

## Correspondence

## Awareness and Attitudes about Disease Mongering among Medical and Pharmaceutical Students

C. Jairaj Kumar, Abhizith Deoker, Ashwini Kumar, Arunachalam Kumar, B. M. Hegde



*This is one of a series of articles on disease mongering in the April 2006 issue*

Pharmaceutical companies throughout the world market their products aggressively through a variety of promotional campaigns [1]. In India, these marketing practices pose a greater problem because the restrictions on drug dispensing are very limited—drugs often being dispensed without a prescription from a licensed physician. The companies take full advantage of this situation. As many patients in India are poor and illiterate, and lack information on health care, they often visit local pharmacists or quacks for medical advice. Pharmacists routinely dispense drugs illegally over the counter. We visited 40 local pharmacy stores for medical advice for a feigned medical ailment, and we found that all 40 pharmacists dispensed drugs, including expensive antibiotics [2].

Pharmaceutical promotional campaigns in India, unlike those in developed countries (where pharmacists have little influence on drug sales), are not only aimed at changing the prescribing habits of physicians but also at pharmacists and quacks. Pharmaceutical companies in India offer various schemes and incentives (including television sets, motorcycles, and the opportunity for higher profit margins) to lure pharmacists into buying more drugs than they would normally need. As a result, the pharmacists make every effort to sell these drugs to patients visiting them for medical advice. They may also associate themselves with quacks or physicians in their efforts to shift their stock of the drugs.

In developed countries, dubious pharmaceutical marketing practices would soon attract the attention of watchdog bodies and social activists, but in India they go undetected. We believe that this situation demands proactive action on the part of the medical profession and also of the government.

The efforts of the pharmaceutical industry to medicalize human life should be resisted. We do not wish India to be in the same position as the countries of the West, where adverse drug reactions are responsible for a significant proportion of hospital admissions and require millions of outpatient visits and corrective measures. In the United States, for example, there are about 100,000 deaths due to medical errors every year, of which about 7,000 are attributed to drug reactions [3].

We believe it is important to assess current awareness about disease mongering among medical and pharmaceutical students, as pharmaceutical promotional campaigns are

aimed at both professions. Assessing current awareness could provide a basis for further research, leading to the development of effective measures that will raise awareness levels and motivate students to participate in future campaigns that seek to combat disease mongering.

Most medical and pharmaceutical students in India are not aware of the issue of disease mongering; neither do most of them know that recent audits have shown medical interventions and adverse drug reactions to be major causes of death and disability in the US [4].

Articles have been published warning the profession about disease mongering [5–7], but for the most part these warnings have not been heeded. One is reminded of Aristotle, who so rightly observed that “truth could influence only half a score of men in a century, while falsehood and mystery would drag millions by the nose.”

We prepared a 20-item questionnaire (Text S1) about disease mongering and the influence of the drug industry on clinical practice. The questionnaires were distributed among a random sample of 250 final-year medical and 250 final-year pharmaceutical students. The overall response rate was 406 out of 500 (81.2%), comprising 199 medical and 207 pharmaceutical students. Of the medical students, 30 out of 199 (15%) were able to explain disease mongering with relevant examples. Of the pharmaceutical students, 114 out of 207 (55%) were able to do so, suggesting that awareness of the problem was much greater among these students. Interestingly, however, 87 out of 114 pharmaceutical students believed the government, not the pharmaceutical industry, was responsible for the problem.

All the students, both medical and pharmaceutical, said they had frequently seen drugs dispensed without prescription. They had also often seen patients visit local pharmacists for medical advice. They agreed that both practices were unethical. However, both the medical and the pharmaceutical students were unaware of the incentives offered by drug companies to pharmacists for buying their drugs, which lead to unethical dispensing.

We believe that our small project, despite its inherent limitations, has thrown some light on the situation. Pharmaceutical students, who are exposed to the drug industry to some extent during their studies, have some idea of the magnitude of the problem, while the majority of medical students have no idea that even their textbooks are written with the help of money that comes from drug companies [8]. We need to make a more concerted attempt to educate the student community of all the health-care professions, in order to counter this unfair tendency. The government should undertake major initiatives to ensure that drugs are only dispensed with a prescription from a licensed physician. Medical associations and medical college administrators should alert their members to cross-check the information provided in drug company literature. Medical students should be warned about disease mongering through the display of posters, and through the organization of essay competitions and interactive plays. Students can play a further role by conducting regional and national surveys of the awareness of the public concerning this serious issue. ■

## Supporting Information

**Text S1.** 20-Item Questionnaire about Disease Mongering and the Influence of the Drug Industry on Clinical Practice

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## Syphilis: A Forgotten Priority

**Damian Walker, Godfrey Walker**

Peter Hotez and colleagues [1] provide a persuasive case for incorporating a rapid-impact package for “neglected tropical diseases” with programs for HIV/AIDS, tuberculosis, and malaria as part of a pro-poor strategy for improving health in the developing world. However, we believe there is a disease that has a high claim to be included in partnerships and initiatives devoted to what the authors term the “Big Three”, and yet has been largely ignored.

On the basis of the criteria identified by Hotez et al., the case for giving explicit priority to programs to control syphilis and particularly congenital syphilis is high [2]. In 2002, there were 157,000 deaths contributing to more than 4 million disability-adjusted life years (DALYs) (see annex tables 2 and 3 in [3]). These estimates exclude the burden attributable

to maternal syphilis, which includes 460,000 abortions or stillbirths, 270,000 low-birth-weight babies, and 270,000 cases of congenital syphilis each year [4]. This burden is concentrated in Africa and exhibits considerable geographic overlap with HIV infection. Syphilis accounts for 20% of genital ulcer diseases and is a cofactor in transmission of HIV, and both infections appear to progress more rapidly when they occur together [5].

Infection with syphilis is curable, and control is possible with existing drugs (specifically penicillin). However, little attention has been given to this in context of the Big Three. Azithromycin is included in the chemotherapy package proposed by Hotez et al. for the control of trachoma, and there are clear synergies with syphilis control. A recent trial in Tanzania demonstrated that a single dose of oral azithromycin is as effective as injectable penicillin G benzathine in treating early and latent syphilis [6]. However, some caution is needed concerning the widespread use of azithromycin for syphilis in view of the recent emergence of azithromycin-resistant *Treponema pallidum* [7].

There are other possible synergies in having a strategy including syphilis control; e.g., during routine antenatal care, chemotherapy for soil-transmitted helminths could be provided at the same time as offering voluntary counselling and testing (VCT) for HIV infection and screening for maternal syphilis. The control of syphilis has been shown to be highly cost-effective. If the control of syphilis was integrated into programs dealing with the four priority disease groups advocated by Hotez et al., then the cost-effectiveness of tackling not only syphilis but also the other four major public health priorities would improve. Furthermore, it would lessen the chance of avoiding death from one disease but dying from another [8].

While it might be hoped that the case for giving priority to syphilis would have been accepted and explicit emphasis given to programs to control this disease, this has not happened. Unfortunately, limited attention is given to syphilis control as part of the several partnerships devoted to the Big Three. Maybe this is because syphilis has historically had a social stigma, and has, therefore, been neglected. Now is the time to change this as part of a pro-poor strategy to meet the Millennium Development Goals. We suggest it is explicitly included in the rapid-impact package for neglected tropical diseases. ■

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Damian Walker and Godfrey Walker [1] make a strong case for adding congenital syphilis to our proposed list of neglected tropical diseases (NTDs). Indeed, we would hasten to add all of the major treponemal infections—including yaws, endemic syphilis (bejel), and pinta—could potentially qualify as NTDs. Leptospirosis and bartonellosis might also qualify as important neglected bacterial infections, while amoebiasis is an important yet neglected protozoan infection. Therefore, it is possible that in the future our list of 13–15 NTDs could expand to approximately 20 conditions. In the meantime, we are working to establish a set of consensus guidelines for this important list of NTDs. ■

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## The Need for an Individual Approach to Lung Cancer Treatment

Hisayuki Shigematsu, Shinichi Toyooka, Makoto Suzuki

Heidi Greulich and colleagues [1] have demonstrated the significance of insertion mutations in the epidermal growth factor receptor (EGFR) (exon 20) for tumorigenesis and responsiveness to tyrosine kinase inhibitors (TKIs) in lung cancers. They reported that different types of *EGFR* mutations conveyed different sensitivity to TKIs. Although several previous studies have suggested that tumors harboring mutations in the EGFR kinase domain were sensitive to TKIs such as gefitinib or erlotinib [2,3], others had reported an association between the *T790M* mutation in exon 20 and the resistance to TKIs [4,5]. As we learn more about the relationship between *EGFR* status (including gene copy number, mutation status, and mutation type) and drug sensitivity, decisions about treatment with TKIs for patients with non-small-cell lung cancer (NSCLC) become more complex.

Previously, we reported *HER2* mutational status, as well as *EGFR* and *KRAS*, in a large number of NSCLCs [6]. We found that 22% of tumors had *EGFR* kinase domain mutations (149 out of 671). Of these 149, 15 of them were insertion mutations in exon 20. The more common types of mutations—i.e., deletion in exon 19 (68 out of 149) and L858R in exon 21 (61 out of 149)—were more frequent in women and in “never smokers” (with *p* values of less than 0.001), whereas the exon 20 insertion mutations showed no bias for sex (seven in males versus eight in females) or smoking status (seven in smokers versus eight in never smokers). We have no data regarding TKI sensitivity for the 15 patients with insertion mutations to date, but based on the results from others and our own in vitro data, they may not benefit from the conventional TKIs, despite the fact that their tumors have *EGFR* kinase domain mutations.

To maximize benefit to patients, we should determine the exact type of mutation for an individual tumor and determine whether it conveys sensitivity or resistance prior to TKI therapy. The development and clinical application of novel agents overcoming resistance should yield a more effective targeted therapy for tumors with all types of *EGFR* mutations. ■

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## Mischievous Odds Ratios

### William Steinsmith

Pieter Reitsma and colleagues have explored—in a population of patients anticoagulated with coumarin congeners—the connection between the presence of mutant alleles of a single gene and the risk of haemorrhage [1].

Using as their denominator the odds for bleeding in a patient without mutant alleles, and using as their numerator the odds for patients with each of the two mutant alleles, the authors propose the resulting odds ratios as surrogates for the relative risk of haemorrhage.

It should be noted, however, that the conflation of an odds ratio with a relative risk is not generally justified [2,3]. The relative risk is the ratio of two probabilities ( $p_2/p_1$ ), whereas the corresponding odds ratio is  $[p_1/(1-p_1)]/[p_2/(1-p_2)]$ . Equating these two ratios requires that  $p_1 = p_2$ , i.e., that the risk ratio be unity.

In Reitsma and colleagues' paper, none of the eight odds ratios presented in Table 2 turn out identical with the corresponding calculated risk ratio, and the most discordant pair of values diverge by a factor of about 1.4, i.e., the odds ratio of 2.6 corresponding to a relative risk of 1.9.

Mischievous conflation of odds ratios with probability ratios is widespread in the literature dealing with laboratory testing, with the odds ratio (confusingly termed the “likelihood ratio”) typically presented as surrogate for the corresponding ratio of probabilities.

The power of a positive laboratory test to enhance the likelihood of disease presence in a given patient (properly termed the “positive probability-based likelihood ratio”) is the ratio of two probabilities: the probability that the patient who tested positive is truly diseased (termed the “positive predictive value”) divided by the probability of disease in the pre-test population (termed the “disease prevalence”).

Expressed explicitly in terms of the subcategories of the test population, the positive predictive value is the ratio represented by (True Positives)/(True Positives + False Positives), and the prevalence is the ratio represented by (True Positives + False Negatives)/(True Positives + False Negatives + True Negatives + False Positives).

The calculus is easily adapted to compute the probability-based likelihood ratio for the absence of disease in a given patient. In this case, the post-negative-test probability of disease absence (termed the “negative predictive value”) is the ratio represented by (True Negatives)/(True Negatives + False Negatives), and the pre-test probability is one minus the disease prevalence. The negative probability-based likelihood ratio is, then, the ratio represented by the post-test probability divided by the pre-test probability.

A more descriptive term for the probability-based likelihood ratio would be the “probability magnifying power,” since it leads to the expanded probability of the presence (or absence) of disease yielded by a positive (or negative) test result. ■

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## Authors' Reply

William Steinsmith is correct that the odds ratio (OR) is used to approximate the relative risk, but incorrect that in this instance, and most other ones, the two would differ by more than a trivial amount, since he has failed to appreciate the case-control design.

Indeed, if the cumulative risk of disease is  $p_1$  in the exposed and  $p_0$  in the nonexposed, the relative risk ( $p_1/p_0$ ) only equates the OR,  $[p_1/(1-p_1)]/[p_0/(1-p_0)]$ , when exposure confers no excess risk. However, in a case-control study,  $p_1$  and  $p_0$  cannot be directly estimated (nor, obviously, can their odds), and the OR is the only possible estimator (hence its frequent use).

We will illustrate the theory starting with a cohort study, and then moving from this to a case-control study. When risks are low, the OR will always be a good approximation of the relative risk because  $OR = (p_1/p_0)/[(1-p_1)/(1-p_0)]$ , in which the second part of the term will be close to one. So, suppose a trait is present in 20% of a population, with a risk of disease of 1% in those without the trait, and 2.5%



in those with the trait, i.e., a relative risk of 2.5. These are likely to be close to the actual annual numbers for risk of haemorrhage under anticoagulant treatment with and without the *VKORC1* variant [1,2]. If we follow 10,000 people for one year—8,000 without the trait, of whom 80 will develop disease; 2,000 with the trait, of whom 50 will develop disease— $RR = (50/2,000)/(80/8,000) = 2.5000$ , and  $OR = (50/1,950)/(80/7,920) = 2.5385$ . When the OR is written out in full to  $[(50/2,000)/(1,950/2,000)]/[(80/8,000)/(7,920/8,000)]$ , this can easily be reduced to the above.

In a case-control study, all cases are included, but there are only a fraction of all noncases (controls). With a sampling fraction of 1/10, the case-control study sampled from this cohort would look like the following: 80 cases without and 50 cases with the trait, 792 controls without and 195 controls with the trait ( $OR = [50/195]/[80/792] = 2.5385$ ).

With a sampling fraction of 1/100, there would be 79.2 unexposed and 19.5 exposed controls, and the OR would still be 2.54. This demonstrates that the actual risk or odds of disease cannot be derived once only a sample of individuals without disease are included, but that the ratio of exposed over unexposed controls (195/792) remains valid whatever the sampling fraction. This has been called the “exposure odds”, and many prefer to write the OR as the exposure odds ratio:  $OR = (50/80)/(195/792) = 2.54$ .

In a cohort study, the OR can be easily recalculated into a risk ratio (RR), since the actual risks ( $p_0$  and  $p_1$ ) are known [3]:  $RR = OR/[(1-p_0) + p_0*OR]$  [3]. In the example above,  $RR = 2.5385/(0.99 + 0.01*2.5385) = 2.5000$ .

In a case-control study, because the number of controls is only a fraction of the actual number of individuals without disease in the cohort, absolute risks cannot be calculated, and a recalculation from OR to RR is not possible (unless there is external information on the absolute risks).

This implies that it is not possible to calculate from our data how different the OR was from the RR, as Steinsmith tried. We can, however, in this particular case, make an estimate, since we know the risk of haemorrhage under anticoagulant treatment from previous studies to be around 1% per year. With a background risk of 1% per year, all the ORs mentioned in our paper are within 2% of the relative risk. The highest OR of 2.6 (2.5641) would relate to a relative risk of 2.5 (2.5246)—a trivial difference. Steinsmith’s further suggestions for analyses, i.e., to use likelihood ratios, are relevant to studies of diagnostic tests in which the aim is to

evaluate the presence or absence of disease. This is not the analysis one would use in aetiologic studies such as ours.

Generally, since most diseases are infrequent, ORs are good estimators of relative risks under this “rare disease assumption”. For a disease with a frequency of 10%, which is high, the difference between OR and RR is still only 10%. On a higher theoretical level, one could argue that the parameter to estimate is not the relative risk, but the rate ratio, i.e., the ratio of two incidence rates. While a cumulative risk is a probability, an incidence has time  $-1$  as its unit, and lies between zero and infinity. Since the incidence rate is the basic measure of disease occurrence, the rate ratio is the prime comparator, to be preferred over relative risks (which, over time, will converge to unity, because, to quote John Maynard Keynes, “in the long run we are all dead”). It can be shown that under certain sampling conditions, i.e., when controls are sampled from a dynamic population, there is no need for the “rare disease assumption”, and the OR is the exact equivalent of an incidence rate ratio [4]. ■

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