

Co-proxamol and suicide

Licence needs to be changed

EDITOR—We agree with Hawton et al that co-proxamol presents a major overdose hazard, their results illustrating the difficulties for licensing authorities in limiting availability of prescription medicines that are only hazardous in overdose.¹

Co-proxamol is more likely to result in death; it causes prolongation of the QRS interval in an electrocardiogram in experimental animals and in humans.^{2,3} This property is usually associated with sodium channel blockade and is a precursor to ventricular arrhythmia. We have shown a significant relation between estimated dextropropoxyphene dose (based on paracetamol concentration) and QRS prolongation in a case of co-proxamol poisoning,⁴ an effect not seen with other opioid combination products.

Dextropropoxyphene is rapidly absorbed from the gastrointestinal tract, increasing early cardiac risk, with death happening within one hour after ingestion.⁵ Most patients probably die of co-proxamol poisoning as a result of its combined cardiac (non-opioid) and central nervous system (opioid) effects before hospital admission. Understanding these factors may also improve acute care.

Prescribing patterns for co-proxamol may show geographical variation, which could alter the risk estimates calculated by Hawton et al. In Edinburgh co-proxamol poisoning accounted for 4.8% of 5583 patients admitted with self harm in the two years from July 2000 to June 2002 (overall 20% of patients took an opioid). These figures seem similar to those of Hawton et al.

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Competing interests: None declared.

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Co-proxamol should be restricted, not banned

EDITOR—Smith suggests that co-proxamol be banned.¹ I am surprised by this reaction to Hawton et al's paper on co-proxamol and suicide.² Hawton et al clearly advocate restricting the availability of co-proxamol.

Dextropropoxyphene is closely related to methadone, and like methadone it has noradrenergic analgesic properties in addition to its opioid effect. Patients who attend pain clinics have often tried several compound analgesics, and occasionally they report that co-proxamol is the most effective. This may reflect a neuropathic component to their pain that is quite different to the post-operative pain for which co-proxamol is no better than paracetamol alone.

The evidence suggests that co-proxamol should be restricted perhaps to specialist use but not banned outright. After all a knee jerk ban of thalidomide would have deprived medicine of a drug still used in the treatment of leprosy.

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Availability of co-proxamol has been successfully reduced in Doncaster

EDITOR—In 1998 an audit of suicides in Doncaster identified the alarming rate of co-proxamol overdose as a method of suicide: of the 44 suicides with prescribed drugs between 1995 and 1998, 18 were with co-proxamol (41%).¹ That this is much higher than the national figure of 18% quoted by Hawton et al² may be because the rates of prescribing of co-proxamol in Doncaster

(around 11 million tablets a year) were 65% higher than the national average.

Hawton et al recommend restricting co-proxamol on the evidence that restricting availability of a specific means of suicide can reduce deaths. Doncaster Health Authority reached the same conclusion in 1998 and undertook to reduce the amount of co-proxamol in circulation by asking general practitioners to be more cautious in prescribing the drug. Doncaster Royal Infirmary also removed co-proxamol from its formulary.

The table shows how, four years on, the policy of reducing prescribing has been successfully implemented: around 60% fewer tablets are currently prescribed than in the period up to 1998 and the prescribing rate is now lower than the national average.

The numbers of suicides among Doncaster residents, also shown in the table, are too small for us to show any relation between the amount of co-proxamol prescribed and the number of suicides with the drug or the total number of suicides. However, we cannot help but be encouraged by the numbers: only five since the beginning of 2000.

The remarkably low number of suicides in 2002 is not a final figure, but many more are unlikely to emerge, and this clearly cannot be attributed to reductions in co-proxamol prescribing. We can, however, be sure that the quantity of tablets in circulation has been massively reduced and that the evidence, as quoted by Hawton et al, implies that this is likely to reduce deaths.

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Effectiveness of reducing prescriptions of co-proxamol in Doncaster

	1996	1997	1998	1999	2000	2001	2002
No of co-proxamol tablets per prescribing unit*:							
Doncaster	27.9	28.0	26.7	17.6	13.1	11.7	10.7
England and Wales	16.9	16.7	16.4	15.9	15.1	14.5	13.8
No of suicides†:							
With co-proxamol	5	3	7	5	2	3	0
All other methods	25	29	36	22	31	26	14

*Based on data from the Prescription Pricing Authority for preceding eight months for 1996 and on first six months only for 2002. †Office for National Statistics public health mortality file; data for 2002 not final.

Antidepressant prescribing and suicide

Analysis is misleading

EDITOR—Hall et al's data on suicide rates and antidepressant prescribing contradict their own conclusions.¹ The conventional and intuitive way of analysing trends in rates of antidepressant use by age group would be to look at ratios of rates of use in 1998-2001 and 1990-1.

Data on *bmj.com* show that rates increased 7.5 times for men aged 25-34 and 2.1 times for men aged 75-84. Spearman correlations using these ratios for all age groups and the difference in suicide rates as defined by Hall et al showed a strong positive correlation. Increases in suicide rates were associated with higher rates of increase in the use of antidepressants. For men, Spearman's correlation coefficient was $r_s=0.86$, $P=0.007$; for women, $r_s=0.76$, $P=0.03$.

Hall et al seem to have analysed absolute differences in rates of prescribing. The use of daily dependent dose is also problematic and not clearly explained. Daily dependent doses represent units of therapeutic doses as defined by the World Health Organization. The increase in the use of antidepressants in older age groups is probably accounted for partly by a change from prescribing lower doses of tricyclic antidepressants to prescribing selective serotonin reuptake inhibitors at standard doses.

Evidence that lower doses of tricyclics are less efficacious than standard doses is not strong.² In addition, daily dependent doses relate to the general adult population. They will therefore underestimate prescribing rates of tricyclic antidepressants in elderly people in whom therapeutic and tolerable doses are accepted to be lower.

That the massive increase in antidepressant prescribing has had any objective and positive impact on the health of populations remains difficult to prove. Other commentators have implied that there is no impact on suicide trends and pointed out that rates of self harm are rising, not falling.³ Long term incapacity due to depression in the United Kingdom continued to rise throughout the 1990s.⁴

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- Hall DW, Mant A, Mitchell PB, Rendle VA, Hickie IB, McManus P. Association between antidepressant prescribing and suicide in Australia, 1991-2000: trend analysis. *BMJ* 2003;326:1008-12. (10 May.)
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Associations attribute possible causality inappropriately

EDITOR—Hall et al say that reductions in suicide rates in older people in Australia could be attributed to their increased exposure to antidepressants, in particular selective serotonin reuptake inhibitors.¹ But the associations seem to attribute possible causality inappropriately.

According to the Australian Bureau of Statistics, suicide rates in people over the age of 40 in Australia have gradually reduced since 1961-5, the peak period of suicide deaths for these age groups since the great depression.² This is true for each five year age group from age 40 years. In most age groups, the greatest reduction occurred in the period before 1990. For example, in 1961-5 suicide rates in men aged 45-9 were 34.9 per 100 000 and in men aged 50-4 39.4 per 100 000. In 1986-90 rates had dropped to 23.5 per 100 000 and 24.7 per 100 000 respectively. By 1996-2000 the rate had dropped to 23.8 per 100 000.

Similarly if we examine men aged 55-64 years, from 1961-5 to 1986-90 suicide rates dropped from 37.8 per 100 000 to 25.1 per 100 000 and to 20.7 in 1996-2000. This scale of pre-1990 suicide rate reductions is also found in women.

Important historical trends of a reduction in suicides prevailed long before selective serotonin reuptake inhibitors were introduced. The reasons for this reduction are unclear, but improved detection and treatment of depression is unlikely to be as effective in preventing suicide as the prevention of depression itself.

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Decline in suicide rate among older people predates 1991

EDITOR—Hall et al say that the association they observed between antidepressant prescribing and suicide may reflect increased recognition, diagnosis, and treatment of depression by general practitioners as much as any pharmacological effects of antidepressants.¹ The time scale they took into account was the decade 1991-2000. If they are right in their conjecture, the processes

involved must have started some 60 or 70 years ago, if not in Australia then in the United States.

Age group (years)	1940	1975
65-69	57.5	35.0
70-74	59.3	37.6
75-79	65.8	44.9
80-84	66.4	44.6

involved must have started some 60 or 70 years ago, if not in Australia then in the United States.

In the United States a steady decline in the suicide rate of people aged 65 and over has been well documented: from 45.3 per 100 000 in 1933 (this is the earliest year for which suicide data for all of the United States are available) to 21.5 per 100 000 in 1986.² Murphy and Wetzel showed the same decline for 1940-75.³ The table, presenting age specific suicide rates in white men in five year intervals, has been extracted from their table 6.

The decline in suicide rates in older age groups started well before the introduction of the tricyclic antidepressants—that is, before there was any effective pharmaceutical treatment of depression.

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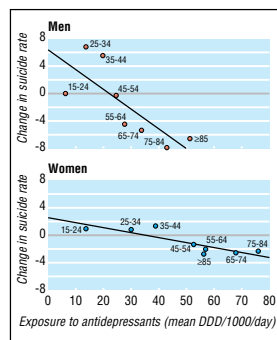
Antidepressants do not reduce suicide rates

EDITOR—Hall et al show that the biggest increase in the use of antidepressants in 1990-2000 has been in the 15-44 age group.¹ Simultaneously the rate of suicide for this age span has increased in Australia. For men aged 25-34 the use of antidepressants has increased more than six times during the period and the suicide rate has increased by almost 17%.

By using this correlation in time in the same way that Hall et al use the total correlation for all ages it could be argued that antidepressants increase the risk of suicide for people younger than 45 and particularly for men aged 25-34. Neither this conclusion nor that of Hall et al is scientifically valid. To make valid conclusions we need controlled studies.

Hall et al say that there is little direct evidence that antidepressants reduce the suicide rate because even large clinical trials have limited power to detect a reduction. They do not mention that three large meta-analyses on antidepressants and suicide have been published since 2000.²⁻⁴

Together these include over 60 000 depressed patients in randomised clinical trials comparing antidepressants with placebo. Most trials were short term, but



several long term trials were also included, with a total of 1949 patients. The results of all meta-analyses, both for short term and long term treatment, were that suicide was slightly more common among patients taking antidepressants compared with patients taking placebo.

Hall et al do not show that antidepressants reduce the rate of suicide. At the same time placebo controlled randomised clinical trials show that the rate of suicide is higher with antidepressants than it is with placebo. The only reasonable conclusion is that antidepressants do not reduce the rate of suicide. There may be a slight increase in suicide rates for patients treated with antidepressants, although further studies are needed to make any firm conclusions.

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- Hall DW, Mant A, Mitchell PB, Rendle VA, Hickie IB, McManus P. Association between antidepressant prescribing and suicide in Australia, 1991-2000: trend analysis. *BMJ* 2003;326:1008-12. (10 May.)
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Authors' reply

EDITOR—Our critical finding was the relation between decline in suicide rate and exposure to antidepressants across age groups in both sexes. We agree that time series data must be interpreted cautiously; that is why we considered alternative explanations.

We disagree with Moncrieff that we should have used ratios of daily dependent doses. This would have been an alternative measure of change in exposure but not of overall antidepressant exposure. We agree that the daily dependent doses will underestimate prescribing levels of tricyclic antidepressants in elderly patients but believe that this would underestimate any correlation between antidepressant prescribing and suicide trend by underestimating elderly exposure to antidepressants.

The fact that, as Verberne and Draper point out, suicide rates in older people declined before the period of increase of the selective serotonin reuptake inhibitors does not mean antidepressants could not be a contributory cause of the decline in suicide rates between 1991 and 2000. Suicide rates in young men did not decrease, yet antidepressant prescribing increased over the same period, albeit from a very low base, as Ankarberg says. We accept that using antidepressants is not the only influence in suicides among young men.

It is true that meta-analyses of placebo controlled randomised controlled trials have not shown a lower rate of suicide among patients receiving antidepressants, as Ankar-

berg says. However, patients at risk of suicide are often excluded from such studies. These studies often entail follow up periods of less than six months so their findings do not necessarily apply to the general population.

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Pharmacological heterogeneity limits antidepressant study

EDITOR—MacGillivray et al potentially make a huge contribution to the understanding of the relative utility of selective serotonin reuptake inhibitors and older antidepressants in the treatment of depression in primary care.¹ However, the usefulness of their meta-analysis is limited by the original data, as is so often the case.

These results are very difficult to interpret, not least because the comparators used in the key studies are pharmacologically heterogeneous. Two studies, including one of the key three crucial studies providing data in an unambiguous format, used mianserin as a comparator. Mianserin is a tetracyclic, not a tricyclic as the paper's title might imply. It is not a potent reuptake inhibitor but a potent and thus sedative antihistamine. A third study used lofepramine as a comparator, a more modern tricyclic with a much more benign anticholinergic side effect profile than its older cousins, which have an adverse event rate similar to the selective serotonin reuptake inhibitors.²

Two of the three studies providing unambiguous data for the efficacy analysis were of paroxetine against amitriptyline. Paroxetine may be considered to be an

atypical selective serotonin reuptake inhibitor in that it has some adrenergic reuptake inhibition and anticholinergic properties. Pharmacologically its profile lies between the more selective selective serotonin reuptake inhibitors and the classic tricyclics, as does lofepramine.³

As an underlying principle of meta-analysis is homogeneity of the material, it is no surprise that a clear answer does not emerge from this work, given the pharmacological heterogeneity.

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- MacGillivray S, Arroll B, Hatcher S, Ogston S, Reid I, Sullivan F, et al. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. *BMJ* 2003;326:1014. (10 May.)
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European Commission's proposal for a council recommendation on cancer screening

EDITOR—The European Commission recently published the *Proposal for a Council Recommendation on Cancer Screening*, based on consensus reached by experts.¹⁻³ For breast, cervical, and colorectal cancer sufficient evidence has been accumulated on cost effectiveness and negative effects to recommend screening at a population level. Mammography should be offered every two years to women aged 50-69. Periodic Pap smear testing should start before the age of 30 but not earlier than the age of 20. Faecal occult blood testing should be recommended to men and women aged 50-74.²

New technologies can be introduced only after their effectiveness and cost effectiveness have been established in randomised controlled trials on public health relevant outcomes. The following methods or policies require evaluation: digital mammography, liquid based cervical cytology, human papillomavirus detection, automated screening devices, immunological faecal occult blood tests, primary colonoscopy, as well as extension of mammographic screening in women aged 40-49.

The European Commission recommends that screening be offered in organised programmes, with quality assurance at all levels and good information about benefits and risks. A reduction in mortality and incidence of advanced disease can be achieved only if coverage is high and standards of rigorous quality assurance are respected. Management and evaluation of programmes require accurate monitoring of data. Data transmission

and linkage systems must be set up with respect of privacy legislation and ethical rules.

The European Commission has given the network for cancer screening the mandate to work out technical guidelines defining standards and benchmarks for best practice.⁴ The current proposal still needs endorsement by the ministers of health. We hope this will happen without delay.

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Opportunistic screening for *Chlamydia*

Microbiological input is essential in *Chlamydia* screening programmes

EDITOR—The strand displacement amplification test used by Moens et al for *Chlamydia trachomatis* screening produced equivocal results in 11.2% of samples.¹ Such a high rate is unacceptable.

A result could be termed equivocal if it is borderline or if a sample gives discrepant results on repeat testing. In addition, this assay has an internal control, a negative result being invalid if the internal control is inhibited. Differentiation between these potential causes is important—borderline and non-repeatable positive results could be due to small amounts of organisms or technical problems such as cross contamination; inhibitors may be prevented by cold chain transportation of urine or by using the urine processing pouch supplied by the manufacturer.²

We have extensive experience with the strand displacement amplification test and have not experienced such a problem with equivocal results. Of 24 130 samples tested, 21 605 (89.5%) were negative while 2224 (9.2%) were repeatable positive results. Only 72 samples gave non-repeatable positive results (prevalence 0.3%, reproducibility rate

96%); 229 samples (0.9%) had evidence of inhibitors. Thus, only 1.2% of the samples gave no definitive positive or negative result.

Although treating all equivocal results as positive is a pragmatic approach, action based on poor quality results will lead to misleading reports, inappropriate labelling of patients as having sexually transmitted infections, unnecessary partner notification, overtreatment with antibiotics, inaccurate statistics, and incorrect epidemiological analysis. Active microbiological input is essential during the planning of such programmes to optimise sample collection and transportation as well as the interpretation of results.

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- 1 Moens V, Baruch G, Fearon P. Opportunistic screening for Chlamydia at a community based contraceptive service for young people. *BMJ* 2003;326:1252-5. (5 June.)
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Authors' reply

EDITOR—We acknowledge the concerns of Tong et al and fully endorse their view that active microbiological input is essential both in planning and introducing a *Chlamydia* screening service using the strand displacement amplification test.

We emphasise that our study was carried out with input from the medical microbiology department that did the testing, which also, as stated in the paper, was informed of our concerns about the high number of equivocal results but could not provide an explanation. Apparently the problem was not confined to samples from our clinic.

We explain in the paper why we decided not to offer a repeat test and instead treat the equivocal result as positive—namely, because we were not confident, given our experience of the high risk client group being tested, that these young clients would return for a repeat test.

Since completing the study, which included as part of the service an information campaign and outreach work in a local school informing pupils about *Chlamydia* and our service, we are much more confident about successfully being able to recall clients who have an equivocal result for a repeat test. Moreover, the rate of equivocal results has fallen to around 1% of samples, perhaps indicating improved procedures with the strand displacement amplification test.

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Guidelines for anecdotes might include more information

EDITOR—We agree with Aronson on the need for a uniform presentation of anecdotes and case reports by using common standardised guidelines.¹ His proposed guidelines are complete and systematic, but some items could be added to improve this format.

In the drug treatment section, the contents should include prescription drugs, over the counter medicines, and preparations of complementary and alternative medicines, including herbal treatments and homeopathic and ethnic preparations. The use of these treatments has increased over the past years, mainly in patients with chronic diseases who are taking multiple drugs, in whom adverse reactions are more likely to develop.

In the history section, it is important to include history of use of psychostimulant substances (such as methylxanthines) and natural or synthetic drugs of abuse (such as cannabis, amphetamines, hallucinogens, or opiates), in addition to drinking and smoking habits.

Other aspects to consider are the compulsory communication of the adverse reaction to the national pharmacovigilance centre or the local World Health Organization drug monitoring programme before submitting a paper for publication.

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- 1 Aronson JK. Anecdotes as evidence. *BMJ* 2003;326:1346. (21 June.)

Two groups were different in cardiovascular risk study

EDITOR—Dunder et al compared two different groups and concluded that the incidence of myocardial infarction was significantly higher in the group receiving antihypertensive treatment.¹

Table 1 shows two heterogeneous groups—the group with hypertension (having treatment) had higher blood glucose concentrations, body mass index, and proinsulin values (implying insulin resistance) than the other group, which had normal blood pressure, lower body mass index, and lower glucose concentrations (implying insulin sensitivity). Up to 40% of patients with hypertension are insulin resistant, and insulin resistance is associated with increased cardiovascular risk.^{2,3} Thus the group with hypertension was at a much higher baseline risk of cardiovascular disease than the group with normal blood pressure.

The two groups remain significantly different over the next 10 years. The normal blood pressure group showed less increase in body mass index and glucose concentrations. Dunder et al say that an increase in

fasting blood glucose predicted myocardial infarction in the group receiving antihypertensive treatment but not in the group without such treatment. However, 5-7% of patients with insulin resistance progress to the next stage of glucose dysregulation yearly. If we presume that 30% of patients with hypertension in this study had insulin resistance then around 1% per year (about 10% over 10 years) of this group would progress to the next stage of insulin dysregulation, irrespective of the treatment.

The conclusion(s) of the study would have been appropriate had Dunder et al compared hypertensive patients receiving treatment with those not receiving such treatment when their baseline risk(s) for development of cardiovascular disease would have been similar.

Although hypertension and diabetes are additive, hypertension seems to be a more potent predictor of vascular risk than glycaemic control, and aggressive treatment of hypertension dramatically reduces this risk.^{4,5}

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- 1 Dunder K, Lind L, Zethelius B, Berglund L, Lithell H. Increase in blood glucose concentration during antihypertensive treatment as a predictor of myocardial infarction: population based cohort study. *BMJ* 2003;326:681. (29 March.)
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Behavioural approaches are helpful in overactive bladder

EDITOR—Herbison et al made a plea for a more pragmatic approach to evaluating patients with an overactive bladder syndrome.¹ A strong criticism of the work performed to date relates to the use of placebo as a control. They argue for the use of a behavioural approach such as bladder retraining as a comparator. This seems logical given that behavioural approaches are offered to most people with lower urinary tract symptoms (many of which will have overactive bladders) as a first line of treatment. Behavioural approaches might prove more effective for longer and lack the harms associated with pharmacotherapy.

We would not stop at bladder drill as one of the potential interventions.² It could be that fluid scheduling, caffeine restriction, pelvic floor exercises, and the optimised management of comorbid conditions could all have a place in the management of the overactive bladder syndrome.^{3,4} In this respect it is interesting that these interventions are routinely offered by continence advisers and urology nurse specialists, but not by doctors.

What is also interesting is that with a few exceptions, doctors have not subjected these interventions to rigorous study.⁵ If they prove to be as effective as many believe them to be, the knowledge will transform the management of all patients with lower urinary tract symptoms and could potentially impact on 60% of the men and women over the age of 50.

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Competing interests: None declared.

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Randomise foundation trusts

EDITOR—Yet another NHS policy initiative is being introduced in a form that does not allow the taxpayer and voter to assess whether the change is helpful or not.¹ Because potential foundation trusts are different from the "average" trust then any effect they have on the delivery of health care will be confounded either by selection bias or through regression to the mean.

The 32 trusts expressing an interest in foundation status should be randomised to be given the status or remain as they are. We will then be able to ascertain whether they work or not. What is likely to happen is that they will be evaluated (if they are evaluated at all) by using non-randomised methods. For critics of foundation trusts a before and after design is likely to be helpful in "proving" such trusts are harmful.

As they are selected on the basis of "high" performance there ought to be a satisfying regression to the mean for several of them. To avoid this supporters of such trusts need to use a case-control approach as this is more likely to show that they work as uncontrolled biases (such as enthusiastic senior management) may favour foundation trusts.

These non-randomised evaluations will provide ammunition both to supporters and critics of foundation trusts, and we consumers are left none the wiser. Whoever makes the decision in the Department of Health: please use randomisation.

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Competing interests: None declared.

- 1 Dixon J. Foundation trusts. *BMJ* 2003;326:1344-5. (21 June.)

Time has come for a medical minister of health

EDITOR—Smith rightly identifies that there is no universally acknowledged leader of the NHS.¹ But medical leadership in the NHS can effect improvements in services. A good example has been the appointment of a national cancer director in England and his equivalent in Scotland.

From a position before 2000, when cancer services showed wide variations in quality, the development of multiprofessional collaboratives in England and the managed clinical networks in Scotland have been key in improving a patient's cancer journey. Reducing the waiting time to diagnosis and surgical treatment for breast cancer exemplifies this.

In a rapidly moving speciality such as oncology, any lay minister necessarily depends on expert medical advice. He or she does not have the knowledge to manage the service directly. Perhaps the prime minister should consider appointing a clinician as the next minister of health.

Recent precedents have been set in Italy and Egypt. He or she might oversee a board of national medical directors in each area of health care supported by the permanent secretary in the Department of Health. With an adequate budget the improvements in cancer services might be replicated in other areas of the NHS.

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Competing interests: None declared.

- 1 Smith R. Changing the "leadership" of the NHS. *BMJ* 2003;326:0. (21 June.)

"Hitting the Headlines" is useful resource

EDITOR—Schwitzer reviewed the media and evidence.¹ One of my favourite sections of the UK National Electronic Library for Health site (www.nelh.nhs.uk) is Hitting the Headlines, produced by the NHS Centre for Reviews and Dissemination.

It takes articles from the British national press that report on issues relating to the effectiveness of an intervention. It then assesses the reliability of the claims by critically appraising the underlying research. It cannot stop the flow of "distorted" articles produced by the national press, but it can provide a useful resource for clinicians in protecting themselves from hordes of newspaper waving patients.

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Competing interests: JRB works on a variety of projects for the National Electronic Library for Health, but not Hitting the Headlines.

- 1 Schwitzer G. How the media left the evidence out in the cold. *BMJ* 2003;326:1403-4. (21 June.)