

## Correspondence

## Is It Just a Marker for Increased Care?

**Richard Hockey**

Because of the nature of the analysis used in this study [1], no conclusion is possible. There are plenty of examples in the literature demonstrating the “ecological fallacy”. Studies such as this have very little utility other than to generate hypotheses. I tend to think that this association is a marker for greater recognition and treatment for depression. However, it’s a brave epidemiologist who would draw any conclusions at all from an ecological association such as this where the outcome is relatively rare. ■

Richard Hockey (rhockey@optusnet.com.au)

Mater Hospital  
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1. Milane MS, Suchard MA, Wong ML, Licinio J (2006) Modeling of the temporal patterns of fluoxetine prescriptions and suicide rates in the United States. *PLoS Med* 3: e190. DOI: 10.1371/journal.pmed.0030190

**Citation:** Hockey R (2006) Is it just a marker for increased care? *PLoS Med* 3(9): e406. DOI: 10.1371/journal.pmed.0030406

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**Funding:** The authors received no specific funding for this article.

**Competing Interests:** The author has declared that no competing interests exist.

**DOI:** 10.1371/journal.pmed.0030406

## Were Eli Lilly Unaware of This Study?

**Aasa Reidak**

The authors of this study [1] claim that no competing interests exist. However, Julio Licinio presented a talk at Lilly Research Laboratory in Indianapolis, Indiana, on March 16, 2005, on “Depression, Antidepressants, and Suicidality: A Critical Appraisal” and “Suicide in the U.S. 1960-2002: Impact of Fluoxetine Prescriptions”, slightly over a year before the study was published. This is noted on page 19 of Dr. Licinio’s 51 page curriculum vitae [2].

In a *Medical News Today* article [3], Eli Lilly claims to not have known about this study until it was accepted for publication. I don’t see how they could not have known about Dr. Licinio’s study, when he presented on the very topic at Eli Lilly Research Laboratory in Indianapolis on March 16, 2005. ■

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3. [No authors listed] (2006 June 14) New study suggests antidepressants save lives. *Medical News Today*. Available: <http://www.medicalnewstoday.com/medicalnews.php?newsid=45055>. Accessed 9 August 2006.

**Citation:** Reidak A (2006) Were Eli Lilly unaware of this study? *PLoS Med* 3(9): e408. DOI: 10.1371/journal.pmed.0030408

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terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Funding:** The authors received no specific funding for this article.

**Competing Interests:** The author has declared that no competing interests exist.

**DOI:** 10.1371/journal.pmed.0030408

## Authors’ Response to Hockey and Reidak

Because the increased prescriptions of antidepressants are correlated to increased medical visits, it is tempting to conclude, as Hockey did [1], that decreased suicides are a function of greater recognition of depression. It should be noted that the biggest cause of suicide is clinical major depression and increased visits do not treat that; antidepressants do.

In a comprehensive review of the literature on the role of long-term antidepressant use to prevent relapse of major depression, Geddes et al. [2] reported that “data were pooled from 31 randomised trials (4410 participants). Continuing treatment with antidepressants reduced the odds of relapse by 70% (95% CI 62-78; 2p<0.00001) compared with treatment discontinuation. The average rate of relapse on placebo was 41% compared with 18% on active treatment”. We therefore conclude that just seeing a doctor is in the long term not protective against major depression and its consequences, such as suicide. The weight of existing data supports a positive effect of antidepressants. It is plausible that effective long-term treatment of depression by other methods might also be beneficial.

In response to the query from Reidak regarding Eli Lilly, I must say that I completely disclose all my activities, and that is why Aasa Reidak was able to write her letter [3]. I had published before on this topic in *Nature Reviews Drug Discovery* and had data (which were widely known to all in the field, including Eli Lilly) that since fluoxetine was introduced, prescriptions had gone up and suicide rates had gone down. There is nothing really conceptually new there. That was what was presented at one of Eli Lilly’s regular weekly scientific sessions, which exist at most research institutions, including Lilly Research Laboratories. The paper published here is on the modelling of suicide rates using pre-1988 data to estimate what suicide rates would be now and therefore to predict a potential putative effect of fluoxetine and other selective serotonin reuptake inhibitors [4]. These mathematical modelling data are new to this paper, and that entire analysis and manuscript content took place without the knowledge, support, or input of Eli Lilly.

The work reported in the article was done in the absence of any conflict of interest or pharmaceutical industry support. After the paper was submitted for publication in *PLoS Medicine*, I agreed to provide consultations for Eli Lilly, the manufacturer of fluoxetine. This has been a minor, occasional role, with very limited compensation. Such a relationship did not exist and was not planned when the work was done or the article written and submitted, and it is being disclosed here in the interests of transparency. ■

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**Citation:** Licinio J (2006) Authors' response to Hockey and Reidak. *PLoS Med* 3(9): e407. DOI: 10.1371/journal.pmed.0030407

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**Funding:** The authors received no specific funding for this article.

**Competing Interests:** JL has consulted for Eli Lilly, as discussed in detail in this Correspondence article.

**DOI:** 10.1371/journal.pmed.0030407

## Crossing the Language Limitations

### Zhenglun Pan, Jin Gao

We read with great interest your editorial “The Impact Factor Game” [1]. We noticed that many of the journals indexed by the Science Citation Index (SCI) pay considerable attention to impact factors and declare their figures on their journals' Web sites. We believe the game has become a most influential one in today's scientific evaluation system. For example, some of China's universities have adopted it as a core factor in the evaluation of the quality of research articles and recommend that students who are pursuing a doctorate publish at least one so-called “SCI-indexed paper”.

In total, 6,090 journals are indexed by SCI, most of which are published in English. However, there are many more scientific journals in the world. Over 6,300 local scientific journals are published here in China, but Chinese journals are rare in the SCI database and most of them have no impact factors.

Some may argue that the SCI database only includes the high-quality journals, but this is not necessarily the case. As a paper published in *PLoS Medicine* [2] has shown: “PubMed-indexed Chinese studies did worse than Chinese studies not indexed in PubMed in defining disease with specific criteria (17/20 [85%] versus 137/141 [97%], respectively; exact  $p = 0.042$ ), and in ascertaining the eligibility of controls (13/20 [65%] versus 129/141 [92%], respectively”. The quality of an article is not determined by its language of publication.

Language accounts for much in today's database, especially when we are searching it for evidence. Language bias should not be neglected. A language revolution could contribute to scientific progress. ■

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**Citation:** Pan Z, Gao J (2006) Crossing the language limitations. *PLoS Med* 3(9): e410. DOI: 10.1371/journal.pmed.0030410

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**Funding:** The authors received no specific funding for this article.

**Competing Interests:** The authors have declared that no competing interests exist.

**DOI:** 10.1371/journal.pmed.0030410

## What Guidelines? Never Saw Them!

### A. D. Gowdy

Fretheim and colleagues' study confirms [1] yet again how difficult it is to change clinical practice. As a manager with a “big organization” National Health Service background, more recently working in practices with general practitioners (GPs), I always was impressed by GPs' shameless ability to ignore incoming paperwork, often to the extent of trashing the envelope unopened, especially the big brown ones from the local health authority.

I now work for a pharmaceutical company (not in my mind a competing interest, but I have declared it as such in the interests of transparency) where the ability to change practice is a key skill. When I compare the pharmaceutical company approach to that of the health authority, there are some key differences. It is easy to deride industry's glossy advert approach, but this is simply the tip of the communications iceberg. In addition to the glossy adverts, there is immense attention by drug companies to detail. The key evidence-based messages are tested, honed, and polished and are then delivered via several channels repetitively. The channels include face-to-face delivery by the “detailers”. Progress is tracked meticulously.

This expensive but effective industry effort contrasts with the typical approach taken by the health authorities and other non-industry groups. The process of creating such guidelines has usually been so slow and difficult in the gestation that their credibility among GPs is low even before the rather dull photocopied paper is issued (by post, big brown envelope) and meets its predictable fate.

Fretheim and colleagues say “Key components were an educational outreach visit with audit and feedback, and computerized reminders linked to the medical record system. Pharmacists conducted the visits”. This feels a bit like a policing approach (another profession watching the GP) allied to computer direction, none of which feel particularly user-friendly. A non-audit nurse (or ex-drug-rep) calling briefly but frequently using the usual pens/mugs/Post-its reminder freebies might get a better response.

One study by Eve et al [2] did look at applying pharmaceutical company techniques to clinical change (“selling” Triple A therapy). It seemed to work. It may be worth bringing it back into focus. ■

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**Citation:** Gowdy AD (2006) What guidelines? Never saw them! *PLoS Med* 3(9): e413. DOI: 10.1371/journal.pmed.0030413

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**Funding:** The author received no specific funding for this article.

**Competing Interests:** The author works for a pharmaceutical company.

**DOI:** 10.1371/journal.pmed.0030413

## Authors' Response to Gowdy

We thank A. D. Gowdy for his comments [1] on our article [2]. He suggests that the National Health Service and other health-care providers have a lot to learn from the pharmaceutical industry. Where is the evidence?

We are not aware of data that convincingly demonstrate the impact of outreach visits by pharmaceutical representatives. Gowdy indicates that such information exists (“Progress is tracked meticulously”). We would very much like to see it!

We have had informal discussions with executives from companies in Norway, and we have been struck by how they themselves question the effectiveness of their marketing strategies. At a recent conference in Denmark, the medical director of a major pharmaceutical company gave a talk on the impact of industry marketing on prescribing habits [3]. He had no other data to show than a handful of anecdotes, and when questioned about this he insisted that neither he nor his marketing department was aware of more rigorous evaluations.

The degree of interaction between the pharmaceutical industry and the medical profession is associated with differences in prescribing patterns [4]. Thus, what the pharmaceutical industry is doing in terms of marketing does seem to work, at least to some extent. However, the marketing effort made by industry is massive and includes a wide range of interventions. It is difficult to know what the relative merit of each component is.

Even more difficult to estimate is the cost-effectiveness of various marketing strategies. Considering that the pharmaceutical industry spends a five-digit amount (\$US) per doctor per year on marketing alone [4], the industry should achieve substantial effects to compare favourably with, for instance, our results: We spent \$US500 per doctor and achieved a doubling of thiazide prescriptions [5].

The only study cited by Gowdy did indeed show promising results. However, changes in prescribing were compared between practices that chose to participate in the programme and practices that chose not to [6], and whether this is a fair comparison is uncertain. Moreover, he does not put this study into the context of a systematic review of the relevant research.

Gowdy thinks our intervention sounds like “a policing approach”. This does not fit with our perception. The doctors were satisfied with the chance of meeting an industry-

independent source of information and appreciated the opportunity to reflect on their own practice in light of the information and feedback that we provided them.

Gowdy's use of the term “evidence-based” when describing the messages conveyed by pharmaceutical companies begs a brief comment. Several investigators have assessed the quality of advertisements and promotional material distributed by the pharmaceutical industry. They consistently conclude with a word of caution against basing clinical practice on claims made by pharmaceutical companies [7–10]. ■

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**Citation:** Fretheim A, Oxman AD (2006) Authors' response to Gowdy. *PLoS Med* 3(9): e414. DOI: 10.1371/journal.pmed.0030414

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**Funding:** The authors received no specific funding for this article.

**Competing Interests:** The authors are employed by the Norwegian government.

**DOI:** 10.1371/journal.pmed.0030414

## Are Nonhuman Primates Good Models for SARS?

Robert J. Hogan

I would like to respond to Haagmans and Osterhaus' Perspective [1] on Lawler et al.'s study [2]. I have been actively studying SARS virus both in vitro and in numerous animal models including mice, cotton rats, ferrets, and macaques since April, 2003 (about six weeks after the virus was first identified). While I do concur with some of

the statements made by Haagmans and Osterhaus, I am compelled to provide an alternative view. I completely agree with the stance that an animal model which mimics the severe disease observed in human cases is needed. However, the continued use of nonhuman primates in these studies is simply not warranted. Indeed, multiple groups have tried unsuccessfully to reproduce this model, including Lawler and colleagues [2]. For example, I attended the WHO meeting on SARS in Rotterdam in February, 2004, at which Steven Jones, of the National Microbiology Laboratory, Winnipeg, Canada, said: "If I were one of those monkeys, maybe I'd just take a Tylenol" [3].

With my colleagues, I conducted a study in which both rhesus and cynomolgus macaques were infected with SARS-CoV. I did not see any clinical signs of disease or marked lung pathology [4]. A study by Subbarao and colleagues had similar findings: "SARS coronavirus (SARS-CoV) administered intranasally and intratracheally to rhesus, cynomolgus and African Green monkeys (AGM) replicated in the respiratory tract but did not induce illness" [5].

Perhaps the most interesting issue is that Lawler and colleagues clearly state that "SARS-CoV infection of cynomolgus macaques did not reproduce the severe illness seen in the majority of adult human cases of SARS" [2]. To my knowledge, only Osterhaus's laboratory and laboratories from China have reported severe disease in SARS-CoV infected macaques. Osterhaus mentions that the variability in results may be due to factors such as the strain of virus used, and this is certainly true. However, he has not released the virus isolate used in these studies to me or my colleagues in spite of requests. Given that so many groups (e.g., the Centers for Disease Control and Prevention, the United States Army Medical Research Institute of Infectious Diseases, the National Institute of Allergy and Infectious Diseases, etc.) with excellent scientific skills and credentials have reported contradictory results with at least two strains of SARS-CoV, it is troublesome that the use of nonhuman primates in SARS pathogenesis, vaccine, and therapeutic testing continues. ■

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**Citation:** Hogan RJ (2006) Are nonhuman primates good models for SARS? *PLoS Med* 3(9): e411. DOI: 10.1371/journal.pmed.0030411

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**Funding:** The author received no specific funding for this article.

**Competing Interests:** The author has declared that no competing interests exist.

**DOI:** 10.1371/journal.pmed.0030411

## Authors' Response to Hogan

In response to our Perspective on nonhuman primate models for SARS [1], which accompanied the article by Lawler et al. [2], Robert Hogan questions the usefulness of nonhuman primates as good models for SARS [3].

As demonstrated by several groups, SARS coronavirus (SARS-CoV) replicates to high titers in the respiratory tract of a surprisingly broad range of animal species, albeit showing remarkable differences in cell tropism. We have argued that efficient infection of type 1 and 2 pneumocytes as seen in macaques and humans—most likely due to the similarities in the spike protein binding domains of the host SARS-CoV receptor ACE2—is a prerequisite for the SARS-CoV infection-induced pathology observed in humans. So far there is no strong evidence that a similar tropism is observed in other animal species.

However, the tropism of SARS-CoV for pneumocytes may not suffice to induce severe clinical signs in primates. In case of a resolving infection in macaques, pathological changes are evident four to six days after infection and may have become inapparent by days 12–14. In addition, in young adult humans, SARS-CoV infection generally causes relatively mild disease. Viral sequence differences in the SARS-CoV isolate HKU 39849 obtained from and distributed to several groups by Peiris et al. [4], as compared to other strains used, may determine the outcome of SARS-CoV infection in macaques. Furthermore, recent experiments from our group indicate that clinical signs after infection with this virus are more likely to occur in aged macaques (unpublished data). Clinical signs observed in our earlier experiments were largely characterised by lethargy, whereas respiratory distress was observed in one animal [5,6].

The apparent differences observed in clinical outcome of the infection in macaques, which is similar to the outcome in humans, may limit the utility of SARS-CoV-infected macaques as a model for severe SARS. However, none of the other models available produces clinical disease related to respiratory distress, except for ferrets that are inoculated with the HKU 39849 virus intratracheally [7]. Therefore, we feel that the macaque model may indeed provide important clues to the pathogenesis of SARS. As also argued by Subbarao and Roberts [8], there is no single preferred model for SARS and combining the data obtained in different animal models may help to solve the question of why SARS is so devastating in some humans. This also holds true for the development of effective vaccines and other intervention strategies against possible future SARS-CoV outbreaks which may be caused by genetically quite distinct viruses. ■

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**Citation:** Haagmans BL, Osterhaus ADME (2006) Authors' response to Hogan. *PLoS Med* 3(9): e415. DOI: 10.1371/journal.pmed.0030415

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**Funding:** The authors received no specific funding for this article.

**Competing Interests:** The authors have declared that no competing interests exist.

**DOI:** 10.1371/journal.pmed.0030415

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## Snakebite: Sociocultural Anthropological Bias

### Arunachalam Kumar

While congratulating the authors of this informative article [1] for throwing light on a serious, yet much neglected health hazard, snakebite envenomation, we would like to add one more vital and cryptic cause for the abnormally high statistics in developing Asian countries: religion.

Both Nepal, cited in the paper as having the highest number of casualties, and India are predominantly populated by Hindus (in fact the only two countries in the world with Hindu majorities). In Hinduism, the cobra is, from time immemorial, revered as a vital element among the Hindu pantheon of holies. Cobra worship for countering infertility, ill fortune, or for tempering the wrath of divine curses, is not only widespread, but also firmly believed and perpetuated.

India is dotted with thousands of shrines and roadside temples dedicated to the “*nag-deva*” (cobra deity).

Cobras are rarely, if ever killed when discovered in unwelcome locales; the trespassing serpents are usually trapped and released out of harm's way [2]. The universal dread of incurring holy herpetological hexes not only allows the poisonous snake a second life, but also allows it to add its might to the ever increasing gene pool and population.

It is futile in this scenario to talk about education and awareness campaigns; thousands of years of religious indoctrination cannot be negated by education or literacy. The best, and perhaps only way, global intervention and funding can contribute to minimizing snakebite casualties is through ensuring anti-venom availability in large quantities over wide geo-locales in sub-continental Asia. ■

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**Citation:** Kumar A (2006) Snakebite: Sociocultural anthropological bias. *PLoS Med* 3(9): e412. DOI: 10.1371/journal.pmed.0030412

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**Funding:** The author received no specific funding for this article.

**Competing Interests:** The author has declared that no competing interests exist.

**DOI:** 10.1371/journal.pmed.0030412