is from genetic and unique environmental factors), in which...
genetic factors account for about 36% of the variance in liability to fracture, but they ignore the fact that the CE model (includes no genetic effects to explain twin similarity in liability to fracture) gave a better fit to the data. It has to be remembered that the statistical power of the study was not sufficient to differentiate between these competing explanations. Clearly, more incident cases are needed for more definitive conclusions.

Finally, we agree with MacGregor et al that there may well be differences in the nature of the genetic risk of osteoporotic fracture between men and women and at different body sites. Further follow up of our cohort and examination of the situation in other populations are thus needed.

With regard to Nemetz and Pena’s letter, analysis of “silent” vertebral fractures will not change the result of the clinically more important non-vertebral fractures. We do not fully agree with the authors’ statement that bone density is a key predictor of osteoporotic fractures. Many recent epidemiological studies indicate that falling is the strongest single predictor of these fractures, and bone mineral density is an independent predictor of only moderate importance. When this fact becomes more widely recognised, the framework of fracture prevention will become shifted more appropriately—towards preventing falls in elderly people.

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Improving the debate on cannabis

Let’s find out whether cannabis has therapeutic value

Editor—In discussions of the use of cannabis one of the biggest problems over the past few years has been the difficulty in separating the debate on the recreational use from that on the therapeutic use. The article by Strang et al also mixes these two issues.

In all my years of working in pain relief I cannot remember the equivalent mix-up taking place over cocaine, morphine, heroin, etc. Although some matters occasionally overlap, the two main elements of the cannabis debate must remain in separate arenas. Only then can we educate politicians and the public about the facts and the real issues.

Meanwhile, let’s get on and find out whether cannabis has significant and valuable therapeutic potential. This agent has been used medicinally for 5000 years and we still don’t know whether it is therapeutically effective.

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Consider public welfare, not just public health

Entorr—Strang et al raise a number of salient issues in the debate over whether cannabis should be legalised.1 However, the eight “domains of the cannabis debate” identified are centred exclusively on a public health conception of the relevant policy issues. Although this is understandable given the audience that the authors are addressing, they fail to consider more fundamental issues of what the public policy objectives should be when considering the recreational use of cannabis. Their discussion reflects the fact that the medical profession has a natural tendency to judge the public regulation and legal control of activities according to their impact on the health of the public. Thus, anything shown to be harmful to health is seen as inherently bad, while activities that promote health are seen as something to be encouraged by public institutions.

An alternative vision of the objective of public intervention and legislative structures is that they should exist to protect and improve public welfare as distinct from public health. Individual welfare is clearly affected by health but it also encompasses a broader class of personal benefits that people enjoy when freely undertaking specific activities (including using cannabis), even in cases in which they are knowingly exposing themselves to possible health risks.

This “welfarist” angle should not be confused with the libertarian line, which would espouse the removal of legal barriers that prevent people having the freedom to do as they wish. In the welfarist paradigm public regulation and control will always be required if the use of cannabis affects the welfare (including the health) of parties who are outside the decision to use. Public intervention is also needed to ensure that users are informed of any risks associated with use, even if this means telling people that at present the risks are largely unknown.

If it is accepted that health is only one aspect of individual welfare and that it is the responsibility of government to promote individual welfare even if in certain instances this means compromising health, then a public health driven debate will never offer satisfactory guidance on the desirability of the legal status quo of cannabis use.

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Social context should be added to domains being considered

Entorr—Strang et al argue that the cannabis debate has been oversimplified into polarised positions that consider cannabis to be either generally harmless and potentially therapeutic or harmful to health and consequently deserving of prohibition.1 To improve the quality of debate the authors usefully identify eight domains within which the health effects of cannabis should be examined. However, these domains represent only a narrow biological view of this difficult issue and focus almost exclusively on examining potentially negative effects. Further overarching domains, in particular of social context, need to be added to the debate.

Social opportunity costs arise as a result of criminalising cannabis users. These include their exclusion from school, university, and employment; incarceration; and blighting of their lives and careers as consequences of their becoming involved with criminal subcultures. Furthermore, cannabis use should be considered against the health consequences of alternative substances, such as alcohol, which compete within a similar social niche. Current ethics do not provide an even handed assessment of alcohol—the drug of choice of large numbers of older people—and cannabis—the drug of choice of many younger people. Testing alcohol against Strang et al’s domains is an informative exercise.

At the other end of the drug spectrum, cannabis legislation ties up disproportionate amounts of police and other judicial time. In 1998, of the 2240 police incidents directly involving drugs in Merseyside, 70.8% related to cannabis while heroin incidents accounted for only 6.3%. Consequently, the cost of current cannabis legislation also includes the diversion of judicial efforts away from drugs that have enormous repercussions for health.

Perhaps we can now begin to have an objective, evidence based, and inclusive discussion of the whole topic of alcohol and drug abuse, which includes tobacco, and which takes a social administration perspective in looking at the costs and benefits of social policy in full rather than being narrowly concerned with selective biological aspects.

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The effects of cannabis on driving are difficult to evaluate

Entorr—in their article on the cannabis debate, Strang et al raise the issue of cannabis and its effects on driving, suggesting that “a clearer understanding will be required of
the extent to which a particular concentra-
tion of the drug (or its metabolites) can reli-
ably be taken as evidence that an individual’s
driving ability was consequently impaired.1”
A review of the literature, however, suggests
that defining an acceptable level of cannabis
consumption for driving is unlikely to be
possible for several reasons.

Firstly, there is a poor correlation
between plasma concentrations of trans-
Δ9-tetrahydrocannabinol (THC) (the constituent of cannabis responsible for the production of
most of the psychoactive response) after
smoking and subjective, self-reported psycho-
logical effects; plasma concentrations of THC
decline long before peak effects are felt.2 Sec-
ondly, the relation between psychological test-
ing and performance in experiments of real
driving is complex because the two modalities
of testing are different. Impairment in
driving has been shown experimentally with
acute intoxication by cannabis;3 however, attempts to correlate driving performance with concentrations of THC will be severely
affected by the observed time lag between
THC concentrations and peak effects.

The issue is further complicated in
people who use cannabis heavily for
prolonged periods. This group has been
shown to develop tolerance to the somatic
and psychological effects of THC; this tol-
erance cannot be correlated with any drop in
cognition below that of users who are not tolerant.4 Chronic heavy users of canna-
bis do, however, show subtle impairment in
memory, organisation, and attention, and
the effect becomes more pronounced the
longer the duration of use.5 Whether these
effects diminish the ability to drive is not
clear, but since they are unrelated to acute
intoxication, it is unlikely that it will ever be
possible to correlate them with concentra-
tions of THC. Furthermore, it is not clear
whether these abnormalities are reversible
with prolonged abstinence.

The pursuit of a definition of a “safe”
amount of cannabis that can be consumed
and still allow for driving is unlikely to be
successful.

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1 String J, Witton J, Hall W. Improving the quality of the
cannabis debate: defining the different domains. BMJ
2000;320:108-10. (8 January.)
2 Perez-Reyes M, DiGuiseppi S, Davis KH, Schindler VH,
Cook CE. Comparison of effects of marijuana cigarettes of
three different potencies. Clin Pharmacol Ther 1982;31:
617-24.
3 Smiley A. Marijuana: on road and driving simulator stud-
ies. In: Kuhnert H, Corigual W, Hall W, Smart R, eds. The
health effects of cannabis. Toronto: Addiction Research
4 Hunt CA, Jones RT. Tolerance and disposition of tetra
hydrocannabinol in man. J Pharmacol Exp Ther
1990;252:35-44.
5 Solowij N. Cannabis and cognitive functioning. Cambridge:

Emergency admissions in
Stockport were exaggerated

Editor—Morgan et al say that the increase in
emergency admissions in Avon from
1989 to 1998 may be an artefact.1 Analyses in
the annual public health report for Stock-
port reached a similar, but not identical,
conclusion.2

We found that the increases were
exaggerated. Information distortions, inter-
hospital transfers, increasing rates of admis-
sion for minor conditions, and changed
patterns of practice affecting a particular provider
unfairly accounted for almost two thirds of
the apparent increase, leaving a true under-
lying pressure of 2.5% a year. Part of this
increase was explained by changed practice—
for example, improved management of chest
pain—and part was unexplained.

The unexplained increase was entirely
among elderly people. A rapid response
scheme for acute care at home was put in
place jointly by health and social services.
For the first six months that the scheme was
in place there was no year on year increase in
emergency admissions for the population
of Stockport. Since our original response
last year,3 however, this halt has not been
sustained and the pattern of emergency
admissions has shifted towards younger age
groups. This shift has not yet been fully
analysed.

Patterns of emergency admission are
complex. They require active management
but this must not simply assume a constantly
rising pressure. Investment in community
services is relevant to a whole system
approach.

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1 Morgan K, Proshiero D, Frankel S. The rise in emergency
admissions—cpr or artefact? Temporal analysis of health
services data. BMJ 1999;319:1350-1. (17 July.)
2 Watkins SJ. Health 2000; four years to go. Annual public
health report for Stockport. Stockport: Stockport Health
Authority; 1998;363:401-3.
3 Electronic response. The rise in emergency admissions—
cpr or artefact? Temporal analysis of health services data
BMJ 1999;319:7203-5. (accessed 10 June.)

Number of embryos allowed in
fertility treatment should be
flexible

Editor—The Royal College of Obstetri-
cians and Gynaecologists’ new guidelines
for the management of infertility in tertiary
care5 are generally welcomed. Guideline
10, however, recommends that the maxi-
mum number of embryos should be
reduced from three to two for all patients.
This is an imprecise way of dealing with a
complex problem, eliminating triplets at
the expense of some couples having their own
child. Regulatory authorities already deprive
some women of having their own children
because of the decision to fix the upper limit
to three in 1987. The college should have
evaluated who is at risk of having a multiple
pregnancy and made recommendations
based on this risk.

A fertility index based on factors associ-
ated with the risk of having a multiple preg-
nancy could be calculated to determine how
many embryos to transfer. This should result
in women with high reproductive potential
receiving one or two embryos and those
with low reproductive potential receiving
three or even more. We have indirect
evidence to support this reasoning. Using
gamete intrafallopian transfer, we have
transferred more than three eggs to women
aged >40 who have a low risk of multiple
pregnancy; this technique does not come
under the supervision of the Human Ferti-
sication and Embryology Authority. Our live
births/ongoing pregnancies for those aged
41-44 is 15%, compared with about 4.8% from
the authority’s national data on in vitro
fertilisation, and there were no triplets.

We believe that the college’s recommen-
dation is flawed. If transferring two rather
than three embryos in women aged ≤40
gives the same chance of a singleton preg-
nancy there should be a comparable
singleton pregnancy rate between centres
with different incidences of two embryo
transfers. Analysis with data from the Human
Fertilisation and Embryology Authority for
all ages in 1999 indicates very different rates
between our centre (12% two embryo trans-
fer) and centres having a higher incidence—
for example, Aberdeen (63%) and Hammers-
smith Hospital (52%).6 The differences were
not simply due to an increase in multiple
pregnancy—mostly twin pregnancies. The
chance of having a birth per embryo
transfer for all treatments, including the use
of frozen embryos, was greater in our centre
(19.5% compared with 14.4% and 12.5%
respectively); the chance of a singleton
birth was 13.3% compared with 11.1% and 9.9%.

Guideline 10 also states erroneously that
there is a significant risk of triplets in women
over 40 when three embryos are transferred,
but the Human Fertilisation and Embryol-
ogy Authority’s data indicate just one set in
808 transfers. The college should acknowl-
dge that infertile women have different
reproductive potentials and risks of multiple
pregnancy; it should amend its recommen-
dation to allow for flexibility rather than
have patients fit an inappropriate and incor-
rect medicopolitical dogma.

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1 Kmiotowicz Z. College urges maximum of two embryos for
2 Human Fertilisation and Embryology Authority. 1999
3 Royal College of Obstetricians and Gynaecologists. The
management of infertility in tertiary care. London: RCOG,
2000. (Evidence based clinical guideline No 6.)

Letters

Rapid responses

Correspondence submitted electronically is
available on our website

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