PUBLIC LIBRARY of SCIENCE | plosmedicine.org | Volume 3 | Issue 4 | APRIL 2006

PLoS MEDICINE

Disease mongering

Water supply and birth rate

Influenza in the subtropics

Genetics of osteoporosis

Published by the Public Library of Science ISSN 1549-1277

Shouldn't all clinical trials be published? And be accessible to everyone?

Here's how.

PLoS

CLINICAL TRIALS

The open-access journal devoted to clinical trials from the PUBLIC LIBRARY OF SCIENCE

Now Accepting Submissions

http://clinicaltrials.plosjms.org

- Accepting results of randomized controlled trials from all fields of healthcare
- Rigorous peer review by statistical and clinical reviewers
- Rapid, electronic-only publication, linked to trial registries
- Free access to the widest possible global audience

Launching *spring* **2006**

http://www.plosclinicaltrials.org

OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

The Fight against Disease Mongering: Generating Knowledge for Action

Ray Moynihan, David Henry*

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

Disease mongering turns healthy people into patients, wastes precious resources, and causes iatrogenic harm. Like the marketing strategies that drive it, disease mongering poses a global challenge to those interested in public health, demanding in turn a global response. This theme issue of *PLoS Medicine* is explicitly designed to help provoke and inform that response.

What Is Disease Mongering?

The problem of disease mongering is attracting increasing attention [1–3], though an adequate working definition remains elusive. In our view, disease mongering is the selling of sickness that widens the boundaries of illness and grows the markets for those who sell and deliver treatments. It is exemplified most explicitly by many pharmaceutical industry–funded disease-awareness campaigns—more often designed to sell drugs than to illuminate or to inform or educate about the prevention of illness or the maintenance of health. In this theme issue and elsewhere, observers have described different forms of disease mongering: aspects of ordinary life, such as menopause, being medicalised; mild problems portrayed as serious illnesses, as has occurred in the drug-company-sponsored promotion of irritable bowel syndrome (see pp. 156–174 in [2]; [4]) and risk factors, such as high cholesterol and osteoporosis, being framed as diseases.

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

Drug companies are by no means the only players in this drama. Through the work of investigative journalists, we have learned how informal alliances of pharmaceutical corporations, public relations companies, doctors' groups, and patient advocates promote these ideas to the public and policymakers—often using mass media to push a certain view of a particular health problem. While these different stakeholders may come to these alliances with different motives, there is often a confluence of interests—resulting in health problems routinely being framed as widespread, severe, and treatable with pills, as has happened recently with social anxiety disorder [5]. Currently, these alliances are working with the media to popularize little-known conditions, such as restless legs syndrome [6] and female sexual dysfunction [7], in each case lending credence to inflated prevalence estimates. In the case of female sexual dysfunction, there has been a serious, though heavily contested, attempt to convince the public in the United States that 43% of women live with this condition (see pp. 175–195 in [2]). This is happening at a time when pharmaceutical companies perceive a need to build and maintain markets for their big-selling products and when pipelines for new and genuinely innovative medicines are perceived as being weak.

"The coming years will bear greater witness to the corporate sponsored creation of disease."

A Context for Disease Mongering

Three decades ago, Ivan Illich argued polemically that the medical establishment was "medicalising" life itself [8], and in the 1990s Lynn Payer described widening the boundaries of illness as "disease mongering" [3], highlighting the role of pharmaceutical companies. Today's debate about this phenomenon, while still maturing, both acknowledges the axiomatic interest of corporations and professionals in maximizing turnover and appreciates that well-informed citizens may choose to embrace the medicalisation of health problems previously regarded as troublesome inconveniences.

It can also be argued that disease mongering is the opportunistic exploitation of both a widespread anxiety about frailty and a faith in scientific advance and "innovation"—a powerful economic, scientific, and social norm. In many nations, government policy priority is to secure market-based economic development, while more equitable social policies, such as public health strategies, can become subordinate or redundant. Disease mongering can thrive in

Funding: RM received a commissioning fee from PLoS to write this article, and to serve as a guest editor, but RM and DH received no other specific funding for this piece.

Competing Interests: The authors declare that they have no competing interests.

Citation: Moynihan R, Henry D (2006) The fight against disease mongering: Generating knowledge for action. PLoS Med 3(4): e191.

DOI: 10.1371/journal.pmed.0030191

Ray Moynihan and David Henry are the guest editors of the April 2006 theme issue of *PLoS Medicine* on disease mongering. Ray Moynihan is a journalist, documentary maker, author, and conjoint lecturer at the University of Newcastle, Newcastle, New South Wales, Australia, and recently co-authored *Selling Sickness: How the World's Biggest Pharmaceutical Companies Are Turning Us All into Patients* (Nation Books, New York, 2005). David Henry is a professor of clinical pharmacology at the University of Newcastle, Newcastle, New South Wales, Australia, and co-founder of Media Doctor (http://www.mediadoctor.org.au), a Web site that monitors media coverage of medicine.

* To whom correspondence should be addressed. E-mail: david.henry@newcastle.edu.au

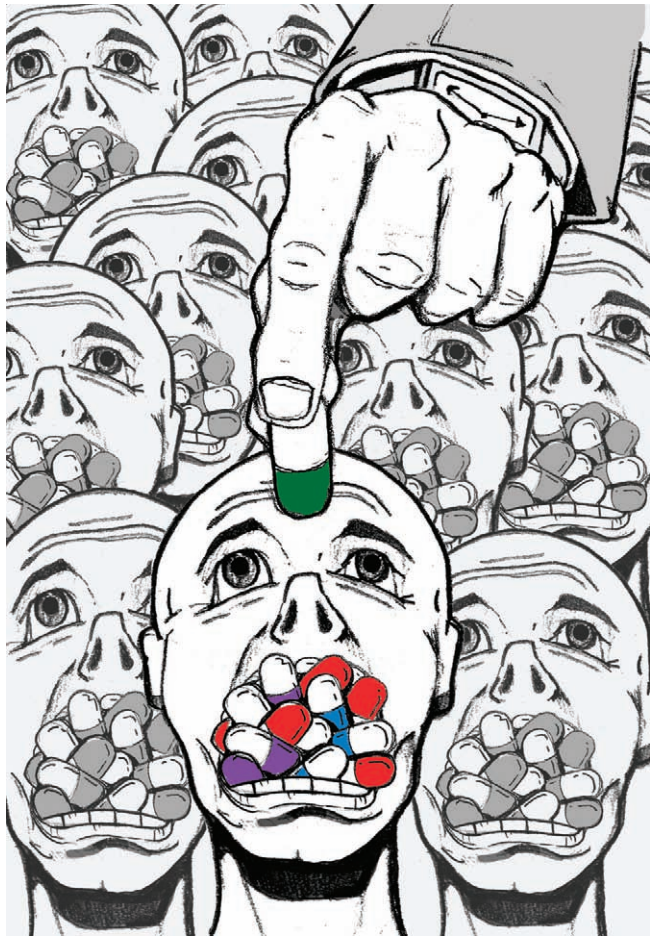
such a normative environment. The practical consequences are that many of the so-called disease-awareness campaigns that inform our contemporary understanding of illness—whether as citizens, journalists, health professionals, industry leaders, academics, or policymakers—are now underwritten by the marketing departments of large drug companies rather than by organizations with a primary interest in public health. And it is no secret that those same marketing departments contract advertising agencies with expertise in "condition branding," whose skills include "fostering the creation" of new medical disorders and dysfunctions [9]. As a recent *Reuters Business Insight* report on so-called lifestyle drugs—designed to be read by pharmaceutical industry leaders—pointed out, "The coming years will bear greater witness to the corporate sponsored creation of disease" [10]. We hope the coming years will also bear witness to a much more vigorous effort from within civil society to understand and to challenge that corporate process.

Problems Defining Disease Mongering

While the term "disease mongering" is now commonly used as shorthand to describe campaigns that inappropriately widen the boundaries of treatable illness, there is uncertainty about how to operationally define the concept. With most disorders or conditions, there will be a number of individuals who suffer severe forms of the problem, who will benefit greatly from treatment and may be helped enormously by the publicity and marketing given to both the treatment and the disorder. For example, industry-funded awareness raising about the treatment and prevention of HIV/AIDS has surely been valuable. But in other cases, the same marketing/awareness-raising campaign will be viewed very differently depending on the perspective of the observer: what an industry-linked professional group may consider to be legitimate public education about an underdiagnosed disease, an activist group free from industry sponsorship may regard as a crude attempt to build markets for potentially dangerous drugs.

The Eli Lilly–sponsored promotion of premenstrual dysphoric disorder to help sell a re-branded version of fluoxetine (rebranded from Prozac to Sarafem) is a case in point (see pp. 99–118 in [2]). Considered by some as a serious psychiatric illness, premenstrual dysphoric disorder is regarded by others as a condition that does not exist.

These discordant views of the same activity reinforce the fact that there are often different motives for the different individuals who get caught up in disease-mongering campaigns. In the pharmaceutical industry and in the public relations companies that serve them, the marketers often now dominate. But these corporations are not heterogeneous, and staff working in research or medical departments may express the same doubts as many working outside industry. For their part, the motives of health professionals and health advocacy groups may well be the welfare of patients, rather than any direct self-interested financial benefit, but we believe that too often marketers are able to crudely manipulate those motivations. Disentangling the different motivations of the different actors in disease mongering will be a key step towards a better understanding of this phenomenon.



DOI: 10.1371/journal.pmed.0030191.g001

Most people in Western countries take medication to treat or prevent illness or enhance well-being
(Illustration: Anthony Flores)

Generating Better Knowledge

The views in this article are based on observations and interpretation informed by interviews with stakeholders and other more journalistic research methods, rather than a deeper academic investigation that employs qualitative and quantitative research techniques. Before embarking on research agendas to investigate disease mongering and its impacts, a broader conception of the phenomenon is warranted—requiring researchers to explore the uncertainty surrounding the definition of the problem, how and why different stakeholders understand it differently, and the deeper social and economic contexts. For example, the broad shift away from government-run programs and towards the marketplace within social democracies worldwide, and the consequent commercialisation and commodification of health services, may be a useful framework for a more profound explanation of this problem. In a climate where governments are encouraging corporations to vigorously pursue for-profit activities within the health-care sector, it is hardly surprising that pharmaceutical companies will use a range of promotional activities to widen the definitions of disease in order to grow the potential markets for their products.

Along with deeper reflection, we suggest researchers start to develop strategies for generating data on the impact of disease mongering. More conventional health-science methodologies may prove to be valuable ways of investigating the potential influences of a disease-marketing campaign on outcomes such as public perceptions of a particular disease, prevalence/incidence rates for that disease, prescription patterns for the drugs linked to that disease, and even health status of those diagnosed with and/or treated for that disease. Multisite controlled studies of drug company–funded disease-awareness campaigns would be the ideal. However, defining appropriate control groups and devising indices to measure outcomes such as inappropriate medicalisation will prove extremely challenging since almost everyone is exposed to disease mongering in some form. Similarly, rigorous studies of publicly funded "counter-detailing"—where noncommercially oriented information about disease is promoted to physicians and citizens—may be warranted, though, again, it is very difficult methodologically.

A challenge to the excesses of disease mongering may come from within the industry.

Apart from these more challenging approaches, we believe there is a range of research projects that are both achievable and urgently needed. First, academic investigation of the prevalence of this problem would be highly desirable. Researchers could, for example, take a group of the most common (high-burden) diseases/conditions, and investigate how and why the definitions of those diseases/conditions have changed over time in different nations. Such retrospective investigations could include analysis of the decisions and recommendations of the panels that define and re-define illness, the evidence informing those decisions, the conflicts of interest of panel members and their respective professional bodies, and the sponsorship of these processes. Early versions of this investigation are happening in a random, ad hoc way [11], but a coordinated systematic effort by a multinational group of respected researchers or research institutes is obviously preferable. As part of such an examination, a series of case studies would inevitably emerge, warranting deeper study and research and serving as a way to popularize awareness of the process of disease mongering.

Another potentially rich research method might involve a prospective study of the launch of a new or recently expanded disease or condition. A global collaboration could, for example, study the way female sexual dysfunction is being constructed and then promoted. "Creating the need" is now an established and integral part of the promotion of any new blockbuster drug, and sometimes that involves introducing a whole new condition to the wider public [12]. The success of sildenafil depended on corporate-funded disease-awareness campaigns promoting erectile dysfunction [13], and similarly the commercial success of any pharmaceutical treatments for female sexual dysfunction will hang in part on similar campaigns. While activists and scholars have begun the process of observing these activities, it is our view that the magnitude of public and private resources spent on these products, the potential harm that can flow from inappropriate medicalisation, and the opportunity cost in terms of treating and preventing genuine pathology demands more rigorous scientific investigation.

Time for Action?

Around the world, there are tentative steps to identify, understand, and combat the threat to human health from the corporate-sponsored selling of sickness. These small steps are being taken by several players within the health field, and we trust this theme issue may support and augment these developments.

At a consumer level, Health Action International (http://www.haiweb.org)—the activist group working for a more rational use of medicines globally—has for a long time been concerned about what it has described as the blurring of boundaries between ordinary life and medical illness in order to expand markets for drugs and other technologies [14]. Unlike many patient advocacy groups, Health Action International does not accept pharmaceutical company sponsorship, and actively warns others about the threats to independence from doing so [15]. By way of contrast, many consumer/advocacy groups around the world now rely on such funding [16], raising questions about their credibility, particularly as they are often used as the human face of disease-awareness campaigns sponsored by their funders. An open debate within the health consumer movement about its close engagement with industry, and its involvement in disease mongering, would be welcome.

Likewise, amongst journalist circles, there are nascent debates about the media's propensity to exaggerate disease prevalence and severity, and how to deal with this problem. In this issue of *PLoS Medicine*, two high-profile scholars with an interest in the area of medicine and the media, Lisa Schwartz and Steven Woloshin, present a timely and relevant case study on the "selling" of restless legs syndrome [6]. In Australia and Canada, a new media watch group called Media Doctor is also investigating the extent to which media stories on medicine either report appropriately on the nature and extent of illness or tend to simply regurgitate the promotional messages of disease-mongering campaigns (http://www.mediadoctor.org.au).

While many professional organizations remain reliant on industry support, some are actively debating the problem of disease mongering. In a submission to the recent House of Commons inquiry into the influence of the pharmaceutical industry in Britain, the Royal College of General Practitioners outlined serious concerns about the process [17]. The subsequent report recommended that industry-funded disease-awareness campaigns should no longer be "veiled advertising" of branded drugs [18].

Shareholders in the world's large pharmaceutical companies have the strongest financial interest in widening the boundaries of treatable illness in order to widen markets for their products. Yet in the debate about research and development for treatments for neglected diseases in the developing world, there are strong signs that shareholders can support policies driven by motivations other than profit [19]. It may be that as key shareholders

and company executives alike understand more of the implications of what their marketing departments do, a challenge to the excesses of disease mongering may come from within industry, just as other parts of the health sector challenge excesses of disease mongering from within.

Conclusion

Genuine sustainable change, however, will not come until policymakers better understand the phenomenon of disease mongering and the potential benefits of responding against it. In Australia, for example, it has been estimated that winding back the public subsidy for inappropriate prescriptions of several high-profile drugs to people with milder health problems could save hundreds of millions of dollars per year [20]. Those responsible for managing Australia's publicly funded national formulary, the Pharmaceutical Benefits Scheme, have become increasingly concerned about what is described as "leakage"—the process where subsidised drugs are prescribed by physicians to people for whom use of the drug has been deemed not cost-effective because of a poor cost–benefit ratio. We suspect that the estimated hundreds of millions of dollars of public money wasted on leakage in Australia annually is in part a result of drug companies promoting their products, through physicians, to people with mild problems for whom a powerful prescription may be unnecessary or even do more harm than good. In summary, combating disease mongering may improve the personal health of individuals, as well as the financial health of public (and private) insurers.

As an initial step toward combating disease mongering at a health policy level, we would urge decision makers to promote a renovation in the way diseases are defined. Continuing to leave these definitions to panels of self-interested specialists riddled with professional and commercial conflicts of interest is no longer viable. As a priority, new panels should be assembled, free of commercial conflicts of interest, involving a much wider, and less self-interested, group of players, who would ultimately generate more credible information.

Until a rigorous research agenda is initiated, and the social renovations and policy reforms that research might inform are enacted and evaluated, our beliefs, like those who argue for the benefits of corporate-sponsored disease-awareness campaigns, will remain based more on opinion than evidence. We hope this theme issue can start to change that. ■

References

1. Moynihan R, Heath I, Henry D (2002) Selling sickness: The pharmaceutical industry and disease-mongering. BMJ 324: 886–891.
2. Moynihan R, Cassels A (2005) Selling sickness: How the worlds biggest pharmaceutical companies are turning us all into patients. New York: Nation Books. 254 p.
3. Payer L (1992) Disease-mongers: How doctors, drug companies, and insurers are making you feel sick. New York: Wiley and Sons. 292 p.
4. Moynihan R (2002) Alosteron: A case study in regulatory capture or a victory for patients rights? BMJ 325: 592–595.
5. Koerner B (2002) Disorders made to order. Mother Jones 27: 58–63.
6. Woloshin S, Schwartz LM (2006) Giving legs to restless legs: A case study of how the media helps make people sick. PLoS Med 3: e170. DOI: 10.1371/journal.pmed.0030170
7. Tiefer L (2006) Female sexual dysfunction: A case study of disease mongering and activist resistance. PLoS Med 3(4): e178. DOI: 10.1371/journal.pmed.0030178
8. Illich I (1976) Limits to medicine. London: Penguin. 294 p.
9. Parry V (2003) The art of branding a condition. Med Mark Media 38: 43–49.
10. Coe J (2003) Healthcare: The lifestyle drugs outlook to 2008, unlocking new value in well-being. London: Reuters Business Insight. 243 p.
11. Moynihan R (2004) The intangible magic of celebrity marketing. PLoS Med 1: e42. DOI: 10.1371/journal.pmed.0010042
12. Moynihan R (1998) Too much medicine. Sydney: ABC Books. 308 p.
13. Lexchin J (2006) Bigger and better: How Pfizer redefined erectile dysfunction. PLoS Med 3: e132. DOI: 10.1371/journal.pmed.0030132
14. Mintzes B (1998) Blurring the boundaries. Amsterdam: Health Action Internatonal. Available: http://haiweb.org/pubs/blurring/blurring.intro.html. Accessed 7 March 2006.
15. Health Action International (1999) The ties that bind: Weighing the risks and benefits of pharmaceutical industry sponsorship. Amsterdam: Health Action International. Available: http://www.haiweb.org/campaign/spon/toc.html. Accessed 7 March 2006.
16. Health and Social Campaigners News International (2004 April) Health campaigners, fundraising and the growth of industry involvement. Knighton (Wales): Patient View. 57 p.
17. Royal College of General Practitioners [RCGP] (2004 August 17) RCGP warns against unhealthy pharmaceutical industry. London: RCGP. Available: http://www.rcgp.org.uk/default.aspx?page=1609. Accessed 7 March 2006.
18. House of Commons Health Committee (2005) The influence of the pharmaceutical industry: Fourth report of session 2004–2005. London: House of Commons. Available: http://www.lindalliance.org/pdfs/HofCHealthCommittee.pdf. Accessed 7 March 2006.
19. Moran M (2005) A breakthrough in R&D for neglected diseases: A new way to get the drugs we need. PLoS Medicine 2: e302. DOI: 10.1371/journal.pmed.0020302
20. Moynihan R, Murphy K (2002 March 18) Doctors causing a drug costs blowout. Australian Financial Review: 1.

Take the Quiz online!

OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

Bigger and Better: How Pfizer Redefined Erectile Dysfunction

Joel Lexchin

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

In the pursuit of profits, pharmaceutical companies are continuously looking to expand the market for their products. This article examines how Pfizer transformed Viagra from an effective product for erectile dysfunction (ED) due to medical problems, such as diabetes and spinal cord damage, into a drug that "normal" men can use to enhance their ability to achieve an erection and to maintain it (in a "harder" state) for a longer period of time.

The Rise of Lifestyle Drugs

An important emerging issue in health care is the availability of medications to treat what until recently have been regarded as the natural results of aging or as part of the normal range of human emotions. Thus, we now see treatments widely advertised for male pattern baldness and shyness. Deviating even further, drug therapy is moving out of treating diseases to providing enhancements to what had hitherto been seen as normal functioning. This evolution in the use of medications has introduced dilemmas and controversies about what are legitimate conditions and treatments for those concerned with prescription medications: is any deviation from normality fair game for treatment? What about people who have nothing medically wrong with them, but just want to feel better? Who will pay for these therapies, and what are the implications for the way we use health-care resources?

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

DOI: 10.1371/journal.pmed.0030132.g002

(Illustration: Giovanni Maki)

Medications that embody these controversies are generally referred to as lifestyle drugs and perhaps the best known of these is sildenafil citrate (Viagra) This article will examine the strategies used by Pfizer, the maker of Viagra, to ensure that the drug was seen as legitimate therapy for almost any man. Pfizer took steps to make sure that Viagra was not relegated to a niche role of just treating men who had ED due to organic causes, such as diabetes or prostate surgery.

There is no doubt that Viagra is an effective and quite safe drug in treating ED secondary to these causes, although a systematic review of the evidence found that the drug probably only results in successful intercourse 50%–60% of the time [1]. Had Viagra been confined to use only in cases of ED secondary to organic causes, the drug would probably have been a modest success for Pfizer. In order to grow the market, Pfizer had to make Viagra the treatment of choice for a much wider population of men. The perceived prevalence of ED needed to be expanded. The impression had to be created that ED was of significant concern to many, perhaps even most, men or at least those over 40 years of age. The criterion of success for

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

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

Citation: Lexchin J (2006) Bigger and better: How Pfizer redefined erectile dysfunction. PLoS Med 3(4): e132.

DOI: 10.1371/journal.pmed.0030132

Abbreviations: ED, erectile dysfunction; MMAS, Massachusetts Male Aging Study

Joel Lexchin is at the School of Health Policy and Management, York University, Toronto, Ontario, Canada; the Emergency Department, University Health Network, Toronto, Ontario, Canada; and the Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada. E-mail: jlexchin@yorku.ca

treating ED had to be redefined. And finally, Viagra had to be seen as an important treatment option for men with any degree of ED, including rare or transitory failures to achieve or maintain erections.

Redefining the Prevalence of ED and Its Psychological Effects

On its Web site, Pfizer states that "in fact, more than half of all men over 40 have difficulties getting or maintaining an erection" (http://www.viagra.com/ed/index.asp). The Web site does not give a reference to support this statement. One possible source of support for this statement is the Massachusetts Male Aging Study (MMAS), a community-based, random sample observational survey of men aged 40 to 70 years old conducted from 1987 to 1989 in cities and towns near Boston, Massachusetts [2]. The authors of the study extrapolated the results to argue that 52% of the entire male population in the United States between the ages of 40 and 70 suffer from ED. The authors stated: "In the MMAS sample the prevalence of impotence of all degrees was estimated at 52%. Projection of these results to 1990 population data would suggest that impotence affects 18 million American men 40 to 70 years old" [2]. However, the MMAS figures must be viewed with a number of caveats.

First, there were actually two different groups of men in this study. The first, and larger, group answered a series of nine questions about sexual activity. The second, and much smaller, group answered the same nine questions, plus an additional question to self-rate themselves as not impotent, minimally impotent, moderately impotent, or completely impotent. The answers to this final question by the men in the second group were then applied to the first group to derive the percent in the various classes of potency. The authors do not provide any information about whether the two groups were similar, and there are reasons to think that differences may exist between the groups. The first group was randomly selected from towns and cities in the Boston Standard Metropolitan Statistical Area [3], while the second group was made up of men presenting to a university center urology clinic [2].

Even if the scores from one group can be transferred to the other, the 52% figure is still deceptive because it doesn't differentiate ED by age. In the MMAS, 40% of 40-year-old men had ED, including 17% who were only minimally impotent, whereas 67% of 70 year olds were impotent. Moreover, not all studies are in agreement with these figures. Analysis of data from the US National Health and Social Life Survey indicates that among men 50–59 years old, 18% complained of trouble achieving or maintaining an erection during the past year [4]. A survey in the Netherlands found that only 1% of men 50–65 years of age had a complete inability to achieve an erection, and it was only in men aged 70–78 years that the rate of ED was similar to that in the MMAS [5]. Out of 13 studies on the prevalence of ED that were published until June 1998, the MMAS results were among the highest [1]. Thus, Pfizer's statement that "more than half of all men over 40 have difficulties getting or maintaining an erection" does not reflect the large variation in the prevalence of ED found in different studies.

The MMAS found a strong association between ED and psychological factors, including "depression, low levels of dominance, and anger either expressed outward or directed inward." The authors suggested that psychological symptoms might be a cause of ED, but these symptoms could also be an effect of ED (they wrote that "a man who has experienced a recent pattern of ED may be expected to be anxious, depressed and lacking self-esteem and self-confidence") [2]. While not to deny that there is an association between ED and psychological symptoms, once again the MMAS may be an outlier. In the Dutch study previously mentioned, only one-third of all men and only 20% of men over the age of 70 with significant ED had major psychological concerns. Furthermore, in sexually active men, 17%–28% had no normal erections, indicating that full erectile function is not essential for sexual functioning [5]. Only 20% of Japanese men 40 to 79 years of age reported more than little worry and concern about sexual functioning, suggesting that perceptions of elderly male sexual function and its impact on health-related quality of life may differ among cultures and ethnic groups with differing values [6].

DOI: 10.1371/journal.pmed.0030132.g001

Figure 1. Pfizer Hired 39-Year-Old Baseball Player Rafael Palmeiro as a Spokesman for Viagra

On its Web site, Pfizer states: "VIAGRA can work for you. In fact, studies show that VIAGRA works for more than 80% of men with ED taking VIAGRA 100 mg versus 24% of men taking a sugar pill" (http://www.viagra.com/whyViagra/highlyEffective.asp). The 80% success rate that Pfizer quotes for Viagra is important, though not critical, to being able to promote its use to a wide variety of men. But that number is qualified on the Pfizer Web site as the number who experience improved erections (http://www.viagra.com/consumer/aboutViagra/index.asp). It is open to speculation whether the goal of most men is improved erections, or successful intercourse and the achievement of an orgasm. In most studies on Viagra, a 50%–60% rate of successful intercourse is recorded (in the dose titration studies reviewed in [1] for patients taking placebo, up to 25% of attempts at intercourse were successful compared with 50%–60% for patients taking Viagra 25–100 mg). This 50%–60% rate is far short of the "more than 80% of men" that Pfizer trumpets.

Viagra for Any Degree of ED

To make Viagra into a lifestyle drug, Pfizer needs to convince men that it is the first choice for therapy for any degree of ED, whatever the genesis of the problem. However, drug therapy may not always be the most appropriate treatment option. The National Health and Social Life Survey data indicate that emotional and stress-related problems such as a deteriorating social and economic position generate elevated risk of experiencing sexual difficulties. In these cases, Viagra may be less important than counseling or help in finding a new job. These

possibilities are never mentioned on the Viagra Web site. Here is a sample of the questions and answers on the "About ED" portion of the Web site:

Question: "I don't have ED because the problem doesn't happen often. Does this mean that VIAGRA is not for me?"

Answer: "Even if erection problems happen only once in a while, VIAGRA can help. You should know that most men with ED only experience problems some of the time. In one study, VIAGRA helped 87% of men with mild-to-moderate ED have better erections versus 36% of men taking a sugar pill" (http://www.viagra.com/faqs/faqs2.asp).

In case the message is missed, there is a couple on the Web page where the man looks to be in his mid-to-late 30s. Pfizer reinforces its message with direct-to-consumer magazine ads, such as one featuring a virile looking man around 40 saying, "A lot of guys have occasional erection problems. I chose not to accept mine and asked about Viagra."

Drug companies have identified lifestyle drugs as a "growth market."

The initial television ads in the US for Viagra used an aging Bob Dole (born 1923) as a spokesman, a 1996 Republican presidential candidate. Since then, Pfizer has refocused its advertising campaign to match the lifestyle message on its Web site. There is now advertising of Viagra at NASCAR races, and Pfizer hired 39-year-old Rafael Palmeiro, a former Texas Ranger baseball player as a spokesman (Figure 1) [7]. Pfizer teamed up with *Sports Illustrated* magazine to create the Sportsman of the Year Trivia Game (http://www.viagra.com/sports/index.asp). Between 1999 and 2001, Pfizer spent over US$303 million in direct-to-consumer advertising to get its message about Viagra to men [8–10]. Besides the large promotion budget, Pfizer has also paid a number of doctors to act as "consultants," delivering public lectures and appearing in the mass media to expound on ED and Viagra [11]

Pfizer denies that it is targeting younger men or that it is positioning Viagra as a lifestyle drug. Mariann Caprino, a spokeswoman for the company, is quoted in the *New York Times* as saying, "Have we gone out and given our advertising agency instructions to speak to this young population? No, we haven't" [7]. But the message from the pictures on the Web site, in magazine ads, and from people like Rafael Palmiero is that everyone, whatever their age, at one time or another, can use a little enhancement; and any deviation from perfect erectile function means a diagnosis of ED and treatment with Viagra. Increasingly, the age profile of men using Viagra reflects the younger audience that Pfizer denies it is targeting. Between 1998 and 2002 the group showing the largest increase in Viagra use was men between the ages of 18 and 45, and only one-third of these men had a possible etiologic reason for needing Viagra [12].

Economic and Social Implications of the Expanding Market for Lifestyle Drugs

Drug companies have identified lifestyle drugs as a "growth market." The problems that they are designed to treat are easily self-diagnosed—we can all see if we are bald or fat—and as the baby boomers age, the population looking to these drugs will continue to grow. Drug companies, driven by profit, go where the money is.

Because of the potential size of the market for Viagra, paying for it in unlimited quantities will be very expensive. Viagra may only be the tip of the iceberg. If we believe the prophets of technology, soon there will be drugs for memory enhancement and the possibility of genetic manipulation to make us taller or to keep a full head of hair. Here we come back to the enhancement debate. Do we accept our limitations with grace, or is it legitimate to seek technological solutions for them? In one corner is the view of health as freedom from disease, where "the central purpose of health care is to maintain, restore, or compensate for the restricted opportunity and loss of function caused by disease and disability" [13]. In this model, a just medical system would not cover treatments and interventions that aim to enhance abilities not affected by disease and disability. Opposing this is an expansionist definition, such as the one offered by the World Health Organization, where health is "a state of complete physical, mental and social well-being" (http://www.who.int/about/definition/en/print.html). If we accept this view, then are we not obliged to provide for people who want to enhance themselves so that they can achieve mental and social well-being?

This debate is further complicated because there is not an equal balance in how we look at the options of accepting limitations and seeking enhancement. In a market-driven world, the money is in promoting enhancements, not in accepting limitations. The ad featuring the man who chooses not to accept even occasional erection problems is one example of how commercial pressures bias the debate [14].

Because of the possibility that large numbers of men would request Viagra from their doctors, getting insurance companies to pay for Viagra presented Pfizer with special problems. Early on, Kaiser Permanente refused to cover Viagra for its 9 million members because of costs expected to be in the range of US$100 million per year [11]. According to one interpretation, reactions from insurers such as Kaiser Permanente were the reason that Pfizer put in place a US$35 million campaign to change insurers' decisions [11]. Another goal of Pfizer's campaign was to make ED an acceptable topic for public discourse, in order to remove the stigma attached to it and increase the possibility that third parties would provide coverage.

Conclusion

Viagra presents a microcosm of the debate surrounding drugs that enhance lifestyle choices. The drug is effective and safe for people with medical problems warranting treatment, but it also can be used by a much wider population. The company that manufactures the drug, recognizing that the potential market is huge, has aggressively targeted that much larger community. Pfizer's well-financed campaign was aimed at raising awareness of the problem of ED, while at the same time narrowing the treatment possibilities to just a single option: medication. Having succeeded in turning Viagra into a consumer product, Pfizer then turned its attention to payers in order to reap the benefits of the expanded market.

Ultimately, there must be a debate about how limited resources for health care should be spent and who should

make those decisions. Are men who seek to enhance their normal sexual function "worthy" enough to have their treatment paid for? If we pay for drugs and other procedures that enhance lifestyles, then other treatments either may not get funded at all or may become inadequately funded. Who will get the lifestyle drugs? Everybody who wants them? And do they get an unlimited supply? As the number of enhancement treatments grows, the scenario surrounding Viagra will become all too familiar with other drugs. Now is the time to start preparing for how we will deal with the inevitable explosion of drugs and other interventions that can make us "better than well" [16]. ■

Acknowledgments

Leonore Tiefer and Annie Potts commented on an earlier version of this manuscript. My special thanks to Arthur Schafer for his gracious help with revisions.

References

1. Burls A, Clark W, Gold L, Simpson S (1998) Sildenafil—An oral drug for the treatment of male erectile dysfunction. Report number 12. Birmingham (United Kingdom): West Midlands Health Technology Assessment Collaboration, Department of Public Health and Epidemiology, University of Birmingham. 94 p.
2. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB (1994) Impotence and its medical and psychological correlates: Results of the Massachusetts Male Aging Study. J Urol 151: 54–61.
3. Longcope C, Goldfield SRW, Brambilla DJ, McKinlay J (1990) Androgens, estrogens, and sex hormone-binding globulin in middle-aged men. J Clin Endocrinol Metab 71: 1442–1446.
4. Laumann EO, Paik A, Rosen RC (1999) Sexual dysfunction in the United States: Prevalence and predictors. JAMA 281: 537–544.
5. Blanker MH, Bosch JLHR, Groeneveld FPMJ, Bohnen AM, Prins A, et al. (2001) Erectile and ejaculatory dysfunction in a community-based sample of men 50 to 78 years old: Prevalence, concern, and relation to sexual activity. Urology 57: 763–768.
6. Masumori N, Tsukamoto T, Kumamoto Y, Panser LA, Rhodes T, et al. (1999) Decline of sexual function with age in Japanese men compared with American men—Results of two community-based studies. Urology 54: 335–345.
7. Warren J (2003 December 14) In an oversexed age, more guys take a pill. New York Times. Available: http://query.nytimes.com/gst/fullpage.html?res=9804E1DD153CF937A25751C1A9659C8B63&sec=health&pagewanted=1. Accessed 1 March 2006.
8. Findlay S (2000) Prescription drugs and mass media advertising. Research brief. Washington: (D. C.): National Institute for Health Care Management. Available: http://www.nihcm.org/finalweb/DTCbrief2001.pdf. Accessed 2 March 2006.
9. IMS Health (2001) Leading 10 products by U.S. DTC spend, 2000. Plymouth Meeting (Pennsylvania): Available: http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_40054629_1004776,00.html. Accessed 1 March 2006.
10. Yuan Y, Duckwitz N (2002) Doctors and DTCA. Pharmaceutical executive. Plymouth Meeting (Pennsylvania). Available: http://www.imshealth.com/vgn/images/portal/cit_759/2005112345DoctorsDTC.pdf. Accessed 1 March 2006.
11. Deer B (1998 September 6) Viagra: Sex drugs & rock 'n' roll. Sunday Times Magazine. Available: http://briandeer.com/pfizer-viagra.htm. Accessed 2 March 2006.
12. Delate T, Simmons VA, Motheral BR (2004) Patterns of use of sildenafil among commercially insured adults in the United States: 1998–2002. Int J Impot Res 16: 313–318.
13. Parens E (1998) Is better always good? The enhancement project. Hastings Cent Rep 28: S1–S16.
14. Parens E (2005) Authenticity and ambivalence. Hastings Cent Rep 35: 34–41.
15. Klein R, Sturm H (2001) Viagra: A success story for rationing? Health Aff 21: 177–187.
16. Caplan A, Elliott C (2004) Is it ethical to use enhancement technologies to make us better than well? PLoS Med 1: e52. DOI: 10.1371/journal.pmed.0010052

OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

Medicine Goes to School: Teachers as Sickness Brokers for ADHD

Christine B. Phillips

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

Over the last twenty years, attention deficit hyperactivity disorder (ADHD) has emerged as a disorder of importance in childhood. Prescription of psychostimulants for ADHD escalated in many countries through the 1990s. Between 1990 and 1995, prescriptions of methylphenidate for young people increased 2.5-fold in the US [1], and 5-fold in Canada [2]. In New South Wales, Australia, rates of treatment for children in 2000 were nine times those in 1990 [3].

ADHD joins dyslexia and glue ear as disorders that are considered significant primarily because of their effects on educational performance. Medicalising educational performance can help children receive specialised medical and educational services; at the same time it can lead to them receiving medications or surgical therapies which may have short-term and long-term ill effects.

In the case of ADHD, there has been a complex, often heated debate in the public domain about the verity of the illness and the personal cost-benefit ratio of treatment with psychostimulant medication [4–6]. Much of the polemic for and against psychostimulants is concerned with the part played by doctors, the prescribers of medication, in diagnosing or discounting ADHD. ADHD is, however, a disorder of educational performance, and so teachers have a critical role in advocating for the illness, and its medical treatment. This essay explores the roles of teachers as brokers for ADHD and its treatment, and the strategies used by the pharmaceutical industry to frame educators' responses to ADHD.

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

The Teacher's Role in Managing ADHD

In his essay on medicalisation processes, Conrad argued that when disorders previously viewed as non-medical are redefined as sicknesses, non-medical people often perform the "everyday routine work" of disseminating understanding of the new sickness [7]. A temperance society worker, for example, might have disseminated the concept of alcoholism as a disease through everyday contacts with alcoholics and their families. With ADHD, the teacher's work extends beyond simply ensuring the disorder is understood by parents. Instead, the teacher participates in the diagnosis, and may broker different forms of treatment, or rejection of treatment. Brokerage is not a disinterested activity: teachers may have a vested interest in detecting and managing disruptive children, or they may adhere to beliefs about learning disorders which lead them to dissuade parents of the need for treatment.

The role of the teacher as the sickness and treatment broker for ADHD has been elaborated more clearly for ADHD than for any other childhood disorder. The DSM-IV diagnostic criteria accord teachers a formal role in diagnosis through specialised assessment instruments such as the Conners Teacher's Rating Scale [8]. Teachers often agree to administer

Prescription of psychostimulants for ADHD escalated in many countries through the 1990s

(Photo: Sponge, published under the GNU Free Documentation License)

Funding: The author received no funding to write this article.

Competing Interests: The author declares that she has no competing interests.

Citation: Phillips CB (2006) Medicine goes to school: Teachers as sickness brokers for ADHD. PLoS Med 3(4): e182.

DOI: 10.1371/journal.pmed.0030182

Abbreviations: ADHD, attention deficit hyperactivity disorder; CHADD, Children and Adults with Attention Deficit/Hyperactivity Disorder

Christine B. Phillips is a Senior Lecturer in Social Foundations of Medicine, Australian National University Medical School, Acton, Australia. E-mail: Christine.phillips@calvary-act.com.au

psychostimulant medication during the school day, although there is in Australia, the UK, and the US no legal compulsion to do so. A subtle incentive for teachers to administer medication in the middle of the day may be the assurance of a tractable child in the afternoon.

An informal role also exists for teachers as "disease-spotters." There appears to be considerable difference internationally in the alacrity with which teachers engage in disease-spotting. In a study of 491 physicians in Washington, D. C., almost half of the diagnoses of ADHD in their patients had been suggested first by teachers [9]. In the UK, on the other hand, parental concerns that a child has ADHD may be discounted by teachers [10].

How Drug Companies Influence Teachers

As teachers have some agency in diagnosing ADHD, and may in fact contest the diagnosis, the pharmaceutical industry has an interest in directing teachers toward medical treatment. Pharmaceutical companies have been able to exploit the Internet to access teachers and to influence their brokerage role. The approach to teachers tends to mirror strategies used to familiarise doctors with pharmaceuticals.

The pharmaceutical company as disinterested purveyor of education. The drug promotion that masquerades as professional education is such a fixture in the medical domain that many universities train medical students to critique promotional material. Both Shire (manufacturer of Adderell) [11] and Novartis (manufacturer of Ritalin) [12] have established educational websites separate from their own industry sites, each of which contains specific resources for teachers. On a page entitled "If parents ask…," Novartis suggests responses teachers might make to concerned parents:

"Make it clear to them that it is important for them—and their child—to understand and follow the doctor's medical advice about medication and other therapies for ADHD. ADHD is a serious condition that may require the child to be on medication and undergo counselling for a long duration [12]."

Each site incorporates links to the manufacturer responsible for the site [13] or directly to the psychostimulant produced by the manufacturer [14], discussion of the diagnostic process, and references to the legislation governing the rights of access for disabled people to treatment, such as the Individuals with Disabilities Education Act in the US. An activity such as Shire's funding of an annual toll-free "ask the experts" ADHD hotline, 1-888-ASK-ADHD, [15] is another example of the provision of advertorial information to teachers in the guise of objective education. Experts provided for this free hotline, now in its seventh year, include teachers, as well as school nurses, doctors, and advocates; suggested topics include the management of ADHD within the school.

Other school personnel are also targeted. In 1997, Novartis collaborated with the National Association of School Nurses in the US to run a nationwide campaign, in which 11,000 school nurses were provided with a resource kit containing information on ADHD, its treatment, and various support organisations [16]. Novartis later collaborated with the National Association of School Nurses and others to produce a resource aimed at curbing misuse of psychostimulant medication, which again provided links to Novartis pharmaceuticals [17].

Support of advocacy groups which lobby teachers. In the US, the pre-eminent advocacy group for people with ADHD is CHADD (Children and Adults with Attention Deficit/Hyperactivity Disorder). In the 2004–2005 financial year (year ended 30 June 2005), 22% of CHADD's total revenue came from the pharmaceutical industry [16]. CHADD undertakes educational programs for teachers [18], including acting as the lead editorial consultant of a special issue on ADHD in Health in Action, a quarterly publication of the American School Health Association [19]. The UK's answer to CHADD, the National Attention Deficit Disorder Information and Support Service (ADDISS), also carries a brief to develop and publicise educational programs for teachers. A charity-based organisation set up by the Department of Health, the service has also received funding from Janssen-Cilag, UCB Pharma, and Eli Lilley, according to reports in the UK press [20].

Box 1. Suggestions to Support Teachers as Independent Advocates for Children with ADHD

- Teachers should be trained to decode and question marketing strategies used by the pharmaceutical industry, just as medical students are.
- Teachers should have a mechanism to report their observations about medication to an independent body, such as Australia's Adverse Drugs Reaction Advisory Committee.
- Teachers should contribute to documenting educational and other outcomes of children with ADHD, through participating in formal collation of data across school regions about outcomes.

Creating a presence in the school for the pharmaceutical industry. A more general staking of claim to a role in schools is provided through the range of online science educational materials now provided by GlaxoSmithKline [21], Pfizer [22], and the Association of the British Pharmaceutical Industry [23]. Although these sites do not mention specific medications, they reinforce the place of the pharmaceutical industry as a benevolent and authoritative presence within the school, much as the provision of branded educational materials to doctors reinforces the position of the pharmaceutical industry within the clinic.

Conclusion

The organised penetration of the pharmaceutical industry associated with ADHD into the education domain is a new phenomenon. While there has been extensive discussion about the ethics of fast-food marketing within schools [24,25], there has been little about the consequences of the pharmaceutical industry's infiltration of schools.

It could be argued that in providing information to teachers, pharmaceutical industries are simply acting as good corporate citizens. Such an argument would carry more weight if these companies also provided education programs addressing autism and dyslexia, two other conditions which impact upon educational performance, but which

do not have accepted pharmaceutical therapies. While there is an argument for providing unbiased education to teachers about a high-profile condition, education provided by pharmaceutical companies is self-serving in that it often provides education which references their own products, and channels the reader toward medical therapy.

There are calls for doctors to learn about pharmaceutical marketing strategies in their training [26,27], to participate in the monitoring of outcomes of medication, through post-marketing surveillance, and to maintain a global watch on pharmaceutical marketing [28]. The wide acceptance of disorders of educational performance, and the penetration of the pharmaceutical industry into schools, point to similar needs for teacher training and participation in surveillance (see Box 1). Children have no agency in this market. To be effective advocates for children, teachers need to be supported to be objective and accurate interpreters of information for parents and healthworkers, rather than franchisees in the sickness marketplace. ■

Acknowledgements

I am grateful for comments on this essay from Clare McGuiness and Marjan Kljakovic.

References

1. Safer DJ, Zito JM, Fine EM (1996) Increased methylphenidate usage for attention deficit disorder in the 1990s. Pediatrics 98: 1084–1088.
2. Miller A, Lee SK, Raina P, Klassen A, Zupanic J, et al. (1998) A review of therapies for attention-deficit/hyperactivity disorder. Ottawa: Canadian Coordinating Office for Health Technology Assessment. Available: http://www.ccohta.ca/newweb/pubapp/pdf/adhd_tech_rep.pdf. Accessed 29 January 2006.
3. Salmelainen P (2002) Trends in the prescribing of stimulant medication for the treatment of attention deficit hyperactivity disorder in children and adolescents in New South Wales. N S W Public Health Bull 13 (Supplement S-1): 1–65.
4. Breggin PR (2002) The Ritalin fact book: What your doctor won't tell you about ADHD and stimulant drugs. Cambridge (Massachusetts): Perseus Publishing. 208 p.
5. Church of Scientology International (2006) Protecting the rights of children. Available: http://www.scientology-europe.org/en_US/pub/human-rights/pg011.html. Accessed 29 January 2006.
6. American Academy of Pediatrics (2006) Children's health topics: ADHD. Available: http://www.aap.org/healthtopics/adhd.cfm. Accessed 29 January 2006.
7. Conrad P (1992) Medicalization and social control. Ann Rev Sociol 18: 209–232.
8. Conners CK (1997) Manual for the Conners' Rating Scales—Revised. North Tonawanda (New York): Multi-Health Systems.
9. Sax L, Kautz KJ (2003) Who first suggests the diagnosis of attention-deficit/hyperactivity disorder? Ann Fam Med 1: 171–174.
10. Malacrida C (2004) Medicalization, ambivalence and social control: Mothers' descriptions of educators and ADD/ADHD. Health 8: 61–80.
11. Shire Pharmaceutical Group (2005) ADHD support. Available: http://www.adhdsupportcompany.com. Accessed 23 December 2005.
12. Novartis Pharmaceuticals Corporation (2005) If parents ask… Available: http://www.adhdinfo.com/info/school/caring/sch_if_parents_ask.jsp. Accessed 19 December 2005.
13. Novartis Pharmaceuticals Corporation (2006) Novartis Pharmaceuticals USA. Available: http://www.pharma.us.novartis.com/index.jsp?TNav. Accessed 14 February 2006.
14. Shire Pharmaceutical Group (2006) Adderell XR. Available: http://www.adderallxr.com. Accessed 14 September 2005.
15. Shire Pharmaceutical Group (2005) Celebrity carpenter Ty Pennington to host ADHD experts on call program [press release]. Available: http://psychcentral.com/news/archives/2005-09/pn-net091405.html. Accessed 14 February 2006.
16. Kidsonline (2006) National Association of School Nurses (NASN) supports educational program about management of attention deficit hyperactivity disorder (ADHD) in schools. Available: http://www.kidsource.com/kidsource/content3/news3/adhd.nurses.html. Accessed 29 January 2006.
17. Novartis Pharmaceuticals Corporation (2002) Straight talk about responsible treatment (START). Available: http://www.adhdinfo.com/startnow/index.jsp. Accessed 29 January 2006.
18. CHADD (2005) CHADD Annual Report 2004–2005. Available: http://www.chadd.org/pdfs/2005_Annual_Report.pdf. Accessed 2005.
19. CHADD (2004) Reaching educators. Available: http://www.chadd.org/webpage.cfm?cat_id=10&subcat_id=77. Accessed 23 December 2005.
20. Foggo D (2005) ADHD advice secretly paid for by drugs companies. Available: http://www.telegraph.co.uk/news/main.jhtml?xml=/news/2005/10/09/nadhd09.xml. Accessed 29 January 2006.
21. GlaxoSmithKline (2004) Partners with education. Available: http://www.gsk.com/education/index.htm. Accessed 23 December 2005.
22. Pfizer (2004) Pfizer Learning Lab. Available: http://www.pfizerlearninglab.co.uk/hp.aspx. Accessed 23 December 2005.
23. Association of the British Pharmaceutical Industry (2005) Resources for schools. Available: http://www.abpischools.org.uk. Accessed 23 December 2005.
24. Story M, French S (2004) Food Advertising and marketing directed and children and adolescents in the US. Int J Behav Nutr Phys Act 10: 3.
25. Linn SE (2004) Food marketing to children in the context of a marketing maelstrom. J Public Health Pol 25: 367–378.
26. Rogers WA, Mansfield PR, Braunack-Mayer AJ, Jureidini JN (2004) The ethics of pharmaceutical industry relationships with medical students. Med J Australia 180: 411–414.
27. Wilkes MS, Hoffman JR (2001) An innovative approach to educating medical students about pharmaceutical promotion. Acad Med 76: 1271–1277.
28. Mansfield PR (1997) MaLAM, a medical lobby for appropriate marketing of pharmaceuticals. Med J Australia 167: 590–592.

OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

Female Sexual Dysfunction: A Case Study of Disease Mongering and Activist Resistance

Leonore Tiefer

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

The creation and promotion of "female sexual dysfunction" (FSD) is a textbook case of disease mongering by the pharmaceutical industry and by other agents of medicalization, such as health and science journalists, healthcare professionals, public relations and advertising firms, contract research organizations, and others in the "medicalization industry." Whether one relies on Lynn Payer's original definition of disease mongering ("trying to convince essentially well people that they are sick, or slightly sick people that they are very ill" [1]), her checklist (Box 1), or the analysis of our pill-popping society that was recently offered by Greg Critser [2], the sequence of events and cast of participants involved in FSD matches the classic disease-mongering tactics [1,2].

Each physical condition or life event that has been subject to disease-mongering tactics has its own unique history. Sexual life has become vulnerable to disease mongering for two main reasons. First, a long history of social and political control of sexual expression created reservoirs of shame and ignorance that make it difficult for many people to understand sexual satisfaction or cope with sexual problems in rational ways. Second, popular culture has greatly inflated public expectations about sexual function and the importance of sex to personal and relationship satisfaction.

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

Thus the public is led to want and expect high rewards from sexual life without having tools to achieve these rewards. People fed a myth that sex is "natural"—that is, a matter of automatic and unlearned biological function—at the same time as they expect high levels of performance and enduring pleasure, are likely to look for simple solutions. This sets the stage for disease mongering, a process that encourages the conversion of socially created anxiety into medical diagnoses suitable for pharmacological treatment.

In this essay, I begin by examining sexual attitudes in the 20th century that were crucial in setting the scene for the creation of FSD. I then highlight key steps in the history of FSD and of the campaign to challenge its reductionist approach to women's sexual problems.

Box 1. The Major Disease-Mongering Tactics Identified by Lynn Payer [1]

1. "Taking a normal function and implying that there's something wrong with it and it should be treated" (p. 88)
2. "Imputing suffering that isn't necessarily there" (p. 89)
3. "Defining as large a proportion of the population as possible as suffering from the 'disease'" (p. 89)
4. "Defining a [condition] as a deficiency disease or disease of hormonal imbalance" (p. 93)
5. "Getting the right spin doctors" (p. 93)
6. "Framing the issues in a particular way" (p. 94)
7. "Selective use of statistics to exaggerate the benefits of treatment" (p. 95)
8. "Using the wrong end point" (p. 96)
9. "Promoting technology as risk-free magic" (p. 96)
10. "Taking a common symptom that could mean anything and making it sound as if it is a sign of a serious disease" (p. 98)

Setting the Scene: Sex and the 20th Century

In the early 20th century, sexual life and interest were stimulated by intensive urbanization and immigration that disrupted old community-based patterns of sexual regulation [3,4]. Sexual choices and expectations, however, were still largely governed by traditional religion and a double standard. Public discourse around sex was moralistic, and sex-education materials were limited and stigmatized. By mid-century, surveys showed wide variation in sexual habits, with behavior patterns related to social class, gender, cohort, and other background factors [5].

Dramatic liberalization occurred after World War II as purity campaigns failed to hold back the sex-promoting impact of changes in longevity, leisure, employment and childrearing, new technology, and mass media [4]. Effective oral contraceptives and medical treatments for venereal diseases removed sexual inhibitions due to fear of pregnancy and disease. A youth culture of charged eroticism developed. Changes in obscenity laws permitted sexual explicitness in the mass media. The women's and gay-

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

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

Citation: Tiefer L (2006) Female sexual dysfunction: A case study of disease mongering and activist resistance. PLoS Med 3(4): e178.

DOI: 10.1371/journal.pmed.0030178

Abbreviations: FDA, US Food and Drug Administration; FSD, female sexual dysfunction; P&G, Procter & Gamble; UCLA, University of California Los Angeles

Leonore Tiefer is Clinical Associate Professor of Psychiatry, New York University School of Medicine, New York, New York, United States of America. E-mail: Leonore.Tiefer@med.nyu.edu

and lesbian-rights movements of the 1960s and 1970s raised the importance of sexual behavior and identity. Each new technological development in communications—movies, car radios, television, videotapes, Internet—was used to promote sex-related products and to escalate the importance of sexual life and the availability of stimulation.

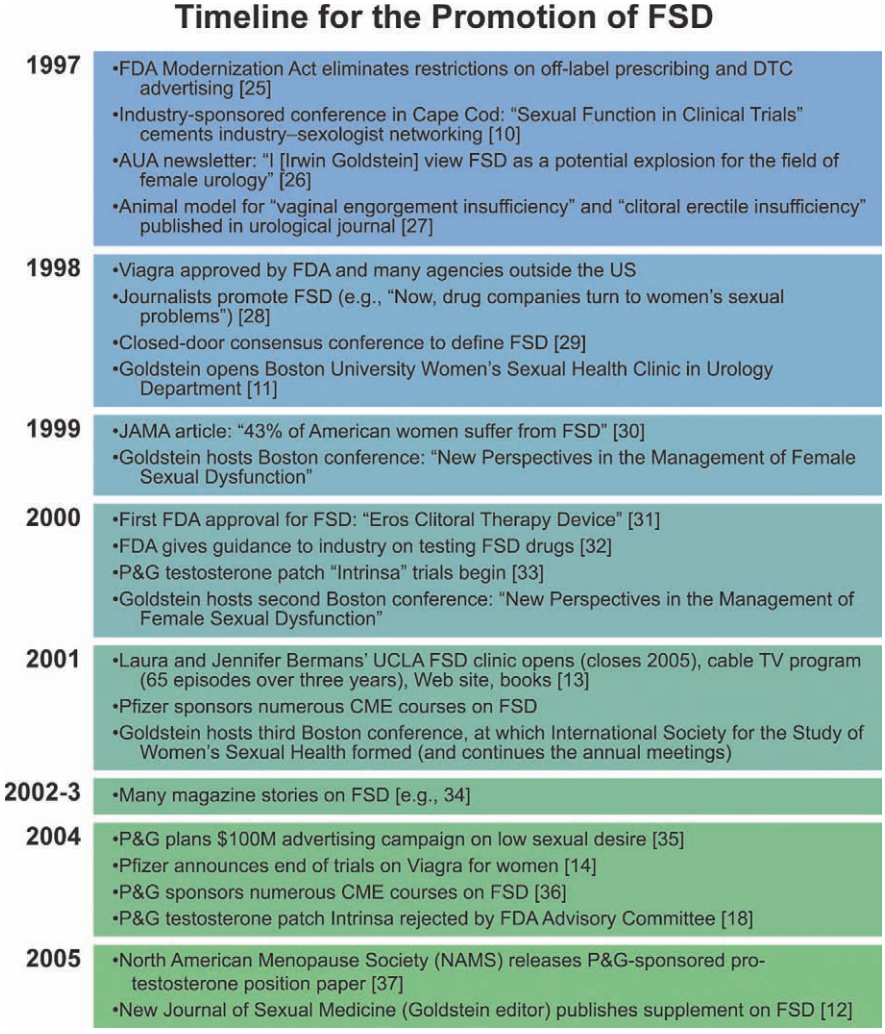
Medicalizing Sexuality

Beginning in the 1970s, along with the increasing sexual explicitness in popular culture, there were two competing academic theories of sexuality. In the social sciences and humanities, a social-constructionist perspective emphasized political, economic, and social determinants of sexual life [6]. It tended to see learning and education as keys to sexual satisfaction. In psychology and medicine, by contrast, a reductionist view of sexuality prevailed that stressed universal, evolution-based patterns of sexual motive, attraction, and conduct. This view saw satisfaction as an inherent result of normal function. In truth, however, there wasn't much academic sex research of any sort, as the topic was controversial and hence underfunded. There were very few academic or professional training programs, and sexological organizations, conferences, and journals were lively but small and somewhat defensive, rather than parts of an established specialty area of sexuality studies.

In the 1980s, the nature of sex research and expertise began to shift as a new "sexual medicine" focused on function was created by urologists, insurance reimbursement programs, diagnostic technologies, science and medicine journalists, and, then, the pharmaceutical industry [7].

Urologists looked to new opportunities in genitourinary sexual medicine as their surgical careers were limited by the new (1984) kidney stone lithotripsy and by effective medications for benign prostate disease. Insurance-based reimbursement for sex-problem treatments (including psychotherapy) became linked to a diagnostic classification system that recognized only discrete sexual "dysfunctions" such as low desire, inadequate arousal/erection, and premature or delayed orgasm/ejaculation. Technologies for measuring genital blood flow and nerve function were widely used to substantiate dysfunction diagnoses. Taking advantage of post-1980s deregulatory policies, the pharmaceutical industry began to redirect its pipeline to new "lifestyle drugs" and its marketing to consumer advertising. Science and medicine journalists played key roles in whetting the public's appetite for medical news about sex by breathlessly covering each new discovery and treatment.

In the 1980s and 1990s, urologists created organizations, journals, and "sexual health clinics" that focused on men's erection problems. In 1992, a US National Institutes of Health consensus conference on "impotence" legitimized this work. Its outcome was a 34-page document that mentioned factors involved in etiology, maintenance, and treatment such as culture, partners, and sexual techniques, but, for the most part, it reified "erection" as the essence of men's sexuality, and called for new treatments and vastly expanded research into physiological details and treatments [8]. The creation of "erectile dysfunction" as a serious, prevalent, and treatable medical disorder was firmly in place by the time Viagra was launched in 1998 with an unprecedented global public-relations campaign, as Joel Lexchin describes in this issue of *PLoS Medicine* [9].



DOI: 10.1371/journal.pmed.0030178.g001

Figure 1. Timeline for the Promotion of FSD from 1997 to Present

AUA, American Urological Association; CME, Continuing Medical Education; JAMA, Journal of the American Medical Association
(Figure: Rusty Howson)

Creating FSD

Although journalists began calling for a "female Viagra" only days after the March 1998 US Food and Drug Administration (FDA) approval of Viagra (examples of journalists' calling

for a "pink Viagra" are collected on http://www.fsd-alert.org/press.html), it was far from clear what medical condition Viagra was supposed to treat in women. Urologists had used the term "female sexual dysfunction" as early as 1997, referring to aspects of genital pathophysiology that might be akin to erectile dysfunction. Figure 1 offers a timeline of events shaping the creation and promotion of FSD, from 1997 to the present.

A May 1997 Cape Cod conference, "Sexual Function Assessment in Clinical Trials," which was sponsored by pharmaceutical companies, was a watershed moment in the FSD story [10]. These companies bypassed existing sexology organizations and their annual conferences to convene an invitation-only industry–sexologist get-together. Papers and discussion were published in a special supplement to the *International Journal of Impotence Research* [10]. Significantly, the introduction stated:

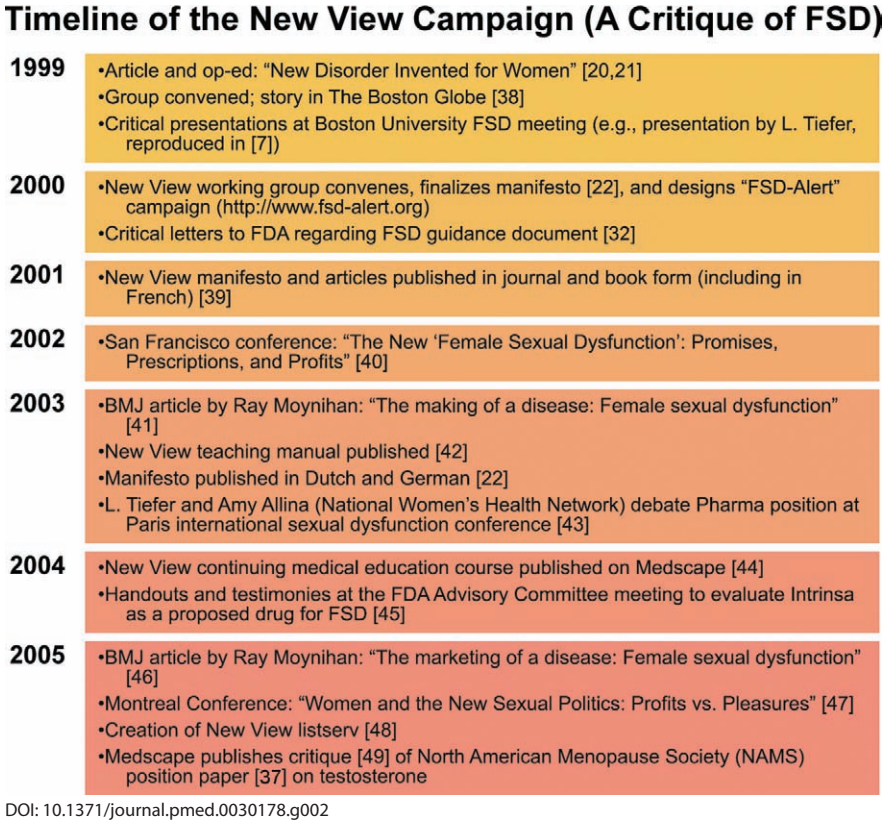
> *"In the area of female sexual dysfunction, there is widespread lack of agreement about the definition of sexual dysfunction, its pathophysiology or clinical manifestations, and the optimal approach for research or clinical assessment (p. S1)."*

Definitional issues have plagued the FSD literature ever since, despite repeated industry-supported attempts to draw a bright line between healthy sexual function and medical disorder. The quest for a valid and reliable FSD assessment instrument has become a small growth industry in and of itself.

For the first few years, the key players in the medicalization of women's sexual problems were a small group of urologists who capitalized on their relationships with industry and recruited many sex researchers and therapists as allies. Irwin Goldstein of Boston University, an active erectile dysfunction researcher, opened the first Women's Sexual Health clinic in 1998 [11]. He convened the first conference on female sexual function (called "New Perspectives in the Management of Female Sexual Dysfunction") in October 1999 in Boston. Goldstein is the editor of a journal that launched in 2004—the *Journal of Sexual Medicine* (http://jsm.issir.org)—which has already published an industry-supported supplement on FSD [12].

Jennifer Berman, Goldstein's urology trainee at Boston University, together with her sister, sex educator Laura Berman, became the female face of FSD, opening a clinic at University of California Los Angeles (UCLA) in 2001, and continuing to popularize FSD and off-label drug treatments on their television program, Web site, and books; in appearances on the television show "Oprah"; and in innumerable women's magazines [13]. The UCLA clinic was closed in 2005, as both Jennifer (in Los Angeles, California) and Laura (now in Chicago, Illinois) opened fee-for-service women's sexual-health centers that offered medical assessments and treatments plus spa and yoga services [13]. Laura will also have her own reality TV sex-advice show later in 2006 (http://www.sho.com/site/announcements/051005sexual.do). One clear future angle to the FSD story will be its intersection with the new "holistic" and "boutique" (specialized, retainer, or cash-paying) medical trends as well as with drug-friendly celebrity experts.

Pfizer, the world's largest pharmaceutical company, was the main promoter of FSD from 1997 to 2004, when its quest to have Viagra approved to treat "female sexual arousal disorder" ended because of consistently poor clinical-trial results. In its public statement, Pfizer said that that several large-scale, placebo-controlled studies including about 3,000 women with female sexual arousal disorder showed inconclusive results on the efficacy of the drug [14]. Commenting on these trial results on Viagra, John Bancroft, director of the Kinsey Institute, told the *BMJ*: "The recent history of the study of female sexual dysfunction is a classic example of starting with some preconceived, and non-evidence based diagnostic categorisation for women's sexual dysfunctions, based on the male model, and then requiring further research to be based on that structure. Increasingly it is becoming evident that women's sexual problems are not usefully conceptualised in that way" [14]. Nevertheless, Viagra (and the idea that it *must* work for women) has



DOI: 10.1371/journal.pmed.0030178.g002

Figure 2. Timeline of Events Beginning in 1999 of Activism, Which Came to Be Called the "Campaign for a New View of Women's Sexual Problems"
(Figure: Rusty Howson)

been so successfully branded that it continues to be prescribed off-label for women [15].

Next in line with a potential drug for FSD has been Procter & Gamble (P&G), the multibillion-dollar soap, shampoo, and snack company that makes only five prescription drugs [16]. P&G's 2004 annual report states that its drug risedronate (Actonel, approved in 1998 for Paget disease and in 2000 for osteoporosis), "became a billion-dollar brand faster than any other brand in P&G history" [17]. Perhaps encouraged by this success in selling medicine to women, P&G had begun investing heavily in a testosterone patch (brand name Intrinsa) to treat "hypoactive sexual desire disorder." The unnoticed shift in 2004 in FSD identity and promotion from female sexual arousal disorder to hypoactive sexual desire disorder is another hallmark moment in the FSD story, illustrating how the effort to match up some drug with FSD moved freely among symptoms and labels. P&G's trials with Intrinsa got many gynecologists and their organizations heavily involved in the new sexual pharma–medicine for the first time. Unfortunately for the drug company, an FDA advisory panel voted unanimously not to approve Intrinsa, saying that P&G had not provided sufficient long-term safety data and questioning the clinical significance of the Intrinsa trials [18]. However, testosterone researcher Jan Shifren estimates that one-fifth of all the prescriptions of testosterone products approved for men are actually written (off-label) for women [19].

By 2006, FSD has become a medical and media reality, despite the obvious ongoing difficulties in defining the condition and in getting a drug approved. Disease mongering has led to the successful "branding" of FSD.

Activist Response

In 1999, I became concerned that the imminent inaugural Boston conference on FSD would represent only the reductionist view of women's sexual problems and would likely ignore the fundamental political and interpersonal reality of women's sexual lives. I had been employed as a research and clinical psychologist in urology departments from 1983 to 1996, and I worried that the mechanistic view of sexuality I had seen applied to men's sexual function would just be transposed to women. Viagra had just been approved, I knew about the Cape Cod conference, and I feared that urologists (with financial backing from Pfizer) would use a conference on FSD to promote Viagra for women.

Although I had no experience in organizing, I felt I had to take steps to make sure a space was created for diverse (i.e., not just medical) opinions about women's sexual problems. I submitted a critical essay about the new FSD to a Boston feminist newsletter [20], and, with Carol Tavris, I wrote an op-ed for the *Los Angeles Times* [21]. Through Internet communication, I invited feminist critics of medicalization to meet with me in Boston and take some action at the FSD conference. Figure 2 offers a timeline, beginning in 1999, of the activism that came to be called the "Campaign for a New View of women's sexual problems" [22].

The pharmaceutical industry has taken an aggressive interest in sex.

The campaign and its challenge to FSD disease mongering have had two crucial components [23]. The first, a theoretical critique of the medical model of sexual problems, was developed in the New View Manifesto, books, articles, and lectures. The manifesto, now available in several languages [22], was authored by a group of feminist academics, activists, and clinicians calling themselves "The Working Group on a New View of Women's Sexual Problems." The second component of the campaign is pharma–watchdog activism, consisting of media interviews, conferences, FDA and professional presentations, and a Web site (http://fsd-alert.org).

The New View Manifesto focuses on weaknesses of the prevailing sexual dysfunction classification and medical model. It promotes a politically sensitive social-constructionist perspective and recommends abandoning the effort to define "normal" sexual function. It offers an alternative classification system of causes for sexual problems rooted in society, relationships, psychology, and disease. The activism challenges claims made for each emerging FSD drug in terms based on recurring biases in clinical trials, dangers of off-label promotion, researchers' conflicts of interest, and neglect of nonmedical theory and research on sexuality.

Conclusion

Sexual life and its pleasures, problems, and satisfactions are subject to changing demands and expectations. Recently, the pharmaceutical industry has taken an aggressive interest in sex, using public relations, direct-to-consumer advertising, promotion of off-label prescribing, and other tactics to create a sense of widespread sexual inadequacy and interest in drug treatments.

The public finds medicalization attractive because the notion of simple but scientific solutions fits in with a general cultural overinvestment in biological explanations and interventions, and promises to bypass sexual embarrassment, ignorance, and anxiety. This wish will inevitably end in stories of personal disappointment, but media promotion, advertising hyperbole, and an active pipeline will create continuing hope for the next new drug along with a neglect of other models of sex and ways to deal with sexual discontent.

The New View Campaign to challenge the disease mongering of FSD can be seen as part of a widespread new arena of public-health advocacy that deals with corporate practices that affect health, such as those in the tobacco, automobile, and food industries [24]. Activism on behalf of women's sexuality leads also to coalition with sexual-rights, sex-education, and reproductive-rights organizations. It has taken the work of many public-spirited people and organizations to shed the necessary light on FSD disease mongering. But the difficulties the industry and its experts continue to have in nailing down FSD testify to some small success on our part. ■

References

1. Payer L (1992) Disease-mongers: How doctors, drug companies, and insurers are making you feel sick. New York: Wiley & Sons. 292 p.
2. Critser G (2005) Generation Rx: How prescription drugs are altering American lives, minds, and bodies. Boston: Houghton-Mifflin. 308 p.
3. Peiss KL (1986) Cheap amusements: Working women and leisure in turn-of-the century New York. Philadelphia: Temple University Press. 244 p.

4. D'Emilio J, Freedman EB (1988) Intimate matters: A history of sexuality in America. New York: Harper & Row. 428 p.
5. Ericksen JA, Steffen SA (1999) Kiss and tell: Surveying sex in the twentieth century. Cambridge (Massachusetts): Harvard University Press. 270 p.
6. Weeks J (1985) Sexuality and its discontents: Meanings, myths and modern sexualities. London: Routledge & Kegan Paul. 324 p.
7. Tiefer L (2004) Sex is not a natural act and other essays, 2nd edition. Boulder (Colorado): Westview Press. 304 p.
8. The National Institutes of Health Consensus Development Program (1992) Impotence. NIH Consensus Statement Online 1992 Dec 7–9 10: 1–31. Available: http://consensus.nih.gov/1992/1992Impotence091html.htm. Accessed 7 March 2006.
9. Lexchin J (2006) Bigger and better: How Pfizer redefined erectile dysfunction. PLoS Med 3: e132. DOI: 10.1371/journal.pmed.0030132
10. Rosen RC, O'Leary MP (1997) Proceedings of The Cape Cod Conference: Sexual Function Assessment in Clinical Trials. Hyannis, Massachusetts, USA. 30–31 May 1997. Int J Impot Res 10 (Suppl 2): S1–S140.
11. Berman J, Berman L, Bumiller E (2001) For women only: A revolutionary guide to overcoming sexual dysfunction and reclaiming your sex life. New York: Henry Holt & Co. 269 p.
12. Goldstein I (2005) Inaugural supplement of The Journal of Sexual Medicine on women's sexual health concerns: Postmenopausal female sexual dysfunction roundtable. J Sex Med 2: 115. DOI: 10.1111/j.1743-6109.2005.00126.x
13. O'Connor AM (2005 October 2) Dr. Berman's Sex Rx. Los Angeles Times. Available: http://www.latimes.com/features/health/medicine/la-tm-sexresearch40oct02,1,7694520.story. Accessed 13 March 2006.
14. Mayor S (2004) Pfizer will not apply for a license for sildenafil for women. BMJ 328: 542.
15. Murdock M (2000) Did it work? Viagra calls off clinical trials on use in women. Available: http://hisandherhealth.com/articles/noviagrawomen.shtml. Accessed 13 March 2006.
16. Procter & Gamble (2006) Prescription drugs. Available: http://www.pg.com/product_card/prod_card_rx_drugs.jhtml. Accessed 7 March 2006.
17. Procter & Gamble (2004) Earning your trust. Annual report. Available: http://www.pg.com/annualreports/2004/pdf/pg2004annualreport.pdf. Accessed 7 March 2006.
18. Zwillich T (2004) FDA rejects libido drug for women. Available: http://www.webmd.com/content/article/97/104342.htm. Accessed 7 March 2006.
19. Kantrowitz B, Wingert P (2005 October 4) Inside the struggle to treat women with dwindling sex drives. Newsweek. Available: http://msnbc.msn.com/id/9546806/site/newsweek. Accessed 7 March 2006.
20. Tiefer L (1999) "Female sexual dysfunction" alert: A new disorder invented for women. Sojourner: The Women's Forum. October: 11.
21. Tiefer L, Tavris C (1999 October 20). Viagra for women is the wrong Rx. Los Angeles Times: B9.
22. New View (2000)A new view of women's sexual problems. Available: http://www.fsd-alert.org/manifesto.html. Accessed 7 March 2006.
23. (2005) Women and the new sexual politics: Profits versus pleasures. Available: http://www.fsd-alert.org/Final%20Montreal%20conf%20report.pdf. Accessed 7 March 2006.
24. Freudenberg N (2005) Public health advocacy to change corporate practices: Implications for health education practice and research. Health Educ Behav 32: 298–319.
25. FDA Center for Biologics Evaluation and Research (2006) FDA Modernization Act of 1997. Available: http://www.fda.gov/cber/fdama.htm. Accessed 7 March 2006.
26. Bankhead C (1997) New field could open for urologists: Female sexual dysfunction. Urology Times 25: 1.
27. Park K, Goldstein I, Andry C, Siroky MB, Krane RJ, et al. (1997) Vasculogenic female sexual dysfunction: The hemodynamic basis for vaginal engorgement insufficiency and clitoral erectile insufficiency. Int J Impot Res 9: 27–38.
28. Johannes L (1998 July 13) Now, drug companies turn to women's sexual problems. Wall Street Journal: B1–B2.
29. Basson R, Berman J, Burnett A, Derogatis L, Ferguson D, et al. (2000) Report of the international consensus development conference on female sexual dysfunction: Definitions and classifications. J Urol 163: 888–893.
30. Laumann, EO, Paik A, Rosen RC (1999) Sexual dysfunction in the United States: Prevalence and predictors. JAMA 281: 537–544.
31. Billups KL, Berman L, Berman J, Metz ME, Glennon ME, et al. (2001) A new non-pharmacological vacuum therapy for female sexual dysfunction. J Sex Marital Ther 27: 435–441.
32. Center for Drug Evaluation and Research (2001) Female sexual dysfunction: Clinical development of drug products for treatment. Available: http://www.fda.gov/cder/guidance/3312dft.htm. Accessed 7 March 2006.
33. Procter & Gamble (2000) Testosterone skin patch improves sexual functioning in surgically menopausal women. Available: http://www.pginvestor.com/phoenix.zhtml?c=104574&p=irol-newsArticleMain&ID=628910. Accessed 7 March 2006.
34. Deer B (2003 September 28) Love sickness. The Sunday Times Magazine (London). Available: http://briandeer.com/sexual-disorder.htm. Accessed 7 March 2006.
35. The Age (2004) The passion patch. Available: http://www.theage.com.au/articles/2004/11/18/1100748140309.html. Accessed 7 March 2006.
36. Baylor College of Medicine (2006) About online meetings on female sexual dysfunction online. Available: http://www.femalesexualdysfunctiononline.org/meetings. Accessed 7 March 2006.
37. The North American Menopause Society (2005) The role of testosterone therapy in postmenopausal women: Position statement of The North American Menopause Society. Available: http://www.menopause.org/aboutmeno/PStestosterone.pdf. Accessed 20 March 2006.
38. Kong D (1999 October 22) Doubts heard over sexual dysfunction gathering. Boston Globe: B1, B6.
39. New View (2002) A new view of women's sexual problems. Available: http://www.fsd-alert.org/newbook.html. Accessed 7 March 2006.
40. New View (2002) Conference. The New "Female Sexual Dysfunction": Promises, Prescriptions, and Profits. March 9, 2002. Available: http://www.fsd-alert.org/2002conference.html. Accessed 7 March 2006.
41. Moynihan R (2003) The making of a disease: Female sexual dysfunction. BMJ 326: 45–47.
42. New View (2003) A new view of women's sexual problems: A teaching manual. Available: http://www.fsd-alert.org/ntm.html. Accessed 7 March 2006.
43. Kelleher S (2005) Clash over "little blue pill" for women. The Seattle Times. Available: http://seattletimes.nwsource.com/html/health/sick5.html. Accessed 7 March 2006.
44. Hicks KM (2005) The "new view" approach to women's sexual problems. Available: http://www.medscape.com/viewprogram/4705. Accessed 7 March 2006.
45. New View (2004) FDA hearing on Intrinsa. Dec. 2, 2004. New View resources. Available: http://www.fsd-alert.org/intrinsa.html. Accessed 7 March 2006.
46. Moynihan R (2005) The marketing of a disease: Female sexual dysfunction. BMJ 330: 192–194.
47. New View (2005) New View Conference 2005. Women and the New Sexual Politics: Profits vs. Pleasures. July 9–10, 2005. Available: http://www.fsd-alert.org/connewviewconf2005.html. Accessed 7 March 2006.
48. New View (2005) The New View campaign began a New View listserv in August, 2005. Available: http://www.fsd-alert.org/listserve.html. Accessed 7 March 2006.
49. Tiefer L (2005) Omissions, biases, and nondisclosed conflicts of interest: Is there a hidden agenda in the NAMS position statement? Available: http://www.medscape.com/viewarticle/513099. Accessed 13 March 2006.

OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

The Latest Mania: Selling Bipolar Disorder

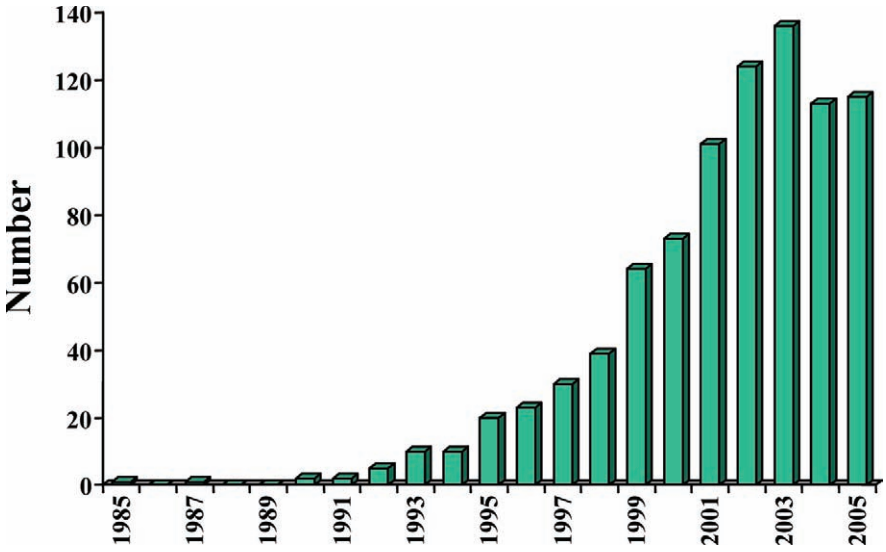
David Healy

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

One of the most famous direct-to-consumer television adverts for a drug begins with a vibrant woman dancing late into the night. A background voice says, "Your doctor probably never sees you when you feel like this." The advert cuts to a shrunken and glum figure, and the voiceover now says, "This is who your doctor usually sees." Cutting again to the woman, in active shopping mode, clutching bags with the latest brand names, we hear: "That's why so many people with bipolar disorder are being treated for depression and not getting any better—because depression is only half the story." We see the woman again depressed, looking at bills that have arrived in the post before switching to seeing her again energetically painting her apartment. "That fast- talking, energetic, quick tempered, overdoing it, up-all-night you," says the voiceover, "probably never shows up at the doctor's office, right?"

No drugs are mentioned. But viewers are encouraged to log onto www.bipolarawareness.com, which takes them to a Web site called "Bipolar Help Center," sponsored by Lilly Pharmaceuticals, the makers of olanzapine (Zyprexa). The Web site contains a "mood disorder questionnaire" (http://www.bipolarhelpcenter.com/resources/mdq.jsp). In the television advert, we see our heroine logging onto www.bipolarawareness.com and finding this questionnaire. The voice encourages the viewer to follow her example: "Take the test you can take to your doctor, it can change your life….getting a correct diagnosis is the first step in treating bipolar disorder. Help your doctor to help you."

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.



DOI: 10.1371/journal.pmed.0030185.g001

Figure 1. Articles Elicited by Medline Using the Mesh Term "Mood Stabilizer"

This advert markets bipolar disorder. The advert can be read as a genuine attempt to alert people who may be suffering from one of the most debilitating and serious psychiatric diseases—manic-depressive illness. Alternatively, the advert can be read as an example of what has been termed disease mongering [1]. Whichever it is, it will reach beyond those suffering from a mood disorder to others who will as a consequence be more likely to see aspects of their personal experiences in a new way that will lead to medical consultations and in a way that will shape the outcome of those consultations. Adverts that encourage "mood watching" risk transforming variations from an emotional even keel into potential indicators of latent or actual bipolar disorder. This advert appeared in 2002 shortly after Lilly's antipsychotic olanzapine had received a license for treating mania. The company was also running trials aimed at establishing olanzapine as a "mood stabilizer," one of which was recently published [2].

Mood Stabilization

From the 1950s on, the depressions of manic-depressive illness have been treated with antidepressants and the manias with antipsychotics or lithium. Lithium was the only agent thought to be prophylactic against further episodes of manic-depressive illness [3]. But lithium was not originally referred to as a mood stabilizer. The term "mood stabilizer" had barely been heard of before 1995 when Abbott Laboratories got a license

Funding: The author received no specific funding to write this article.

Competing Interests: DH has been a speaker, consultant, or clinical trialist for Lilly, Janssen, SmithKline Beecham, Pfizer, Astra-Zeneca, Lorex-Synthelabo, Lundbeck, Organon, Pierre-Fabre, Roche, and Sanofi. He has also been an expert witness in ten legal cases involving antidepressants and suicide or homicide and one case involving the patent on olanzapine (Zyprexa). None of these interests played any part in the submission or preparation of this paper.

Citation: Healy D (2006) The latest mania: Selling bipolar disorder. PLoS Med 3(4): e185.

DOI: 10.1371/journal.pmed.0030185

David Healy is at the North Wales Department of Psychological Medicine, Cardiff University, Cardiff, Wales, United Kingdom. E-mail: healy_hergest@compuserve.com

for using the anticonvulsant sodium valproate (Depakote) for treating acute mania [4].

After 1995, there was a dramatic growth in the frequency with which the term "mood stabilizer" appeared in the title of scientific articles (see Figure 1). By 2001, more than a hundred article titles a year featured this term. Repeated reviews make it clear that the academic psychiatric community still has not come to a consensus on what the term "mood stabilizer" means [5–7]. But this lack of consensus did not get in the way of the message that patients with bipolar disorders needed to be detected and once detected needed mood stabilizers, and perhaps should only be given these drugs and not any other psychotropic drugs [8,9].

The growth of awareness of mood stabilization was sensational.

The first group of drugs to colonize this new mood stabilizer niche was anticonvulsants. Anticonvulsants are beneficial in epilepsy and were until recently widely thought to be beneficial by quenching the increased risk of succeeding epileptic fits brought about by fits that have gone before. Robert Post in the 1980s suggested that anticonvulsants might stabilize moods by a comparable quenching of the kindling effect of an episode of mood disorders on the risk of further episodes [10]. It was this idea that provided a pharmacological rationale for treatment of bipolar disorders that was so attractive to pharmaceutical companies, and, in their hands, the growth of awareness of mood stabilization and of bipolar disorders was sensational.

Bipolar disorders entered the DSM *(Diagnostic and Statistical Manual of Mental Disorders)* in 1980. At the time, the criteria for bipolar I disorder (classic manic-depressive illness) involved an episode of hospitalization for mania. Since then, the community-based disorders bipolar II disorder, bipolar disorders NOS (not otherwise specified), and cyclothymia have emerged. With their emergence, estimates for the prevalence of bipolar disorders have risen from 0.1% of the population having bipolar I disorder (involving an episode of hospitalization for mania) [11] to 5% or more when the definition of bipolar disorders includes the aforementioned community disorders [12]. A range of academic institutions has also grown more interested in the condition.

There has always been a rationale to using antipsychotics in bipolar disorders, as they are effective in acute manic states [13,14]. However, no companies making antipsychotics had previously sought a license for *prophylaxis* against bipolar disorders. Against a background of epidemiological studies indicating that the prevalence of bipolar disorders might be greater than previously thought [15,16], and growing academic interest in the condition, Lilly, Janssen, and Astra-Zeneca, the makers of the antipsychotics olanzapine, risperidone, and quetiapine (Seroquel), respectively, marched in on the new territory to market these drugs for prophylaxis of bipolar disorder. This, in turn, greatly expanded the number of companies with an interest in making the "bipolar market." There was, however, no consensus on a theoretical rationale that would lead the average clinician to think these three drugs might "quench" the propensity to further affective episodes, as opposed to simply assist in the management of acute manic states.

But the increased prevalence estimates were based on community surveys that had no clear disability criterion, while acute treatment trials of antipsychotics for mania, and prophylactic trials of lithium for manic-depressive illness, have for the most part been conducted on bipolar I disorder. This necessarily raises the prospect that increased efforts to detect and to treat people risks crossing the line where the benefits of treatment outweigh its risks.

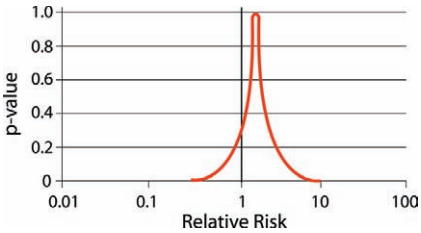
Along with this expansion in prevalence estimates came new journals, *Bipolar Disorders* (http://www.blackwellpublishing.com/journal.asp?ref=1398-5647) and the *Journal of Bipolar Disorders* (published by Lippincott, Williams, and Wilkins), a slew of bipolar societies, and annual conferences, many heavily funded by pharmaceutical companies. There is a growing amount of patient Web site and patient support materials that in the case of Zyprexa state that "bipolar disorder is often a lifelong illness needing lifelong treatment; symptoms come and go, but the illness stays; people feel better because the medication is working; almost everyone who stops taking the medication will get ill again and the more episodes you have, the more difficult they are to treat" [17]. Information available from Janssen (the makers of Risperdal) states "medicines are crucially important in the treatment of bipolar disorders. Studies over the past twenty years have shown beyond the shadow of doubt that people who receive the appropriate drugs are better off in the long term than those who receive no medicine" [18].

What Lies Beneath

There is, however, much less evidence than many might think to support these claims for the prophylactic drug treatment of manic-depressive illness (bipolar I). And there is almost no evidence to support such claims in the case of whatever community disorders (bipolar II, bipolar NOS, cyclothymia) are now being pulled into the manic-depressive net by the lure of bipolar disorder.

With the possible exception of lithium for bipolar I disorder, there are no randomized controlled trials to show that patients with bipolar disorders in general who receive psychotropic drugs are better in the long term than those who receive no medicine [19]. This may stem in part from difficulties in conducting trials on psychotropic drugs that last more than a few weeks in conditions as complex as manic-depressive illness. One short-term, randomized, placebo-controlled trial (in which patients were only followed for up to 48 weeks) that some see as a basis for claiming that olanzapine may be prophylactic in bipolar disorder [2] has been regarded by others as indicating that this drug produces a withdrawal-induced decompensation when stopped [20]. Even in the case of lithium, there is some dispute over what has been demonstrated [19], with the best evidence stemming from large open studies in dedicated lithium services rather than from randomized trials [21].

This evidence of benefit for one agent (lithium) and possible



DOI: 10.1371/journal.pmed.0030185.g002

Figure 2. Author's Graph of *p*-Value Function Based on Data in [30]
(Illustration: Sapna Khandwala)

benefit for one more (olanzapine) must be weighed against two harms associated with use of antipsychotics: (1) a consistent body of evidence indicates that regular treatment with antipsychotics in the longer run increases mortality [22–26]; and (2) there is evidence that in placebo-controlled trials of antipsychotics submitted in application for schizophrenia licenses there is a statistically significant excess of completed suicides on active treatment [27]. A range of problems associated with antipsychotics, from increased mortality to tardive dyskinesia, never show up in the short-term trials aimed at demonstrating treatment effects in psychiatry.

But aside from these hazards, there are also grounds to question whether the treatment effects that some think have been demonstrated in bipolar disorder trials translate into therapeutic efficacy. If use of these agents based on demonstrated effects leads on to efficacy, admissions for bipolar disorder might be expected to fall, but the evidence for this is difficult to find. In North Wales before the advent of modern pharmacotherapy, patients with bipolar I disorder had on average four admissions every ten years. In contrast, against a background of a constant incidence of bipolar I disorder, and dramatic improvements in service provision, bipolar I patients show a 4-fold increase in the prevalence of admissions despite being treated with the very latest psychotropic medications [11]. This is not ordinarily what happens when treatments "work," but quite often is what happens when treatments have effects.

The selling of bipolar disorder stresses that the disorder takes a fearsome toll of suicides. And indeed the controversy surrounding the provocation of suicide by antidepressants has been recast by some as a consequence of mistaken diagnosis. If the treating physician had only realized the patient was bipolar, they would not have mistakenly prescribed an antidepressant. Because of the suicide risk traditionally linked to patients with bipolar disorders who needed hospitalisation, most psychiatrists would find it difficult to leave any person with a case of bipolar disorder unmedicated. Yet, the best available evidence shows that unmedicated patients with bipolar disorder do *not* have a higher risk of suicide.

Storosum and colleagues analyzed all placebo-controlled, double-blind, randomized trials of mood stabilizers for the prevention of manic/depressive episode that were part of a registration dossier submitted to the regulatory authority of the Netherlands, the Medicines Evaluation Board, between 1997 and 2003 [28]. They found four such prophylaxis trials. They compared suicide risk in patients on placebo compared with patients on active medication. Two suicides (493/100,000 person- years of exposure) and eight suicide attempts (1,969/100,000 person-years of exposure) occurred in the group given an active drug (943 patients), but no suicides and two suicide attempts (1,467/100,000 person-years of exposure) occurred in the placebo group (418 patients). Based on these absolute numbers from these four trials, I have calculated (see Figure S1 showing calculation, and see Figure 2) that active agents are most likely to be associated with a 2.22 times greater risk of suicidal acts than placebo (95% CI 0.5, 10.00).

The Bipolar Future

Until recently the general clinical wisdom was that it was very rare for manic-depressive illness to have an onset in the preteen years. But there is now a surge of diagnoses of bipolar disorder in American children [29,30], even though these children do not meet the traditional criteria for bipolar I disorder (from the *Diagnostic and Statistical Manual of Mental Disorders*) [31]. The mania for pediatric bipolar disorder hit the front cover of the American edition of *Time* in August 2002, which featured nine-year-old Ian Palmer and a cover title *Young and Bipolar*, with a strapline, *why are so many kids being diagnosed with the disorder, once known as manic-depression?*

A recent book, *The Bipolar Child* [32], brings out the extent of the current mania. Published in 2000, this book sold 70,000 hardback copies in six months in the US. As the *Star Telegram* reported in July 2000 [33], *The Bipolar Child* made all the difference to Heather Norris, whose mother, after reading it, challenged her physician to correct Heather's diagnosis from ADHD, treatment of which had made her daughter worse, to the correct diagnosis of bipolar disorder. As a result, Heather, at the age of two, became the youngest child in Tarrant County, Texas, to have a diagnosis of bipolar disorder. The *Star Telegram* article noted that "along with the insurance woes, lack of treatment options and weak support systems that plague most families with mentally ill children, parents of the very young face additional challenges. Finding the proper diagnosis for treatment is a nightmare because of scant research into childhood mental illness and the drugs that combat them."

If we consider adults alone for a moment, there is already the potential for creating an "epidemic" of bipolar disorder, because people are being diagnosed with the condition based on operational criteria that depend upon subjective judgements (rather than an objective criterion of disability, such as hospitalization or being off work for a month). The potential is compounded in the pediatric domain by the fact that the diagnosis is based on caregiver reports with little scope in most clinical practice for critical scrutiny of the social forces that may lead to these reports. Experts that appear willing to go so far as to accept the possibility that the first signs of bipolar disorder may be patterns of overactivity in utero [32] can only further compound these problems. If the resulting diagnoses were provisional, aimed at researching the natural history of childhood irritability, rather than reaching diagnoses that lead on to pharmacotherapy, there might be little problem. However, drugs such as Zyprexa and Risperdal are now being used for preschoolers in America with little questioning of this development [31].

Far from research bringing a skeptical note to bear on clinical

enthusiasm, it appears to be adding fuel to the fire. What might once have been thought of as sober institutions, such as Massachusetts General Hospital, have run trials of Risperdal and Zyprexa on children with a mean age of four years old [34,35]. Massachusetts General Hospital in fact recruited trial participants by running its own television adverts featuring clinicians and parents alerting parents to the fact that difficult and aggressive behavior in children aged four and up might stem from bipolar disorder. This does more than recruit patients with a clear disorder; it suggests that everyday behavioral difficulties may be better seen in terms of a disorder. Given that bipolar disorder in children is all but unrecognised outside the US, it seems likely that a significant proportion of these children will not meet conventional DSM criteria for bipolar I disorder. And given that it is all but impossible for a short-term trial of sedative agents in pediatric states characterized by overactivity *not* to show some rating scale changes that can be regarded as beneficial, the outcomes of this research are likely to appear to validate the diagnosis and increase the pressure for treatment.

Several years after Heather Norris was diagnosed with bipolar disorder, the rationale for mood stabilization was greatly weakened by the results of the largest-ever randomized trial of immediate versus deferred anticonvulsant therapy for people who had experienced a single seizure [36]. The trial found that although immediate antiepileptic drug treatment reduces the occurrence of seizures in the next 1–2 years, such treatment does not affect long-term remission in individuals with single or infrequent seizures. The use of psychotropic medication for bipolar disorders was based on an analogy with epilepsy, rather than on demonstrations of proven clinical benefits over the long term or on the basis of a correction of a known pathophysiology. The absence of a solid theoretical or empirical basis for using psychotropic medication as "mood stabilizers" raises questions as to what lies in store for the Heather Norris's and others of this world exposed to these complex psychotropic agents from such a young age. ■

Supporting Information

Figure S1. Episheet Showing Author's Relative Risk Calculation, Based on Data in [30]

Found at DOI: 10.1371/journal.pmed.0030185.sg001 (792 KB XLS).

References

1. Moynihan R, Cassels A (2005) Selling sickness. New York: Nation Books. 254 p.
2. Tohen M, Calabrese JR, Sachs G, Banov MD, Detke HC, et al. (2006) Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. Am J Psychiatry 163: 247–256.
3. Healy D (1997) The antidepressant era. Cambridge (Massachusetts): Harvard University Press. 317 p.
4. Department of Health and Human Services (1995) NDA 20-320: Depakote. Proceedings of the 44th Psychopharmacologic Drugs Advisory Committee Meeting. Washington (D. C.) 6 February 1995.
5. Sachs G (1996) Bipolar mood disorder: Practical strategies for acute and maintenance phase treatment. J Clin Psychopharmacol 16: 32s–47s.
6. Bowden CL (1998) New concepts in mood stabilization: Evidence for the effectiveness of Valproate and Lamotrigine. Neuropsychopharmacology 19: 194–199.
7. Ghaemi SN (2001) On defining "mood stabilizer." Bipolar Disord 3: 154–158.
8. Ghaemi SN, Sachs GS, Chiou A, Pandurangi AK, Goodwin FK (1999) Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? J Affect Disord 52: 135–144.
9. Ghaemi SN, Lenox MS, Baldessarini RJ (2001) Effectiveness and safety of long-term antidepressant treatment in bipolar disorder. J Clin Psychiatry 62: 565–569.
10. Post RM, Weiss SRB (1989) Kindling and manic-depressive illness. In: Bolwig TG, Trimble MR, editors. The clinical relevance of kindling. London: Wiley. pp. 209–230.
11. Harris M, Chandran S, Chakroborty N, Healy D (2005) The impact of mood stabilizers on bipolar disorder: the 1890s and 1990s compared. Hist Psychiatry 16: 423–434.
12. Angst J (1998) The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 50: 163–173.
13. Rendell JM, Gijsman HJ, Bauer MS, Goodwin GM, Geddes JR (2006) Risperidone alone or in combination for acute mania. Cochrane Database Syst Rev 1: CD004043.
14. Rendell JM, Gijsman HJ, Keck P, Goodwin GM, Geddes JR (2003) Olanzapine alone or in combination for acute mania. Cochrane Database Syst Rev 3: CD004040.
15. National Advisory Mental Health Council (1993) Health care reforms for Americans with severe mental illnesses. Am J Psychiatry 150: 1447–1465.
16. Kessler RC, McGonagle KA, Zhao S, et al. (1994) Lifetime and 12-month prevalence of DSM-IIIR psychiatric disorders in the United States: Results from the National Comorbidity Study. Arch Gen Psychiatry 51: 8–19.
17. Manic-Depressive Fellowship (2004) Staying well . . . with bipolar disorder. Relapse Prevention Booklet. London: Produced in Association with the Manic-Depressive Fellowship Sponsored by Eli Lilly and Company. p. 17.
18. De Hert M, Thys E, Magiels G, Wyckaert S (2005) Anything or nothing. Self-guide for people with bipolar disorder. Commentary by P. Grof. Antwerp: Uitgeverij Houtekiet. p. 35.
19. Harris M, Chandran S, Chakroborty N, Healy D (2003) Mood stabilizers: The archaeology of the concept. Bipolar Disord 5: 446–452.
20. Ghaemi NS (2005) Uses and abuses of evidence based medicine in psychiatry. American Psychiatric Association meeting; Atlanta Symposium 37A; May 2005; Atlanta, Georgie, United States. Evidence based psychiatry. What it is and what it is not. Available: http://www.mobiltape.com and http://www.psych.org/edu/other_res/lib_archives/archives/meetings/2005saps.cfm. Accessed 6 March 2006.
21. Tondo L, Baldessarini RJ, Floris G (2001) Long-term clinical effectiveness of lithium maintenance treatment in types 1 and 11 bipolar disorders. Br J Psychiatry 178 (Supplement 41): 184–190.
22. Joukamaa M, Heliovaara M, Knekt P, Aromaa A, Raitasalo R, et al. (2006) Schizophrenia, neuroleptic medication and mortality. Br J Psychiatry 188: 122–127.
23. Healy D (2006) Neuroleptics and mortality: A 50-year cycle: Invited commentary on… schizophrenia, neuroleptic medication and mortality. Br J Psychiatry 188: 128.
24. Brown S, Inskip H, Barraclough B (2000) Causes of the excess mortality of schizophrenia. Br J Psychiatry 177: 212–217.
25. Mortensen PB (2003) Mortality and physical illness in schizophrenia. In: Murray R, Jones P, Susser E, editors. The epidemiology of schizophrenia. Cambridge: Cambridge University Press. pp. 275–287.
26. Osby U, Correia N, Brandt L, et al. (2001) Mortality and causes of death in schizophrenia in Stockholm County, Sweden. Schizophr Res 45: 21–28.
27. Healy D (2004) Shaping the intimate. Influences on the experience of everyday nerves. Soc Stud Sci 34: 219–245.
28. Storosum JG, Wohlfarth T, Gispen de Wied CC, Linszen DH, Gersons BP, et al. (2005) Suicide-risk in placebo controlled trials of treatment for acute manic episode and prevention of manic-depressive episode. Am J Psychiatry 162: 799–802.
29. Findling RL, Kowatch RA, Post RM (2003) Pediatric bipolar disorder. A handbook for clinicians. London: Martin Dunitz.
30. Isaac G (2001) Bipolar not ADHD. Unrecognized epidemic of manic-depressive illness in children. Lincoln (Nebraska): Writers Club Press (http://www.iuniverse.com). 102 p.
31. Harris J (2005) The increased diagnosis of juvenile "bipolar disorder," what are we treating? Psychiatr Serv 56: 529–531.
32. Papolos D, Papolos J (2000) The bipolar child. New York: Random House. 416 p.
33. Brooks K (2000 July 19) Families with mentally ill children confront health care shortcomings, undeserved stigma of "bad parenting." Fort Worth Star-Telegram: 1.
34. Mick E, Biederman J, Dougherty M, Aleardi M (2004) Comparative efficacy of atypical antipsychotics for pediatric bipolar disorder [abstract]. Acta Psychiatr Scand 110: 29.
35. Mick E, Biederman J, Aleardi M, Dougherty M (2004) Open trial of atypical antipsychotics in pre-schoolers with bipolar disorder [abstract]. Acta Psychiatr Scand 110: 29.
36. Marson A, Jacoby A, Johnson A, Kim L, Gamble C, et al. (2005) Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: A randomised controlled trial. Lancet 365: 2007–2013.

OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

Pharmaceutical Marketing and the Invention of the Medical Consumer

Kalman Applbaum

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

It is often said that leading drug companies now spend more on marketing than on research and development [1]. While such contemporary pharmaceutical marketing practices are sometimes believed to be a modern phenomenon, they are in fact a direct continuation of 19th-century patent medicine advertising. "Nostrum-mongers," as the novelist Henry James dubbed them, are noted in the history of advertising as having been the leading spenders on, and foremost originators of, advertising technique [2,3]. Nostrum sellers pioneered print advertising, use of trademarks and distinctive packaging, "pull" or demand-stimulation strategies, and even the design and commissioning of medical almanacs that functioned as vehicles for promotion of disease awareness. Henry James's psychologist brother, William James, was so exasperated by "the medical advertisement abomination" that in 1894 he declared that "the authors of these advertisements should be treated as public enemies and have no mercy shown" (see page 235 in [4]).

There is no doubt that drug company discoveries have profoundly improved upon our capacity to treat illness. But pharmaceutical marketing is more closely aligned with consumer marketing in other industries than with medicine, for which the consequences are not trivial. Once we view pharmaceutical industry activities in this light, we can disentangle industry's influence on contemporary medicine. Because we believe that we owe corporations our wealth and well-being, we tend not to question corporations' fundamental practices, and they become invisible to us. What follows is an attempt to demystify some of the assumptions at work in the "culture of marketing," toward the goal of explaining contemporary disease mongering.

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

Beliefs about the Free Market

There are three beliefs commonly associated with the "free market." The first is that human beings are creatures of limitless but insatiable needs, wants, and discomforts. The second is that the free market is a place where these needs might be satisfied through the exercise of free choice. The last of these beliefs is that the surest avenue to innovation in all industries is unfettered competition in the market.

Insatiable needs. The anthropologist Marshall Sahlins theorizes that the belief in unlimited wants is unique in the West, and stems from the Christian notion of "fallen man" as sufferer. This results, says Sahlins, in a peculiar idea of the person "as an imperfect creature of need and desire, whose whole earthly existence can be reduced to the pursuit of bodily pleasure and the avoidance of pain" [5]. A historical and philosophical examination of professional marketing shows that an assumption of boundless needs and wants is also at the heart of marketing theory. In this sense, marketing can be regarded as the institutionalization of this view of human nature. The marketer's challenge is to translate those limitless needs into profits.

Sahlins also points out that "in the world's richest societies, the subjective experience of lack increases in proportion to the objective output of wealth" [6]. In other words, the richer we get, the more we want. One explanation of this paradox lies in the way marketing activities are instrumental in getting us to think more about what we lack. Marketers and advertisers project and reflect back to us our discontent with the status quo. Americans are said to spend, on average, three years of their lives watching television advertisements, and the effect is that they are conditioned to want more and more. According to the advertisements, the viewer's personal anxieties and dissatisfactions are best addressed by consumption. This same message lies at the heart of much pharmaceutical advertising.

DOI: 10.1371/journal.pmed.0030189.g001

Pills are often marketed as a solution to human anxieties and dissatisfactions

Lifestyle choices. In a consumer society, when individuals make choices toward the satisfaction of their needs and wants, they experience this as constructing their own individuality

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

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

Citation: Applbaum K (2006) Pharmaceutical marketing and the invention of the medical consumer. PLoS Med 3(4): e189.

DOI: 10.1371/journal.pmed.0030189

Kalman Applbaum teaches medical anthropology at the University of Wisconsin Milwaukee, Milwaukee, Wisconsin, United States of America. KA is the author of *The Marketing Era: From Professional Practice to Global Provisioning* (Routledge 2004). E-mail: applbaum@uwm.edu

and identity. This special consumer identity is what people refer to when they use the word lifestyle, though they may not realize the consumerist implications of the word. Marketing claims to provide a solution to the problem of unlimited needs and wants, while simultaneously enhancing free choice and the construction of lifestyle.

In pharmaceuticals specifically, "lifestyle drug" marketing techniques were honed in the 1980s and 1990s for cosmetic and sexual enhancements [7,8]. These techniques have been broadened to include other areas of medicine. The campaigns used to market cosmetic and sexual enhancements were focused on expanding perceived need for these products, and in this respect were a simple extension of customary marketing conduct that had existed for over half a century. The crossover to curative medicine occurred with psychotropic drugs, which have a very wide range of active properties, thus granting the marketer latitude in reinterpreting their value back to the consumer. For example, one class of antidepressants, the specific serotonin reuptake inhibitors, is marketed for eight distinct psychiatric conditions, ranging from social anxiety disorder to obsessive-compulsive disorder to premenstrual dysphoric disorder. And "lifestyle marketing" has now extended to the promotion of many of the blockbuster "maintenance drugs" intended for daily, lifelong consumption, such as drugs for allergies, insomnia, and acid reflux.

As a result of this sequence of events, industry opened the treatment of the inside of the body—the final frontier—to the same logic that governs all other marketing. Whether, in the antidepressant market, the "distribution channel captain," as marketers refer to the predominant competitor, ends up sailing the serotonin reuptake channel (the serotonin reuptake inhibitors) or the norepinephrine reuptake channel (the challenger, serotonin–norepinephrine reuptake inhibitors) may yet be determined by marketing rather than by medical jockeying.

Competition among drug companies yields innovation. It is an article of faith among free market devotees that breakthroughs spring not from paternalistic expert systems such as medicine but from industrial competition. As long as firms are committed to producing medications to treat diseases—as they are classified by medical science—this argument has some authority. But once a firm becomes principally driven by marketing—the case for most companies in most industries since the 1980s—then innovation comes to mean an elaboration of meaningless differences among a field of comparable "me too" products. "If marketing is seminally about anything," said Theodore Levitt, one of the towering figures of marketing and former editor of the *Harvard Business Review*, " it is about achieving customer-getting distinction by differentiating what you do and how you operate" [9]. More harmfully, expanding and altering the consumer's perception of disease is just as effective, and evidently a lot easier, than finding new cures.

An assumption of boundless needs and wants is at the heart of marketing theory.

From Patients to Medical Consumers

Since, in a consumer society, we see ourselves as individuals and as free agents when we exercise consumer choice, it is not difficult for pharmaceutical companies and other privatized health-care deliverers to convince us that it is empowering to think of ourselves not as patients but as consumers. This conversion from patient to consumer also paves the way for the erosion of the doctor's role as expert. A startling report of this was described in a recent *New York Times* article: "For a sizable group of people in their 20's and 30's, deciding on their own what drugs to take—in particular, stimulants, antidepressants and other psychiatric medications—is becoming the norm. Confident of their abilities and often skeptical of psychiatrist's expertise, they choose to rely on their own research and each other's experience in treating problems like depression….A medical degree, in their view, is useful but not essential" [10]. This phenomenon, the article suggested, is "driven by familiarity" with the drugs. The emergence of this potentially dangerous situation demonstrates an unchecked expansion of the drug industry into an already accepted mode of thought—that "every minor mood fluctuation," as the article reported, can and should be remedied.

Promoting consumer familiarity with drugs is one example of the very broad influence of the pharmaceutical industry. This influence extends to clinical trial administration, research publication, regulatory lobbying, physician and patient education, drug pricing, advertising and point-of-use promotion, pharmacy distribution, drug compliance, and the legal and ethical norms by which company practices themselves are to be evaluated. Actors traditionally found outside the "distribution channel" of the market are now incorporated into it as active proponents of exchange. Physicians, academic opinion leaders, patient advocacy groups and other grass roots movements, nongovernmental organizations, public health bodies, and even ethics overseers, through one means or another, have one by one been enlisted as vehicles in the distribution chain. The inclusion of patients in the distribution chain fundamentally changes their role from recipients of medical care to active consumers of the latest pharmaceuticals, a role which surely helps to support industry profits.

Ethical Justification for Marketing

Because illness is one of the most tangible forms of suffering, the pharmaceutical industry, more than other industries, can link its marketing activities to ethical objectives. The result is a marriage of the profit-seeking scheme in which disease is regarded as "an opportunity" to the ethical view that mankind's health hangs in the balance. Marketers and consumers in the West to some extent share a common vision of needs and the terms of their satisfaction. This apparent complicity helps even the most aggressive marketers trust that they are performing a public service. Pharmaceutical company managers that I speak to signal this when they characterize their engagement with the public as "doing good while doing well."

These managers also see nothing wrong with integrating doctors, patients, and other players into the drug distribution channel. On the contrary, they say, this is state-of-the-art management, making it professionally principled and tactically astute. Marketers also regard the incorporation of consumers into the channel as ethical because then people's needs can best be determined and satisfied, conferring upon them the power of self-determination through choice.

But this choice is an illusion. For in our pursuit of a near-utopian promise of perfect health, we have, without realizing it, given corporate marketers free reign to take control of the true instruments of our freedom: objectivity in science, ethics and fairness in health care, and the privilege to endow medicine with the autonomy to fulfill its oath to work for the benefit of the sick. ■

References

1. Angell M (2004) Over and above: Excess in the pharmaceutical industry CMAJ 171: 1451.
2. Young JH (1961) The toadstool millionaires: A social history of patent medicines in America before federal regulation. Princeton (New Jersey): Princeton University Press. 282 p.
3. Lears J (1994) Fables of abundance: A cultural history of advertising in America. New York: Basic Books. 512 p.
4. Laird PW (1998) Advertising progress: American business and the rise of consumer marketing. Baltimore (Maryland): Johns Hopkins University Press. 480 p.
5. Sahlins M (1994) Cosmologies of capitalism: The trans-pacific sector of "The World System." In: Eley G, Dirks NB, Ortner SB, eds. Culture/power/history: Reader in contemporary social theory. Princeton (New Jersey): Princeton University Press. pp. 412–456.
6. Sahlins M (1996) The sadness of sweetness: The native anthropology of Western cosmology. Curr Anthropol 37: 395–428.
7. Lexchin J (2006) Bigger and better: How Pfizer redefined erectile dysfunction. PLoS Med 3: e132. DOI: 10.1371/journal.pmed.0030132
8. Tiefer L (2006) Female sexual dysfunction: A case study of disease mongering and activist resistance. PLoS Med 3: e178. DOI: 10.1371/journal.pmed.0030178
9. Levitt T (1986) The marketing imagination. New York: Free Press. 238 p.
10. Harmon A (2005 November 16) Young, assured and playing pharmacist to friends. New York Times. Available: http://www.nytimes.com/2005/11/16/health/16patient.html?ex=1289797200&en=ecbeab25b58126c4&ei=5088&partner=rssnyt&emc=rss. Accessed 6 March 2006.

OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

Combating Disease Mongering: Daunting but Nonetheless Essential

Iona Heath

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

The challenge of combating the current epidemic of disease mongering is daunting, and anyone looking for ready solutions should read no further. Those seeking a way forward find themselves ranged against powerful economic, political, and professional interests. There is an apparently limitless amount of money to be made from marketing pharmaceutical remedies for diseases and even more from remedies to reduce risk factors for disease. An emphasis on the treatment of disease minimises political responsibility for those fundamental causes of disease that are located within the structure of society, and substantial and lucrative professional careers have been built on the endless pursuit of new diseases or risk factors for disease.

More fundamentally, disease mongering exploits the deepest atavistic fears of suffering and death. Throughout history, humanity has kept such fears at bay by accepting burdens and sacrifices in the present in the hope of future salvation. In earlier times, the mediator was religion and the salvation was to come after death. Now, for those without religious belief, death has become more final, and salvation must be sought before death in an ever-expanding longevity. An adequate response to the false hopes raised by disease mongering will demand, from those in positions of power and influence, an ability to acknowledge, accommodate, and move beyond these profound existential fears [1]. Such ability is rare.

The way forward will rely on a capacity to rediscover courage and stoicism as both private and civic virtues, alongside seeking a radical realignment of the relationship between economic, political, and professional interests. Doctors and biomedical scientists, in particular, have a responsibility not only to put their own house in order but to provide much better advice to politicians and to the public, both as patients and as citizens.

The Challenge to Professionals

The first step has to be a genuine disentanglement of the medical profession from the pharmaceutical industry—there really is no such thing as a free lunch [2]. The pharmaceutical industry spends millions of dollars supporting the "education" of doctors because it is in its economic interest to do so (Figure 1). If prescribing activities and industry profits were not affected by this support, it would not be offered. Doctors can only provide appropriately independent and authentic advice to patients and, indeed, to politicians if they are seen to be completely independent of other powerful interests. Politicians genuinely interested in the welfare of patients and the health of citizens should actively promote such independence [4].

Disease mongering exploits the deepest atavistic fears of suffering and death.

Beyond this, there is a need for better science that has the integrity to demand more explicit acknowledgment of the limits of medical knowledge, less extrapolation beyond research findings, and much more responsible use of statistics, so that the true extent of the benefits and harms of proposed treatments can be properly understood.

The rhetoric surrounding disease mongering suggests that it will promote health, but the effect is in fact the opposite. Much disease mongering relies on the pathologising of normal biological or social variation and on the portrayal of the presence of risk factors for disease as a disease state in itself. When pharmaceuticals are used to treat risk factors, the vicious circle is completed because "anyone who takes medicines is by definition a patient" [5].

Most variables are distributed across a continuum, but despite this, the medical tradition has been to dichotomise the continuum into normal and abnormal [6]. Within a continuum, there can never be a clear boundary, so the definition of disease is inevitably both arbitrary and fluid. It is in the interests of pharmaceutical companies to extend the range of the abnormal so that the market for treatments is proportionately enlarged. We have seen this process operating, for example, in the continual lowering of thresholds for treatment of blood pressure and lipids—the most recent guidelines from the European Society of Cardiology can be used to identify 76% of the total adult population of a county of Norway as being at "increased risk" [7].

We need to reverse this situation so that instead of defining an arbitrary threshold of abnormality, governments

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

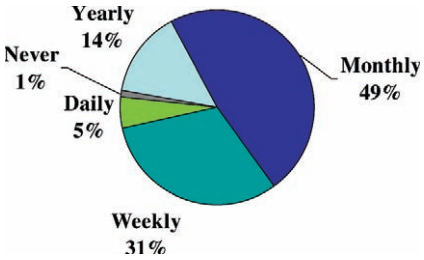
Funding: The author received no specific funding for this article.

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

Citation: Heath I (2006) Combating disease mongering: Daunting but nonetheless essential. PLoS Med 3(4): e146.

DOI: 10.1371/journal.pmed.0030146

Iona Heath is a general practitioner at the Caversham Practice, London, United Kingdom. E-mail: iona.heath@dsl.pipex.com



DOI: 10.1371/journal.pmed.0030146.g001

Figure 1. Percentage of Doctors That Use Information Provided by Drug Company Representatives in Their Clinical Practice
Data derived from [3].
(Image: Adapted from a slide presentation created by No Free Lunch, http://www.nofreelunch.org/downloads/Nofreelunch%20Presentation.ppt)

would make a judgement about the appropriate level of investment in preventive technologies for currently healthy populations, and set the thresholds for intervention accordingly. For example, a government might decide to treat the 10% of the population most at risk of ischaemic heart disease, and could then calculate the thresholds of blood pressure and cholesterol, which would identify this most vulnerable 10% of the population. Clearly, these thresholds would be much higher than those recommended today.

Preventing Disease through Population-Based Measures

The seeds of the current situation were already present 21 years ago, when Geoffrey Rose wrote his seminal paper entitled "Sick individuals and sick populations" [4]. In this paper, he showed that risk factors for health are almost always distributed across a bell curve and argued that more could be achieved by attempting to shift the whole of the bell curve than by targeting those at highest risk (Figure 2). His rationale was that the large number of people at low risk may give rise to more cases of disease than the small number who are at high risk. There has been general acceptance of this argument, but Rose's own warnings seem to have been lost.

Rose was careful to list the *disadvantages* of attempting to shift the whole bell curve, which included (1) a "worrisome" benefit–risk ratio (there is only a small possibility of benefit for any one individual, but everyone is exposed to the intervention and thereby to any adverse effects, such as medicalisation, anxiety, and side effects of treatments) and (2) poor motivation on the part of individual patients, each of whom had a very small chance of benefit. These predicted disadvantages have become more and more apparent, so there has been a systematic attempt to improve motivation through the explicit use of fear, which in itself erodes and undermines health. "If you don't take more exercise, improve your diet or take this medication, you actively put yourself at risk of an untimely death."

Rose was also very careful to distinguish between two approaches to shifting the bell curve. The first restores biological normality by preventing exposure to hazards such as tobacco smoke or industrial air pollution. The second approach is to interpose some new, supposedly protective intervention, but this is much less robust because it leaves the underlying causes intact. The current use of pharmaceuticals for public health policy falls into this category. As more and more risk factors are identified, closely followed by a pharmaceutical treatment for each, the ambition to shift the whole bell curve legitimises the wholesale drug treatment of healthy populations at vast expense and with huge pharmaceutical profits. There is a clear need to reiterate Rose's distinction and prioritise the reduction of exposure to biological hazards above the application of pharmaceutical prophylaxis.

Current trends raise the prospect of exponential spending on preventive pharmaceuticals, justified by potential long-term benefits to an unidentifiable, but statistically significant, number of people in the population. When doctors treat patients with diseases, progress can be assessed and the outcome is measurable. This means that if the patient responds to treatment, it can be continued; if not, the treatment can be stopped. When doctors treat people who are merely at risk of disease, the outcome is probabilistic, so whether disease is prevented or was never going to develop, the treatment continues indefinitely [9].

Shifting the bell curve through population-based interventions aimed at protecting health is part of a long and magnificent tradition which began when John Snow capped the Broad Street pump; shifting the bell curve through the mass pharmaceutical treatment of individuals turns out to be something quite different. Further, where individualised solutions become prevalent, societal, population-based interventions tend to fall away, and the result is worsening health inequalities.

The medical profession needs to do much more to define sensible limits to medical intervention. There is a clear and urgent need for more research into the psychological impact and the wider health consequences of being labelled "at risk" [10]. Doctors, and society as a whole, need to stop confusing health with happiness [11]. This confusion is at the root of much of the medicalisation of normal human variation that we are witnessing. Male pattern baldness and shyness, to take just two examples, are not diseases but normal parts of the range of human experience. We are witnessing diagnostic drift in a whole range of conditions, from depression [12] to hypertension [13], with pressure for more and more people to be included within the range of abnormal and offered treatment. The justification for these treatments is often based on short-term studies, which are then extrapolated over much longer time periods. There is insufficient recognition of the fact that the less the need for treatment, the higher the number needed to treat for given outcomes and the higher the risk to patients, since the rate of adverse effects remains constant.

The Challenge to Politicians

Politicians are charged with overseeing the organisation of society for the benefit of all. A major political achievement of Western societies, with the very notable exception of the United States, has been the provision of universal health-care systems available and accessible to all. There is now a pressing need for politicians to recognise the threat to these systems, and to the social solidarity that they embody, posed by exponential increases in pharmaceutical expenditure. No universal health-care system funded by taxation can pay for the pharmaceutical treatment of all risks to health. There are very difficult decisions to be made, but politicians must balance the wish to support a vibrant and innovative

pharmaceutical industry—and the undoubted economic, employment, and therapeutic benefits that drug companies bring—against the increasing capacity of this industry to bankrupt universal health-care systems.

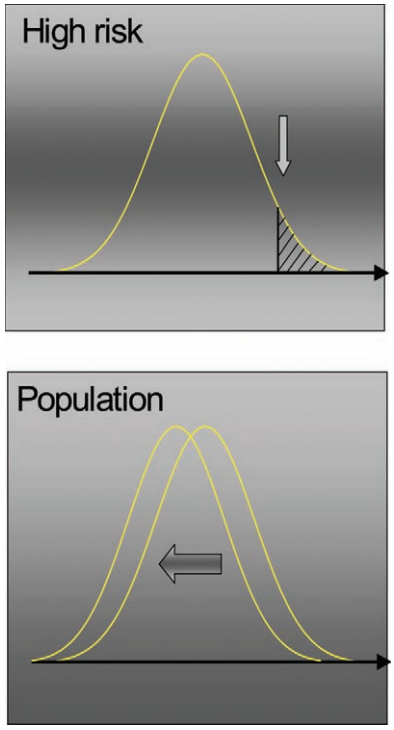
Part of the rationale for expenditure on the treatment of health risks is that it will reduce health costs in the long run, but such arguments do not stand up to close scrutiny. The costs of health care are highest during the year before death, regardless of the age at which death occurs. Everyone must die and be cared for while dying, and no amount of preventive pharmaceuticals can reduce the cost of providing this crucial end-of-life care [14]. The aim of preventive health care should be the reduction of untimely deaths in relatively young people, but the fear of accusations of ageism in health care means that doctors are encouraged to go on prescribing preventive pharmaceuticals to people well into their late eighties and nineties [15].

In any system of health care predicated on social solidarity, the rights of individuals to treatment have to be balanced against the duties of citizens to provide the appropriate level of funding. Citizens agree to pay tax for the care of those who are sick, with the understanding that they, too, will be cared for should they, in turn, become sick. It remains unclear how far this pact of social solidarity extends to paying for the treatment of risk factors and marginal "diseases", where the benefits in terms of reducing suffering are much less clear. Publicly funded preventive treatment of risk factors for those who have already exceeded the average life expectancy seems particularly hard to justify.

Socioeconomic deprivation has been described as a "fundamental cause" of disease, which works through a multiplicity of risk factors and pathophysiological pathways to produce multiple disease states [16]. Even if one of these pathways is interrupted by the application of a preventive technology, an association between a fundamental cause and disease will reappear in a different form. The closer to the individual the intervention is situated, the less likely the improvement in health status is to be maintained.

In mental health problems, we see this process operating when people are helped to cope with poor housing and lack of rewarding employment through the provision of counselling, rather than better social conditions. Population-based interventions favour the poor because such interventions are applied universally and the poor are the most at-risk; individually based interventions favour the rich because they are more likely to make use of what is offered. For this reason, population approaches to tackling the fundamental causes of socioeconomic deprivation must remain the most effective way of tackling health inequalities [17]. However, there is also a continuing role for individually based treatment of those at the highest risk of particular diseases, but this must be effectively targeted if inequalities are not to be exacerbated.

Age is another fundamental cause of disease, less remediable than poverty but again generating multiple risk factors and multiple disease outcomes. All clinicians are familiar with the processes by which treating one disease in a frail, older person will often mean that symptoms reappear through another pathway. Authentic health care for the old and frail has much more to do with helping to preserve their dignity, treating them with affection, and supporting their continued involvement in social activities, rather than the pursuit of ever-more elusive cures. Politicians have a responsibility, alongside doctors and many others, to make such care available, and this in itself will be an important part of the way forward.



DOI: 10.1371/journal.pmed.0030146.g002

Figure 2. Risk Factors for Health Are Almost Always Distributed across a Bell Curve

Geoffrey Rose argued that more could be achieved by attempting to shift the whole of the bell curve (the "population approach" to prevention) than by targeting those at highest risk (the "high-risk" approach).
(Image: Adapted from a figure by John Emberson from [8])

The huge amount of money that can be made from preventive technologies has diminished the economic importance of treatment technologies, particularly for those illnesses that primarily affect poorer people in poorer countries [18]. This has meant a shift of attention from the sick to the well and from the poor to the rich [19]. This effect of global markets requires a response in the form of an assertion of global human solidarity. Health inequalities matter globally as well as locally. A way forward might be through taxation or other means, to make the sale of preventive technologies in countries with above-average expectation of life conditional on the availability of treatment for those diseases that cause the most catastrophic shortening of life in poor countries.

Conclusion

Human societies are riven by the effects of greed and fear. The rise of preventive health technologies has opened up a new arena of human greed, which responds to an enduring fear. The greed is for ever-greater longevity; the fear is that of dying. The irony and the tragedy is that the greed inflates the fear and poisons the present in the name of a better, or at least a longer, future. Ultimately, the only way of combating disease mongering is to value the manner of our living above the timing of our dying. ■

References

1. Barnard D (1988) Love and death: Existential dimensions of physicians' difficulties with moral problems. J Med Philos 13: 393–409.
2. Abbasi K, Smith R (2003) No more free lunches. BMJ 326: 1155–1156.
3. Caudill TS, Johnson MS; Rich EC, McKinney WP (1996) Physicians, pharmaceutical sales representatives, and the cost of prescribing. Arch Fam Med 5: 201–206.
4. Moynihan R (2003) Who pays for the pizza? Redefining the relationship between doctors

and drug companies. 2: Disentanglement. BMJ 326: 1193–1196.
5. Rose G (1985) Sick individuals and sick populations. Int J Epidemiol 14: 32–38.
6. McKinlay JB, Marceau LD (1999) A tale of 3 tails. Am J Public Health 89: 295–298.
7. Getz L, Kirkengen AL, Hetlevik I, Romundstad S, Sigurdsson JA (2004) Ethical dilemmas arising from implementation of the European guidelines on cardiovascular disease prevention in clinical practice. Scand J Prim Health Care 22: 202–208.
8. Makover ME, Ebrahim S (2005) What is the best strategy for reducing deaths from heart disease? PLoS Med 2: e98. DOI: 10.1371/journal.pmed.0020098
9. O'Donnell JL, Smyth D, Frampton C (2005) Prioritizing health-care funding. Intern Med J 35: 409–412.
10. Getz L, Sigurdsson JA, Hetlevik I (2003) Is opportunistic disease prevention in the consultation ethically justifiable? BMJ 327: 498–500.
11. Saracci R (1997) The World Health Organisation needs to reconsider its definition of health. BMJ 314: 1409–1410.
12. Dowrick C (2005) Beyond depression. Oxford: Oxford University Press. 240 p.
13. Woodman R (1999) Open letter disputes WHO hypertension guidelines. BMJ 318: 893.
14. Higginson IJ (1999) Evidence-based palliative care. BMJ 319: 462–463.
15. Health and Social Care Information Centre (2006) Quality and outcomes framework information. London: Health and Social Care Information Centre. Available: http://www.ic.nhs.uk/services/qof. Accessed 10 February 2006.
16. Link BG, Phelan J (1995) Social conditions as fundamental causes of disease. J Health Soc Behav 1995 (Spec No.): 80–94.
17. McAlister A, Puska P, Salonen JT, Tuomilehto J, Koskela K (1982) Theory and action for health promotion: Illustrations from the North Karelia Project. Am J Public Health 72: 43–50.
18. Freemantle N, Hill S (2002) Medicalisation, limits to medicine, or never enough money to go around? BMJ 324: 864–865.
19. Heath I (2005) Who needs health care—The well or the sick? BMJ 330: 954–956.

OPEN ACCESS Freely available online

PLoS MEDICINE

Policy Forum

Giving Legs to Restless Legs: A Case Study of How the Media Helps Make People Sick

Steven Woloshin☯*, Lisa M. Schwartz☯

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

"[Restless legs syndrome] is quite a serious sleep disorder that affects a lot of people....Their sleep is disturbed and, unless they are really awake, they will not be aware of it" [1].

Life can be hard. Sometimes you feel sad or distracted or anxious. Or maybe you feel a compelling urge to move your legs. But does that mean you are sick? Does it mean you need medication?

Maybe, maybe not. For some people, symptoms are severe enough to be disabling. But for many others with milder problems, these "symptoms" are just the transient experiences of everyday life. Helping sick people get treatment is a good thing. Convincing healthy people that they are sick is not. Sick people stand to benefit from treatment, but healthy people may only get hurt: they get labeled "sick," may become anxious about their condition, and, if they are treated, may experience side effects that overwhelm any potential benefit.

"Disease mongering" is the effort by pharmaceutical companies (or others with similar financial interests) to enlarge the market for a treatment by convincing people that they are sick and need medical intervention [2]. Typically, the disease is vague, with nonspecific symptoms spanning a broad spectrum of severity—from everyday experiences many people would not even call "symptoms," to profound suffering. The market for treatment gets enlarged in two ways: by narrowing the definition of health so normal experiences get labeled as pathologic, and by expanding the definition of disease to include earlier, milder, and presymptomatic forms (e.g., regarding a risk factor such as high cholesterol as a disease in itself).

Discussions about disease mongering usually focus on the role of pharmaceutical companies—how they promote disease and their products through "disease awareness" campaigns and direct-to-consumer drug advertising, and by funding disease advocacy groups. But diseases also get promoted in another way: through the news media. News reports are a major source of health information for people [3]. Unless journalists approach stories about new diseases skeptically and look out for disease mongering by the pharmaceutical industry, pharmaceutical consultants, and advocacy groups, journalists, too, may end up selling sickness.

The Policy Forum allows health policy makers around the world to discuss challenges and opportunities for improving health care in their societies.

What Is Restless Legs Syndrome?

The diagnosis of restless legs syndrome requires the presence of the following four criteria [4]:

- An urge to move the legs due to an unpleasant feeling in the legs.
- Onset or worsening of symptoms when at rest or not moving around frequently.
- Partial or complete relief by movement (e.g., walking) for as long as the movement continues.
- Symptoms that occur primarily at night and that can interfere with sleep or rest.

The severity of disease is judged by the frequency of these symptoms, which can range from less than once a month to many times a day. Recommended treatments include stretching exercises and less caffeine for intermittent disease and various prescription drugs (e.g., benzodiazepines and dopamine agonists) for daily symptoms [5].

The Case of Restless Legs Syndrome

To get a sense of how the media works in the context of a major disease promotion effort, we examined news coverage of "restless legs" (see sidebar). In 2003, GlaxoSmithKline launched a campaign to promote awareness about restless legs syndrome, beginning with press releases about presentations at the American Academy of Neurology meeting describing the early trial results of using ropinirole (a drug previously approved for Parkinson disease) for the treatment of restless legs [6,7]. Two months later, GlaxoSmithKline issued a new press release entitled "New survey reveals common yet under recognized disorder—restless legs syndrome—is keeping Americans awake at night"

Funding: SW and LMS were supported by Robert Wood Johnson Generalist Faculty Scholar Awards. This study was supported by a grant from the National Cancer Institute (R01CA104721) and from a Research Enhancement Award from the Department of Veterans Affairs. The views expressed herein do not necessarily represent the views of the Department of Veterans Affairs or the United States government.

Competing Interests: The funders played no role in the submission or preparation of this paper. The authors have declared that no competing interests exist.

Citation: Woloshin S, Schwartz LM (2006) Giving legs to restless legs: A case study of how the media helps make people sick. PLoS Med 3(4): e170.

DOI: 10.1371/journal.pmed.0030170

Abbreviation: FDA, Food and Drug Administration

Steven Woloshin and Lisa M. Schwartz are at the Veterans Affairs Outcomes Group, White River Junction, Vermont, United States of America, and the Center for the Evaluative Clinical Sciences, Dartmouth Medical School, Hanover, New Hampshire, United States of America.

* To whom correspondence should be addressed. E-mail: steven.woloshin@dartmouth.edu.

☯ These authors contributed equally to this work.

Table 1. Key Elements of Disease Mongering and How the Media Could Do Better

Key Elements of Disease Mongering	When the Media Can Get Co-opted	Suggestions for Doing Better
Exaggerate the prevalence of disease		
Create a broad disease definition based on vague and prevalent symptoms.	Uncritically accepts disease definition.	Learn exact definition of disease and question whether it is appropriately specific.
Publicize a large prevalence estimate.	Uncritically repeats a broad prevalence estimate.	Determine whether the prevalence estimate is credible: Are the "gold standard" diagnostic criteria being used as designed? Does the sample truly represent the general population?
Blur the distinction between mild and severe disease.	Highlights the important physical, social, and emotional consequences of severe disease; only telling anecdotes of people with very severe disease.	Be clear about the spectrum of disease. When describing important consequences or personal anecdotes, provide the appropriate prevalence estimate by stating proportion with disease this severe.
Encourage more diagnosis		
Highlight that doctors fail to recognize disease.	Quotes an "expert" about how doctors miss the diagnosis; provides anecdotes of people whose diagnoses were missed.	Acknowledge the problems of overdiagnosis (e.g., downside of labeling people with disease or medicalizing healthy people).
Encourage people to see themselves as sick.	Presents anecdotes or descriptions of people who are unaware that they are sick; encourages self-diagnosis (e.g., symptom checklist).	Same as above.
Promote disease awareness (e.g., disease awareness week, screening clinics, support groups, disease foundations).	Publicizes disease awareness activities without noting industry involvement (e.g., "nonprofit" foundation).	Learn and state whether disease awareness activities are industry sponsored.
Suggest that all disease should be treated		
Exaggerate the benefits of the drug for everyone with disease.	Overstates the benefit by providing only qualitative descriptions (e.g., only stating "significant improvement" or telling stories of dramatic benefit).	Objectively report benefit by quantifying how well the drug works (e.g., present the proportion with clinically important symptom improvements in the drug and comparison group). Be clear about the populations studied (i.e., acknowledge that the benefit is much smaller for people with mild disease).
	Overstates the benefit by using miracle language to describe the benefit.	Avoid miracle language.
	Overstates the benefit by quoting a strong claim of benefit from researchers with strong industry ties.	Learn and state industry ties of researchers who make strong claims about a drug's benefit.
Imply that there is no downside to treatment.	Minimizes the harms by not mentioning the possibility of them or by only telling stories of people who did not experience any harms.	Quantify side effects (e.g., present the proportion with side effects in the drug and comparison group).
Imply that long- term treatment is safe and effective.	Ignores concerns about duration of clinical trials (e.g., not mentioning length of follow-up).	Caution readers that although treatment is generally long term, the longest study was x weeks. So, the long-term benefits and harms are unknown.

DOI: 10.1371/journal.pmed.0030170.t001

about an internally funded and, at the time, unpublished study [8]. In 2005, the US Food and Drug Administration (FDA) approved ropinirole for the treatment of restless legs syndrome (the first drug approved specifically for this indication). Since then, the restless legs campaign has developed into a multimillion dollar international effort to "push restless legs syndrome into the consciousness of doctors and consumers alike" [9].

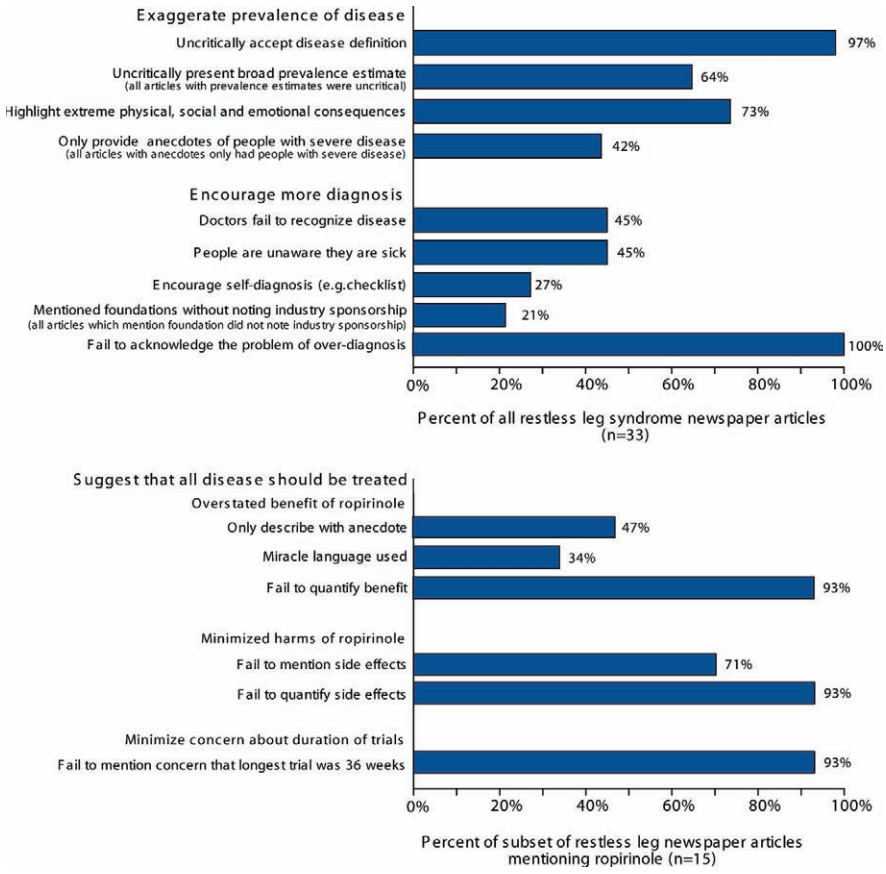
Newspaper Coverage of the Restless Legs Syndrome

To identify media coverage related to this campaign over two years (November 2003–November 2005), we did full-text searches of "major newspapers" in Lexis-Nexis and ProQuest databases and found 187 unique articles with the phrase "restless legs." We excluded articles not about the syndrome (e.g., "Elvis's restless legs"), nonnews stories (e.g., health advice columns, notices of restless legs health screenings/support groups), and articles with only passing mention of restless legs (most of these were about sleep disorders, another "new yet largely unrecognized problem"). We analyzed the remaining 33 articles (all focused on restless legs syndrome) using an explicit coding scheme organized around the key elements of disease mongering, as outlined in the first column of Table 1: exaggerating the prevalence of the disease (e.g., uncritically accepting a broad prevalence estimate), encouraging more diagnosis (e.g., doctors fail to recognize it), and suggesting that all disease should be treated (e.g., overstating the benefits or minimizing the harms of treatment).

Exaggerating Disease Prevalence

Figure 1 shows that the news articles often included elements exaggerating disease prevalence. Only one article questioned the disease definition at all (and portrayed the act of questioning the definition as insensitive: "[the patient] knows it can sound trivial. That's one of the problems with restless legs. Radio show host Rush Limbaugh, for example, has mocked it as a pseudoillness" [10]).

Almost two-thirds of articles provided an estimate of disease prevalence (most commonly, statements such as "at least 12 million Americans suffer from the syndrome" [11] or "[it] affects 1 in 10



DOI: 10.1371/journal.pmed.0030170.g001

Figure 1. Frequency of Key Elements of Disease Mongering in Newspaper Articles

Top bar graph analyzes all articles about restless legs syndrome. Bottom bar graph analyzes the subset that mentions ropinirole.

adults in the United States" [12]). No article questioned the validity of the prevalence estimates. In fact, there are reasons to believe the estimates overstate the prevalence of clinically meaningful disease. For example, the frequently cited 10% estimate came from a study that used a single question to identify restless legs syndrome rather than the four standard criteria [13]. The less stringent definition inflates the estimate because people with other causes of leg symptoms (e.g., leg cramps or diabetic neuropathy) are counted incorrectly as having the syndrome.

In a recent large study, only 7% of respondents reported all four diagnostic criteria, and only 2.7% reported moderately or severely distressing symptoms two or more times per week (i.e., the group for whom medical treatment might be appropriate) [14]. Even the 2.7% estimate is probably too high, because of bias inherent in the study sample. The authors claimed an implausible 98% response rate to their random-digit dial survey (typical response rates are 50%–70% [15]). Most likely, the authors meant that 98% of individuals who agreed to participate completed the survey. But respondents agreeing to participate in a restless legs study are more likely to have leg-related symptoms than nonrespondents.

Nearly three-quarters of newspaper articles highlighted the potentially serious physical, social, and emotional consequences of restless legs: "…the condition sounds like a joke, but its consequences can be devastating. Driven to despair by years of sleepless nights, patients have become suicidal" [16]). While over 40% of the articles provided anecdotes about people with severe disease, no article provided anecdotes about people who did not find their symptoms especially bothersome.

Encourage More Diagnosis

The articles also reinforced the need for more diagnosis. About half reported that the syndrome is underdiagnosed by physicians ("…relatively few doctors know about restless legs. This is the most common disorder your doctor has never heard of" [17]) and underrecognized by patients ("…many people can suffer in silence for years before it is recognized" [18]). One-quarter of articles encouraged patient self-diagnosis and suggested people ask their doctor whether restless legs might explain various problems (including insomnia, daytime fatigue, attention deficit disorder in children, and depression). One-fifth of articles referred readers to the "nonprofit" Restless Legs Foundation for further information; none reported that the foundation is heavily subsidized by GlaxoSmithKline. No article acknowledged the possibility of overdiagnosis (the idea that some people will be diagnosed unnecessarily and take medication they do not really need).

Suggest That All Disease Should Be Treated

About half the news stories mentioned the drug ropinirole by name. Only one story quantified the drug's benefit. By contrast, about half the stories mentioning ropinirole included anecdotes about patients who took the drug (and in most cases noted substantial improvement). One-third of articles used "miracle language" to describe patient response to medication (e.g., "it has been a miracle drug for me" [19]). The actual benefit of the drug is modest. The drug label reports that in a 12-week US clinical trial, restless legs symptom scores (measured on a 40-point scale) improved by 13.5 points for patients taking ropinirole compared with 9.8 points for those taking placebo [20]. In more clinical terms, 73% taking ropinirole responded to the drug (i.e., restless legs scores improved by six points) compared with 57% taking placebo.

The drug label [20] also notes that ropinirole has a number of side effects, including nausea (40% in ropinirole group versus 8% in placebo group) and dizziness (11% versus 5%, respectively). Somnolence and fatigue (ostensibly, the real target of the drug) were also higher in the ropinirole versus the placebo group (12% versus 6%; 8% versus 4%, respectively). Nonetheless,

only five of the 15 articles mentioning ropinirole noted that it could have side effects and just one quantified the chance of any side effect ("nausea was the most common side effect, reported in 38% of patients" [18]). Finally, only one news story noted that the ropinirole trials were "relatively short" in duration (the longest was 36 weeks), despite the fact that many people would use the drug for years or even a lifetime.

Suggestions for How the Media Could Do Better

Unfortunately, there is no obvious way to distinguish information from infomercial. In Table 1, we highlight clues that should alert journalists to the presence of disease mongering, and suggest some things they can do to expose these efforts.

First, journalists should be very wary when confronted with a new or expanded disease affecting large numbers of people. If a disease is common and very bothersome, it is hard to believe that no one would have noticed it before. Prevalence estimates are easy to exaggerate by broadening the definition of disease. Journalists need to ask exactly how the disease is being defined, whether the diagnostic criteria were used appropriately, and whether the study sample truly represents the general population (e.g., patients at an insomnia clinic cannot be taken to represent the general public).

Journalists should also reflexively question whether more diagnosis is always a good thing. Simply labeling people with disease has negative consequences [21]. Similarly, journalists should question the assumption that treatment always makes sense. Medical treatments always involve trade-offs; people with mild symptoms have little to gain, and treatment may end up causing more harm than good.

Finally, instead of extreme, unrepresentative anecdotes about miracle cures, journalists should help readers understand how well the treatment works (e.g., what is the chance that I will feel better if I take the medicine versus if I do not?) and what problems it might cause (e.g., whether I might be trading less restless legs for daytime nausea, dizziness, and somnolence).

Conclusion

The news coverage of restless legs syndrome is disturbing. It exaggerated the prevalence of disease and the need for treatment, and failed to consider the problems of overdiagnosis. In essence, the media seemed to have been co-opted into the disease-mongering process. Although our review was limited to the coverage of a single disease promotion campaign, we think it is likely that our findings would apply to others. It is easy to understand why the media would be attracted to disease promotion stories and why they would be covered uncritically. The stories are full of drama: a huge but unrecognized public health crisis, compelling personal anecdotes, uncaring or ignorant doctors, and miracle cures.

The problem lies in presenting just one side of the story. There may be no public health crisis, the compelling stories may not represent the typical experience of people with the condition, the doctors may be wise not to invoke a new diagnosis for vague symptoms that may have a more plausible explanation, the cures are far from miraculous, and healthy people may be getting hurt.

We think the media could report medical news without reinforcing disease promotion efforts by approaching stories like "restless legs" with a greater degree of skepticism. After all, their job is to inform readers, not to make them sick. ■

Acknowledgments

We would like to thank Elliott Fisher and Brenda Sirovich for helpful comments on earlier drafts.

References

1. Revill J (2004 September 19) Restless legs keep 6m awake. The Observer. Available: http://observer.guardian.co.uk/uk_news/story/0,,1307797,00.html. Accessed 2 March 2006.
2. Moynihan R, Cassels A (2005) Selling sickness. How the world's biggest pharmaceutical companies are turning us all into patients. New York: Nation Books. 254 p.
3. Kaiser Family Foundation (2005) Kaiser health poll report: Public opinion snapshot on health information sources—July 2005. Menlo Park (California): Kaiser Family Foundation. Available: http://www.kff.org/kaiserpolls/pomr071805oth.cfm. Accessed 2 March 2006.
4. Reuters (2005 May 6) Glaxo drug for restless legs syndrome is approved. The New York Times; Sect C: 3.
5. Silber M, Ehrenberg B, Allen R, Buchfuhrer M, Earley C, et al. (2004) An algorithm for the management of restless legs syndrome. Mayo Clin Proc 79: 916–922.
6. GlaxoSmithKline (2003 April 1) Restless legs syndrome can significantly impair quality of life. Research Triangle Park (North Carolina): GlaxoSmithKline. Available: http://www.gsk.com/ControllerServlet?appId=4&pageId=402&newsid=175. Accessed 7 March 2006.
7. GlaxoSmithKline (2003 March 31) Study shows Requip® (ropinirole HCl) improves symptoms of Restless legs syndrome. Research Triangle Park (North Carolina): GlaxoSmithKline. Available: http://www.gsk.com/ControllerServlet?appId=4&pageId=402&newsid=71. Accessed 7 March 2006.
8. GlaxoSmithKline (2003 June 10) New survey reveals common yet under recognized disorder—Restless legs syndrome—is keeping America awake at night. Research Triangle Park (North Carolina): GlaxoSmithKline. Available: http://gsk.com/press_archive/press2003/press_06102003.htm. Accessed 7 March 2006.
9. Rundle RL (2005) Motion sickness: Restless legs syndrome has long been misdiagnosed and misunderstood; that's about to change. The Wall Street Journal; Sect R: 5.
10. Lerner M (2005) Respect, relief for restless legs; pill helps relieve pain and exhaustion for those who suffer from syndrome. Star Tribune, Metro ed; Sect B: 1.
11. O'Connor A (2004 May 25) Restless legs; uncomfortable and overlooked. The New York Times. Available: http://www.nytimes.com/2004/05/25/health/25legs.html?ex=1141448400&en=2bf6d431bc7f2b69&ei=5070. Accessed 2 March 2006.
12. Rackl L (2005 May 23) Drug to calm sleep-robbing leg syndrome okayed by FDA; uncontrollable urge to move limbs affects 1 in 10, runs in families. Chicago Sun-Times. Available: http://www.zoeticzone.com/p/articles/mi_qn4155/is_20050523/ai_n14648506. Accessed 2 March 2006.
13. Phillips B, Young T, Finn L, Asher K, Hening WA, et al. (2000) Epidemiology of restless legs symptoms in adults. Arch Intern Med 160: 2137–2141.
14. Allen R, Walters A, Montplaisir J, Hening W, Myers A, et al. (2005) Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 165: 1286–1292.
15. Groves R, Fowler F, Couper M, Lepkowski J, Singer E, et al. (2004) Survey methodology. Hoboken (New Jersey): John Wiley and Sons. 448 p.
16. Lantin B (2004 December 1) No sleep for those with restless legs. The Daily Telegraph. Available: http://www.telegraph.co.uk/health/main.jhtml?xml=/health/2004/01/12/hrest12.xml.
17. O'Neill P (2004) Restless legs treatments under study in Oregon. The Oregonian; Sect B: 1.
18. Cresswell A (2005) Relief at hand for restless legs. The Weekend Australian; Sect C: 29.
19. Fiely D (2005) Restless legs syndrome; ads for drug raise awareness of annoying condition. The Columbus Dispatch. Home Final Edition ed; Sect G: 1.
20. GlaxoSmithKline (2005) Requip® (ropinirole hydrochloride)—Prescribing information. Research Triangle Park (North Carolina): GlaxoSmithKline. Available: http://www.fda.gov/cder/foi/label/2005/020658s013lbl.pdf. Accessed 2 March 2006.
21. Haynes R, Sackett D, Taylor D, Gibson E, Johnson A (1978) Increased absenteeism from work after detection and labeling of hypertensive patients. N Engl J Med 299: 741–744.

OPEN ACCESS Freely available online

PLoS MEDICINE

Policy Forum

Cholinesterase Inhibitors: Drugs Looking for a Disease?

Marina Maggini*, Nicola Vanacore, Roberto Raschetti

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

Randomized controlled trials (RCTs) are generally considered to be a robust form of evidence, free from bias, and the trial results are often used as a powerful tool to promote new drugs [1,2]. However, because the inclusion criteria for many RCTs are often very restrictive (for example, trials generally exclude patients with serious concomitant illnesses) and because patients in trials tend to receive better care than those in standard-care settings, clinicians should be careful about generalizing RCT results to their own patients. Unfortunately, many drug treatments are widely used in clinical practice, sometimes beyond the approved indications, even when doubts remain about whether the results of RCTs of these drugs should be generalized. In this article, we discuss the use of cholinesterase inhibitors in patients with a variety of types of dementia and cognitive impairment, looking critically at the clinical trial evidence on these drugs.

If the results of these trials are not carefully evaluated, together with evaluating the methodological quality of the studies, this could lead to inappropriate prescribing of cholinesterase inhibitors. Drug companies have invested heavily in developing treatments for Alzheimer disease, and then were actively involved in expanding the market to other forms of dementia. In the last decade, donepezil, galantamine, and rivastigmine have been tested not only in patients with Alzheimer disease but also in patients with vascular dementia, dementia with Lewy bodies, dementia associated with Parkinson disease, and mild cognitive impairment (MCI). Even when the evidence on the efficacy of these drugs is lacking, or inconclusive, the results are often presented in such a way as to create a false perception of efficacy. For example, about 23 different scales or instruments (on average six per trial) were used, in the trials considered here, as primary or secondary outcome measures. Most of them were not validated for the disease for which the drugs were tested and are not currently used in clinical practice, undermining the translation of these research findings into clinical practice. Moreover, the treatment effect in the trials is usually expressed through the average change from baseline in test scores, without discussing the clinical importance of the usually small effect size observed.

Alzheimer Disease: Waiting for New Treatments

The cholinesterase inhibitor donepezil was licensed in the US in December 1996, before the full results of clinical trials were available in medical journals [3]. The drug was launched with claims that it had produced "highly significant improvements in cognitive and clinical global assessments" in randomized trials lasting 30 weeks and had increased the proportion of "treatment successes" by 245% in patients with mild to moderate Alzheimer disease [3]. Donepezil, galantamine, and rivastigmine went on to be approved in many countries for the treatment of Alzheimer disease, even though it was clear that the efficacy, in the short term, was modest, symptomatic, and evident only in a subgroup of patients [4–8].

In a meta-analysis of randomized, double-blind placebo-controlled trials of cholinesterase inhibitors, Lanctôt and colleagues found that the pooled mean proportion of responders to drug treatment in excess of that for placebo treatment was only 10% (95% confidence interval, 4%–17%) [9]. In this study, response to therapy was defined (according to a definition first proposed by the US Food and Drug Administration) as an improvement of four or more points on the Alzheimer Disease Assessment Scale–cognitive portion (ADAS-cog) [10].

Search Strategy

For this article, we searched the MEDLINE database from 1996 to 2005 using the terms donepezil, galantamine, and rivastigmine to find randomized controlled clinical trials, systematic reviews, and meta-analyses. Our article is not itself a systematic review, but we discuss all the major RCTs, systematic reviews, and meta-analyses of these drugs as treatments for Alzheimer disease, and we discuss the major RCTs of these drugs for other forms of dementia.

The Policy Forum allows health policy makers around the world to discuss challenges and opportunities for improving health care in their societies.

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

Competing Interests: The authors' research is often funded by the Italian National Health Service and by the Italian Medicines Agency, which is the authority responsible for drug reimbursement procedures (including costs connected to the prescribing of acetylcholinesterase inhibitors). The authors themselves have no role in decisions concerning such reimbursement.

Citation: Maggini M, Vanacore N, Raschetti R (2006) Cholinesterase inhibitors: Drugs looking for a disease? PLoS Med 3(4): e140.

DOI: 10.1371/journal.pmed.0030140

Abbreviations: ADAS-cog, Alzheimer Disease Assessment Scale–cognitive portion; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; NICE, National Institute for Health and Clinical Excellence; RCT, randomized controlled trial

Marina Maggini, Nicola Vanacore, and Roberto Raschetti are at the National Center for Epidemiology, National Institute of Health, Rome, Italy.

* To whom correspondence should be addressed. E-mail: mmaggini@iss.it

The most recent systematic review of RCTs, by Hanna Kaduszkiewicz and colleagues, analyzed the scientific evidence for the clinical use of cholinesterase inhibitors in Alzheimer disease, together with the methodological quality of the trials [11]. The authors concluded that the benefits are minimal, the methodological quality of the available trials is poor, and the scientific basis for recommendations of these drugs for Alzheimer disease is questionable [11].

A similar conclusion was reported in the preliminary draft of recommendations on the use of cholinesterase inhibitors that is being developed by the United Kingdom's National Institute for Health and Clinical Excellence (NICE), an independent organization responsible for providing national guidance on treating and preventing illness [12,13]. In its preliminary draft appraisal document, the organization stated "that the RCT evidence on outcomes of importance to patients and carers, such as quality of life and time to institutionalisation, was limited and largely inconclusive." Moreover, the NICE committee reported that the quality of the reviewed trials was mixed, and that "the assessment group suspected selection bias, measurement bias and attrition bias." The preliminary recommendations of the appraisal committee were that "donepezil, rivastigmine and galantamine are not recommended for use in the treatment of mild to moderate Alzheimer's disease," and that further research is required to identify subgroups of people for whom cholinesterase inhibitors may be effective. The committee recently updated its guidance, as shown in the Sidebar.

NICE Recommendations on Cholinesterase Inhibitors

Revised draft guidance on the use of drugs to treat Alzheimer disease has recently been published (23 January 2006) on the NICE Web site (http://www.nice.org.uk/page.aspx?o=288826).

The preceding draft guidance from NICE (http://www.nice.org.uk/page.aspx?o=245908), published 1 March 2005, concluded that there was not enough evidence to support the use of these drugs for all patients. However, responses received from stakeholders during consultation on this first draft suggested that the drugs may be more effective for certain groups of people. NICE, therefore, asked the pharmaceutical companies involved in the appraisal to look for evidence to support this, from the data in their clinical trials.

In conclusion, "the Committee considered not just the initial evidence and submissions, but also the comments raised in consultation on the first Appraisal Consultation Document (notably the improved infrastructure around dementia care) and the evidence that was submitted during consultation and the additional analyses undertaken. The Committee concluded that taking all these factors into account, the resulting estimates of cost effectiveness could be considered sufficiently acceptable to allow the prescribing of AChE inhibitors," donepezil, galantamine, and rivastigmine, for people with Alzheimer's disease of moderate severity only (that is, those with an MMSE score between ten and 20).

As in the earlier draft, the committee "noted, however, that the evidence available on the long-term effectiveness of the AChE inhibitors on outcomes of importance to people with Alzheimer's disease and their carers, such as quality of life and delayed time to nursing home placement, was limited and largely inconclusive."

As for memantine, it continued to be "not recommended as a treatment option for people with Alzheimer's disease except as part of properly constructed clinical studies."

Patients with Alzheimer Disease and Vascular Risk Factors or Patients with Vascular Dementia

The therapeutic potential of cholinesterase inhibitors has been explored in clinical trials of patients with Alzheimer disease with concurrent vascular risk factors, and also in patients with vascular dementia.

One 26-week placebo-controlled RCT evaluated the efficacy and safety of rivastigmine for patients with mild to moderately severe Alzheimer disease with or without concurrent vascular risk factors [14]. The authors concluded that the drug is effective in patients with or without vascular risk factors, and that those with vascular risk factors "experience greater clinical benefit (cognition, activities of daily living, and disease severity)." However, the withdrawal rate was higher for patients given the drug than for patients given placebo, and there was no intention-to-treat analysis.

The effect of galantamine was examined in a six-month RCT in a mixed population of patients diagnosed as having probable vascular dementia, Alzheimer disease with cerebrovascular disease, or an intermediate diagnosis [15]. Unfortunately, the study was not powered to detect treatment differences in the three subgroups; moreover, as in the study on rivastigmine [14], the primary statistical assessment of efficacy was not based on an intention-to-treat analysis, but only on an observed case analysis.

Two trials have been conducted to evaluate the efficacy and tolerability of donepezil in patients diagnosed with vascular dementia; these trials showed modest and inconsistent effects [16,17]. The study design was similar to the design used in trials of cholinesterase inhibitors for Alzheimer disease: the vascular dementia trials used similar drug doses and similarly lasted only six months. As with trials of cholinesterase inhibitors for Alzheimer disease, a six-month trial period is unjustified for a pathology that develops over decades. Moreover, the assessment scales used in the vascular dementia trials are intended for assessing Alzheimer disease, and are not validated for the evaluation of vascular dementia. The investigators did not find improvement for all primary and secondary efficacy parameters, and a reverse dose effect was shown: that is, improvement in global function was observed in a greater proportion of patients treated with donepezil than those treated with placebo in the 5-mg group but not in the 10-mg group [16].

The study population was, as reported by the authors, not typical of all patients with vascular dementia (in fact, only patients who were stable with respect to comorbid conditions, hypertension, diabetes, and heart disease were included in these clinical trials) [16]. Even in this highly selected population, an excess of stroke (fatal and nonfatal) was observed among treated patients. The potential implications for clinical practice still remain to be clarified. Nevertheless, the drug was presented in

the trial reports as a safe and effective means of treating vascular dementia. After a pooled analysis of the two trials, the authors wrote that "the results ... are somewhat confusing," and "further data on donepezil's impact on executive functioning would be certainly desirable" [18,19].

At the time of writing this article, the data from these vascular dementia trials have not been considered sufficient evidence to license donepezil for treating vascular dementia. However, the positive messages contained in the published RCTs may promote the off-label use of the drug.

Dementia Associated with Parkinson Disease and Dementia with Lewy Bodies

A Cochrane systematic review identified only one RCT (involving 120 patients) of the efficacy of rivastigmine in patients with probable dementia with Lewy bodies [20,21]. The Cochrane reviewers concluded that the trial "showed no statistically significant difference between the two groups at 20 weeks. A possible beneficial effect on neuropsychiatric features was found only in analysis of observed cases, and may therefore be due to bias." Hence the evidence of any benefit is currently weak [21].

Two clinical trials have investigated the effect of cholinesterase inhibitors in patients with dementia associated with Parkinson disease. The first one [22], which found a trend (not statistically significant) toward better scores on the ADAS-cog is not further discussed here because of its small size (only 22 patients were randomized to receive donepezil or placebo).

The second trial, by Emre et al., investigated the effect of rivastigmine in 541 highly selected patients recruited from an unspecified number of centers from 12 countries [23]. Patients included in the trial had received a diagnosis of dementia 6.6 ± 5.2 years (treated arm) and 7.3 ± 5.2 years (placebo arm) after the diagnosis of Parkinson disease. It would be difficult to find such a population in a clinical setting for a number of reasons. Beyond the diagnostic challenge of differentiating dementia associated with Parkinson disease from dementia of the Lewy body type, there is also evidence that the risk of dementia in Parkinson disease is associated with age and severity of extrapyramidal signs, and the mean time from onset of Parkinson disease to dementia is estimated to be 10.5 years [24–26]. But the exact clinical implications of this RCT are still not clear.

The outcome measures used in Emre and colleagues' trial were the ADAS-cog and the Alzheimer Disease Cooperative Study–Clinician's Global Impression of Change scale.

In their trial, the authors considered a mean improvement of 2.25 points in the ADAS-cog score as clinically meaningful, even though this scale has never been used to monitor the progression rate of dementia in Parkinson disease. Among adverse events, Parkinsonian symptoms were reported more frequently in the rivastigmine group than in the placebo group. The authors concluded that rivastigmine was associated with moderate but significant improvements in all symptoms of dementia associated with Parkinson disease, but also with high rates of adverse events, and that the findings may have implications for clinical practice. But the exact clinical implications of this RCT are still not clear.

Clinicians should be careful about generalizing RCT results to their own patients.

Mild Cognitive Impairment: A New Clinical Entity or a New Market Frontier?

Whether MCI can be considered a clinical entity is still a matter of debate (for example, Gauthier and Touchon have argued that "there is epidemiological evidence that many subjects labeled as having MCI do not worsen over time and may revert to normal cognitive abilities" [27]). Nevertheless, specific drug treatment for MCI has been proposed.

Two RCTs have been conducted to investigate whether donepezil delays the onset of dementia in people with MCI. These studies failed to demonstrate any efficacy, while showing a worse safety profile among patients receiving active drug compared with the placebo group. In the first published trial [28], significant treatment effects were not seen in the primary efficacy measures, while more patients treated with donepezil experienced adverse events compared with patients treated with placebo (88% versus 73%). Despite this negative result, a new trial was conducted by Petersen et al., comparing donepezil, vitamin E, and placebo [29]. This study did not show a significant difference among the three groups in the rate of progression from MCI to Alzheimer disease over a three-year period. Nevertheless, the authors stress some limited effects on secondary measures: a reduced likelihood of progression to Alzheimer disease only during the first 12 months of treatment, and a benefit of donepezil among carriers of one or more apolipoprotein E ε4 throughout the three-year follow-up. This latter claim, in particular, was not supported by the data as the study was not statistically powered to evaluate the effect of the treatment in separate groups of apolipoprotein E ε4 carriers.

Harms-related data were inadequate: the flow of participants through the study phases was not described; the reasons and timing for discontinuation per treatment arm were not reported; only adverse events observed in at least 5% of patients were reported; and the causes of the 23 deaths observed (17 in the double-blind phase and six in the subsequent open-label phase) were not specified. In the double-blind phase, a higher number of deaths was observed in the donepezil arm ($n = 7$) compared with the vitamin E arm ($n = 5$) and the placebo arm ($n = 5$). For the six deaths that occurred during the open-label phase, the original arm (active drug or placebo in the previous double-blind phase) was not reported. (The distribution of these six deaths across the three arms of the trial in the open phase was subsequently reported by Jelic et al. [30]—there were three deaths in the donepezil group, one in the vitamin E group, and two in the placebo arm; thus, the total number of deaths per arm in the whole trial was ten in the donepezil group [three from cardiac arrest], six in the vitamin E group, and seven in the placebo group.) Although Petersen et al. conceded that the results "do not provide support for a clear recommendation for the use of donepezil in persons with mild cognitive impairment," they did suggest that their findings "could prompt a

discussion between the clinician and the patient about this possibility" [29].

Two trials, each lasting two years and not yet published, evaluated the effect of galantamine on a total of 2,048 patients with MCI randomized to receive galantamine or placebo [31,32]. Overall, the studies did not show that the drug could improve cognition or delay the conversion to dementia. Increased mortality (mostly due to myocardial infarction and stroke) was observed among patients treated with galantamine compared with patients given placebo. On the basis of these results, the US Food and Drug Administration issued a safety warning concerning galantamine [33].

In these trials, the treatment duration (two years) was longer than that of most previous RCTs on Alzheimer disease (typically only six months). The short trials on Alzheimer disease had shown no increased mortality associated with cholinesterase inhibitors compared with placebo. In clinical practice, though, these drugs would likely be prescribed for several years, and the galantamine trials [31,32] have shown that such prolonged use may be associated with increased mortality. A recent review on clinical trials in MCI concluded that none of the reviewed studies met their primary objectives; that is, none of the trials showed a benefit of cholinesterase inhibitors in delaying the conversion to dementia or in slowing symptom progression [30].

Conclusion

At present, donepezil, galantamine, and rivastigmine are licensed only for the treatment of mild to moderate Alzheimer disease. The treatment effect is modest, and there is evidence of wide variability in the outcomes reported: "some patients will have improved, others stayed the same, while others will have deteriorated. This variance should be comparative in both the treatment and the placebo groups but care should be taken over the interpretation of the mean scores" [34].

However, a minority of people with Alzheimer disease may benefit from the cholinesterase inhibitors, and further research is needed to identify these subgroups of people, considering, in particular, long-term and worthwhile improvements such as delay in institutionalization. A cohort study of the effectiveness of cholinesterase inhibitors in Alzheimer disease has been conducted in Italy on 5,462 patients [35]. This study showed that the patients most likely to respond to treatment are those without concomitant diseases and those who had demonstrated an early response at three months. Response to treatment did not vary among groups with different Mini Mental State Examination (MMSE) scores at baseline. Based on these results, we suggest that physicians should accurately reevaluate their patients after three months of therapy, and should communicate realistic information to patients and their families about the very modest benefits of these drugs.

Since 1996, when the first cholinesterase inhibitor was licensed in the US for the symptomatic treatment of Alzheimer disease, each new published trial on the effect of cholinesterase inhibitors on the various different forms of dementia has raised new questions about the benefit–risk profile of these drugs. Reduced cholinergic neurotransmission was the rationale for the use of cholinesterase inhibitors in patients with dementia. Nevertheless, what seemed a biologically plausible intervention has not led to a proven, real improvement in patients' well-being. ■

References

1. Rothwell PM (2005) External validity of randomised controlled trials: "To whom do the results of this trial apply?" Lancet 365: 82–93.
2. McCormack J, Greenhalgh T (2000) Seeing what you want to see in randomised controlled trials: Versions and perversions of UKPDS data. BMJ 320: 1720–1723.
3. Melzer D (1998) New drug treatment for Alzheimer's disease: Lessons for healthcare policy. BMJ 516: 762–764.
4. Rogers SL, Fralow MR, Doody RS, Mohs R, Friedhoff LT, et al. (1998) A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology 50: 136–145.
5. Rosler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, et al. (1999) Efficacy and safety of rivastigmine in patients with Alzheimer's disease: International randomised controlled trail. BMJ 318: 633–640.
6. Wilcock GK, Lilienfeld S, Gaens E (2000) Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: Multicentre randomised controlled trial. BMJ 321: 1–7.
7. AD2000 Collaborative Group (2004) Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): Randomised double-blind trial. Lancet 363: 2105–2115.
8. Doody RS, Stevens JC, Beck C, Dubinsky RM, Kaye JA, et al. (2001) Practice parameter: Management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 56: 1154–1166.
9. Lanctôt KL, Herrmann N, Yau KK, Khan LR, Liu BA, et al. (2003) Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: A meta-analysis. CMAJ 169: 557–564.
10. US Food and Drug Administration (1989) Peripheral and Central Nervous System Drugs Advisory Committee Meeting; 1989 July 7; Rockville (Maryland): Department of Health and Human Services, Public Health Service. 227 p.
11. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H (2005) Cholinesterase inhibitors for patients with Alzheimer's disease: Systematic review of randomised clinical trials. BMJ 331: 321–327.
12. Kmietowicz Z (2005) NICE proposes to withdraw Alzheimer's drugs from NHS. BMJ 330: 495.
13. National Institute for Clinical Excellence [NICE] (2006) Appaisal consultation document: Alzheimer's disease—Donepezil, rivastigmine, galantamine and memantine. London: NICE. Available: http://www.nice.org.uk/page.aspx?textsize=10&o=245908. Accessed 16 February 2006.
14. Kumar V, Anand R, Messina J, Hartman R, Veach J (2000) An efficacy and safety analysis of Exelon in Alzheimer's disease patients with concurrent vascular risk factors. Eur J Neurol 7: 159–169.
15. Erkinjutti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, et al. (2002) Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: A randomized trial. Lancet 359: 1283–1290.
16. Black S, Roman GC, Geldmacher DS, Salloway S, Hecker J, et al. (2003) Efficacy and tolerability of donepezil in vascular dementia. Positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. Stroke 34: 2323–2332.
17. Wilkinson D, Doody R, Helme R, Taubman K, Mintzer J, et al. (2003) Donepezil in vascular dementia. A randomized, placebo-controlled study. Neurology 61: 479–486.
18. Geldmacher DS (2003) Donepezil in vascular dementia. A viewpoint. Drugs Aging 20: 1137–1138.
19. Black S (2003) Donepezil in vascular dementia. A viewpoint. Drugs Aging 20: 1137–1138.
20. McKeith, Del Ser T, Spano P, Emre M, Wesnes K, et al. (2000) Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double blind, placebocontrolled international study. Lancet 356: 2031–2036.
21. Wild R, Pettit T, Burns A (2003) Cholinesterase inhibitors for dementia with Lewy bodies. Cochrane Database Syst Rev 2003: CD003672.
22. Ravina B, Putt M, Siderowf A, Farrar JT, Gillespie M, et al. (2005) Donepezil for dementia in Parkinson's disease: A randomised, double blind, placebo controlled, crossover study. J Neurol Neurosurg Psychiatry 76: 934–939.
23. Emre M, Aarsland D, Albanese A, Byrne J, Deuschl G, et al. (2004) Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med 351: 2509–2518.
24. Levy G, Schupf N, Tang MX, Cote LJ, Louis ED, et al. (2002) Combined effect of age and severity on the risk of dementia in Parkinson's disease. Ann Neurol 51: 722–729.
25. Apaydin H, Ahlskog E, Parisi JE Boeve BF, Dickson DW (2002) Parkinson Disease neuropathology. Later-developing dementia and loss of the levodopa response. Arch Neurol 59: 102–112.
26. Aarsland D, Ballard CG, Halliday G (2004) Are Parkinson's disease with dementia and dementia with Lewy bodies the same entity? J Geriatr Psychiatry Neurol 17: 137–145.

27. Gauthier S, Touchon J (2005) Mild cognitive impairment is not a clinical entity and should not be treated. Arch Neurol 62: 1164–1166.
28. Salloway S, Ferris S, Kluger A, Goldman R, Griesing T, et al. (2004) Efficacy of donepezil in mild cognitive impairment. A randomized placebo-controlled trial. Neurology 63: 651–657.
29. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, et al. (2005) Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 352: 2379–2388.
30. Jelic V, Kivipelto M, Winblad B (2005) Clinical trials in mild cognitive impairment: Lessons for the future. J Neurol Neurosurg Psychiatry. Epub ahead of print 23 November 2005.
31. Clinical Study Results Database. Protocol number GAL-INT-11. Available: http://www.clinicalstudyresults.org/documents/company-study_96_1.pdf. Accessed 28 February 2006.
32. Clinical Study Results Database. Protocol number GAL-INT-18. Available: http://www.clinicalstudyresults.org/documents/company-study_96_2.pdf Accessed 28 February 2006.
33. US Food and Drug Administration [FDA] (2005) Alert for healthcare professionals on galantamine hydrochloride (marketed as Reminyl). Rockville (Maryland): FDA. Available: http://www.fda.gov/cder/drug/InfoSheets/HCP/galantamineHCP.htm. Accessed 16 February 2006.
34. Takeda A, Loveman E, Clegg A, Kirby J, Picot J, et al. (2006) A systematic review of the clinical effectiveness of donepezil, rivastigmine and galantamine on cognition, quality of life and adverse events in Alzheimer's disease. Int J Geriatr Psychiatry 21: 17–28.
35. Raschetti R, Maggini M, Sorrentino GC, Martini N, Caffari B, et al. (2005) A cohort study of effectiveness of acetylcholinesterase inhibitors in Alzheimer's disease. Eur J Clin Pharmacol 61: 361–368.

OPEN ACCESS Freely available online

PLoS MEDICINE

Policy Forum

Disease Mongering in Drug Promotion: Do Governments Have a Regulatory Role?

Barbara Mintzes

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

Ray Moynihan and colleagues describe disease mongering as, "widening the boundaries of treatable illness in order to expand markets for those who sell and deliver treatments" [1]. In this article, I examine one aspect of disease mongering: activities financed by drug companies to promote sales by expanding the pool of patients potentially treated by their products, when no benefit in terms of reduced morbidity is likely. New diseases may be "created" or existing conditions redefined. In theory, these activities are covered by national laws governing drug promotion that forbid misleading or deceptive advertising. However, enforcement is piecemeal and largely ineffective.

Drug regulation remains limited in many parts of the world. In 2004, fewer than one-sixth of countries had a well-developed system of drug regulation, and one-third had little to no regulatory capacity [2]. Although 89 countries (46%) reported active regulation of drug promotion, resources devoted to this work may be limited [3].

Full direct-to-consumer advertising (DTCA) of prescription drugs is legal in only the United States and New Zealand. However, in many other countries, unbranded disease-oriented advertising (in which no drug names are mentioned, but patients are often advised to "see your doctor") is increasingly common. The Dutch Health-Care Inspectorate reviewed 28 product-specific marketing plans for prescription drugs, from ten companies, obtained through subpoenas from 1999 to 2002; 3.5% of their budgets were devoted to DTCA [4]. A market analyst reports that drug companies spent US$85 million on unbranded DTCA in Europe in 2004 [5]. Spending is expected to reach US$345.5 million by 2008. In 2005, the Australia–US free trade agreement allowed unbranded advertising in Australian media to be linked to branded information on Web sites [6]. Canada introduced more lenient policies on unbranded advertising in 1996, a shift that has occurred without legislative change [7].

A claimed benefit of disease-awareness campaigns is that the public becomes more aware of untreated health problems and seeks effective care at an earlier stage, leading to better health [8]. For this to happen, the campaigns must address important health concerns, focus on patients likely to benefit from diagnosis and treatment, and steer them towards appropriate care. For the individual patient, drug treatment is worth pursuing if potential benefits outweigh potential harm. But as healthier people are targeted, the added benefit of drug treatment can become increasingly elusive.

Limited Regulatory Oversight of Unbranded Disease-Awareness Adverts

The US Food and Drug Administration (FDA) published a guidance in 2004 stating that unbranded adverts that are perceptually similar or otherwise linked to branded adverts are subject to FDA regulation, as are unbranded adverts by the manufacturer of the only drug in its class [9]. Otherwise, the FDA has no authority over the content of disease-oriented advertising, although it recommends responsible public health messages. The United Kingdom Medicines Health-Care Products Regulatory Agency has issued guidelines stating that the primary purpose of disease-awareness advertising must be health education on a disease and its management, not product promotion

Box 1. Forms of Disease Mongering Used to Expand Drug Sales

- Promotion of anxiety about future ill-health in healthy individuals
- Inflated disease prevalence rates
- Promotion of aggressive drug treatment of milder symptoms and diseases
- Introduction of questionable new diagnoses—such as PMDD or social anxiety disorder—that are hard to distinguish from normal life
- Redefinition of diseases in terms of surrogate outcomes (i.e., osteoporosis becomes a disease of low bone density rather than fragility fractures)
- Promotion of drugs as a first-line solution for problems previously not considered medical, such as disruptive classroom behaviour or problematic sexual relationships.

The Policy Forum allows health policy makers around the world to discuss challenges and opportunities for improving health care in their societies.

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

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

Citation: Mintzes B (2006) Disease mongering in drug promotion: Do governments have a regulatory role? PLoS Med 3(4): e198.

DOI: 10.1371/journal.pmed.0030198

Abbreviations: DTCA, direct-to-consumer advertising; FDA, United States Food and Drug Administration; HRT, hormone replacement therapy; NSAID, nonsteroidal anti-inflammatory drug; PMDD, premenstrual dysphoric dysfunction; SSRI, selective serotonin reuptake inhibitor

Barbara Mintzes is part of the Therapeutics Initiative, Department of Anaesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, British Columbia, Canada. E-mail: bmintzes@chspr.ubc.ca

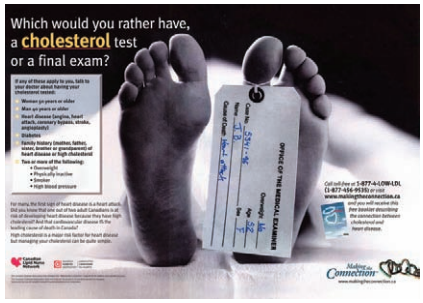
[10]. However, the Medicines Health-Care Products Regulatory Agency allowed Novartis' advertising on fungal nail infections (onychomycosis), which stressed high prevalence and infectiousness and guided viewers to prescription drugs, including Novartis' drug terbinafine (Lamisil) [10].

In the Netherlands, a similar Novartis campaign for onychomycosis prompted the Dutch government to take Novartis to court for illegal DTCA. The government lost the case as neither the product nor the manufacturer was named [11]. 't Jong and colleagues subsequently analyzed the effects of the campaign on primary care, using administrative data covering 150 practices. They studied the changes in rates of prescriptions of oral terbinafine (Lamisil) and itraconazole (Sporanox, a competitor to Lamisil), and the onychomycosis consultation rate, before and after the start of the campaign. Both onychomycosis consultations and prescriptions for terbinafine (Lamisil) grew, whereas prescriptions for the competitor drug declined [12]. Thus, an unbranded campaign had a brand-specific effect on sales, most likely because of concurrent branded promotion to physicians. 't Jong et al. noted the effects of promotion of a condition that is largely cosmetic (it usually causes no pain or suffering) on physicians' workload.

Promoting Sales through Fear of Death

Pfizer, the manufacturer of Lipitor (atorvastatin), ran a campaign in France and Canada in 2003 with print adverts that used images of a tagged toe of a corpse (the Canadian campaign was in association with the Canadian Lipid Nurse Network and the Canadian Diabetes Association) (Figure 1). On television, a youthful, healthy man died suddenly of a heart attack, leaving his family devastated with grief. The message of these two adverts was that cholesterol testing and treatment could prevent premature death from heart attacks in healthy people. This was at odds with existing scientific evidence: a 2003 meta-analysis of cholesterol-lowering drugs in primary prevention found no difference in mortality between drug and placebo [13].

Jonathan Quick and colleagues at the World Health Organization raised concerns in the *Lancet* that the



DOI: 10.1371/journal.pmed.0030198.g001

Figure 1. Disease-Awareness Campaign Sponsored by Pfizer, the Manufacturer of Lipitor

(Image copyright: Pfizer Canada Inc./Making the Connection. All rights reserved.)

adverts misinformed the public about cardiovascular risks and could lead to harm from medically unjustified drug use [14]. They argued that governments should take a more active role in regulating disease-awareness campaigns to prevent misleading information from reaching the public. Complaints in Canada, which included the *Lancet* letter, resulted in no regulatory action [15]. A subsequent advert shows a man walking down a city street, unaware that he is about to be charged by a rhinoceros. The tagline is the following: "Living with high cholesterol, you never know what's around the corner." The text stresses the risk of death from heart attacks. The only risk factor discussed is cholesterol.

Disease-awareness advertising is often the visible face of broader commercial influences. Eight of the nine authors of the US cholesterol treatment guidelines released in 2004 had financial links to manufacturers (Cleeman was the only member of the panel with no such ties; see http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3upd04_disclose.htm) [16]. These guidelines extended treatment of high cholesterol to patient groups in which a morbidity and mortality advantage had not been established. A Pfizer financial report on atorvastatin (Lipitor) states, "There continues to be an opportunity for further growth of the cholesterol-lowering market....Evolving treatment guidelines continue to encourage the broad use of statin therapy" [17].

Hormone Replacement Therapy and Menopause: An Ongoing Saga

Promotion of hormone replacement therapy (HRT) for disease prevention is a key example of disease mongering linked to drug sales. Women learned to view menopause in terms of increased health risks that could be prevented with HRT. The first long-term randomized controlled trial of HRT in healthy women, the Women's Health Initiative, found a 1% increase in absolute risks for serious harm over five years, mainly due to cardiovascular adverse effects [18]. The negative public health impact of HRT use by millions of women worldwide is likely to have been considerable. Regulatory agencies have changed labelling to warn potential users of serious risks and to advise limiting use to short-term symptomatic treatment, but have taken no broader action to review marketing of drugs for disease prevention.

On 28 December 2005, the first hit on a Google search on "menopause and estrogen deficiency" was a Merck Web site promoting an estrogen patch, and linking postmenopausal estrogen deficiency to reduced performance, fine motor skills, memory, and a reduction in "planned, targeted, flexible and adaptable thought" [19].

In 2006, a handbook for journalists, called *The Journalist's Menopause Handbook*, which was funded by Wyeth Canada and produced by a medical society (the Society of Obstetricians and Gynaecologists of Canada), fails to mention increased risks of strokes, heart attacks, pulmonary emboli, or symptoms of probable dementia associated with HRT [20]. The magnitude of breast cancer risk is described as no greater than lifestyle-associated risks. Hot flushes, mood and memory, appearance (wrinkles), sleep disturbances, bladder control, and sexual changes are listed as menopausal symptoms. Short-term HRT for moderate to severe symptoms is recommended as safe and effective, with "short-term" defined as up to five years [20]. Beyond the lack of established link between wrinkles and menopause (rather than ageing per se), is HRT really a reasonable treatment for wrinkles, given the cardiovascular, cancer, and dementia risks?

Lower Thresholds for Symptomatic Treatment and Public Health

Mamdani and colleagues found that following the launch of celecoxib (Celebrex) and rofecoxib (Vioxx), more elderly patients in Ontario

were treated with nonsteroidal anti-inflammatory drugs (NSAIDs) than previously [21]. The increase was attributable to use of Cox-2 inhibitors by people not previously taking NSAIDs. Paradoxically, although these newer drugs were promoted for greater gastrointestinal safety, Mamdani and colleagues found that approximately 650 more hospitalizations for gastrointestinal bleeds occurred per year after the drugs' introduction. In their conclusion, the authors stated the following: "Although we cannot prove causation, we believe that the striking temporal correlation, biological plausibility, and lack of any other trends that would explain the association strongly suggest that the two events are directly related" [21].

Another heavily promoted class of drugs are the proton pump inhibitors. Bashford and colleagues analyzed why patients were prescribed proton pump inhibitors during a five-year period in which prescribing increased 10-fold. By 1995, 46% of prescriptions were for off-label uses, mainly milder problems [22]. In 2004, researchers found a link between use of proton pump inhibitors and higher risks of *Clostridium difficile* infection in hospitalized patients [23]. A US magazine advertisement for esomeprazole (Nexium) in November 2005 (e.g., printed in *Family Circle*), a year after this study, warns readers that "something could be brewing" beneath their heartburn. A distressed woman is shown with a red scarf around her neck, and on the scarf is the following statement: "Behind this scarf acid could be burning the lining of her esophagus." The advert quotes a high rate of erosive esophagitis among people with acid reflux, one in three, based on data on file at AstraZeneca. Although the advert contains the disclaimer that "only a doctor can determine if you have this condition," the image of distress and the larger headlines—such as "Acid reflux disease can damage your esophagus" and "Nexium heals the damage"—convey the message to be anxious about heartburn and consider it a possible sign of more serious disease. Like many US adverts, this one offers a free trial.

Questionable New Indications

Regulatory agencies have differed in their response to manufacturers' bids to market selective serotonin reuptake inhibitor (SSRI) antidepressants for "premenstrual dysphoric dysfunction" (PMDD). Business analysts linked the launch of the first drug in the US for this indication, fluoxetine (Sarafem), to Eli Lilly's pending loss of patent protection for Prozac (also fluoxetine) [24].

The European Medicines Evaluation Agency refused to approve drugs for PMDD, raising concerns that women "with less severe pre-menstrual symptoms might erroneously receive a diagnosis of PMDD resulting in widespread inappropriate short- and long-term use of fluoxetine" [25]. The US and Australia have approved SSRIs for PMDD, but Australia does not cover their costs [26].

Soon after Sarafem's launch, the FDA judged a TV advert to violate US law because it failed to distinguish clearly between PMDD and premenstrual syndrome [27]. A US community survey of women aged 14–24 found a 6% prevalence of PMDD. An additional 19% were "near-threshold" cases [28]. This survey likely overestimated PMDD, as classification was based on recall rather than daily symptom diaries (and most women were only mildly impaired), but the high "near-threshold" prevalence highlights the profitability of broadening diagnostic boundaries [29].

Disease Claims in US DTCA: A Mixed Regulatory Response

Unlike many countries that rely primarily on industry self-regulation, the FDA regulates prescription drug promotion directly. Letters of violation to manufacturers are posted on the FDA Web site, with detailed rationales for regulatory decisions [30]. Of the 51 letters sent to companies in 2004 to mid-December 2005, 21 were either on DTCA exclusively ($n = 15$) or on both DTCA and promotion for health professionals ($n = 6$). For 15 out of 21 (71%) letters, reviewers from the FDA's Division of Drug Marketing, Advertising, and Communications raised concerns related to disease mongering (Table 1). These concerns often consisted of (1) off-label promotion broadening approved indications and (2) misrepresentation of disease so as to exaggerate treatment effectiveness.

Many examples also exist of disease mongering in US DTCA that has not been subject to regulation. In a recent article in *PLoS Medicine*, Lacasse and Leo reviewed the evidence supporting the hypothesis that depression is caused by a serotonin deficiency, concluding that a lack of evidence exists to support this hypothesis [31]. They questioned the FDA's lack of attention to the claims in SSRI adverts for antidepressants that depression and anxiety disorders are caused by a chemical imbalance in the brain. The Irish regulatory agency has prohibited GlaxoSmithKline from making similar claims to support the use of paroxetine (Paxil) [32].

Kravitz and colleagues found more broadly that patient requests for advertised medicines could lead to off-label antidepressant prescribing for "adjustment disorder," a disorder involving temporary distress due to a troubling life situation that rarely requires drug treatment [33]. Standardized patients received antidepressant prescriptions just over half the time if they requested the advertised antidepressant Paxil, whether they had symptoms of depression or adjustment disorder. If patients had not requested a drug, physicians were much less likely to prescribe antidepressants for adjustment disorder. This study provides experimental evidence of a link between patient requests for medicines and unnecessary medicalization.

Conclusion: Is a More Robust Regulatory Response Needed?

Box 1 summarizes the types of disease-mongering activities companies can use to stimulate drug sales, including those described above.

The rationale for regulation of drug promotion is health protection, encouragement of appropriate medicine use, and prevention of deceptive advertising. The European community code on medicinal products for human use states that advertising of medicinal products "must encourage the rational use of the product and may not be misleading" [34]. Canada's Food and Drugs Act prohibits advertising of a drug that is "false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, merit or safety" [35]. The World Health Organization's Ethical Criteria for Medicinal Drug

Table 1. FDA Letters of Violation on Consumer-Directed Advertising, January 2004 to mid-December 2005

Brand	Product	Indication	Key Violations Identified in FDA Letter	What the FDA Said about the Disease-Related Aspects of the Adverts
Atrovent, Combivent	Ipratropium, ipratropium/albuterol	Chronic obstructive pulmonary disease	Unsubstantiated effectiveness claims	Adverts "suggest that anticholinergics are essential for the treatment of COPD [Chronic obstructive pulmonary disease], and that COPD is not appropriately treated without an anticholinergic. This is false or misleading, because COPD can be treated without using anticholinergics" (http://www.fda.gov/cder/warn/2004/Atrovent1.pdf)
Celebrex, Bextra[a]	Celecoxib, valdecoxib	Arthritis	Omits risks; unsubstantiated effectiveness and superiority claims	Television infomercial "overstates the effectiveness of the drugs while minimizing, by complete omission, the risks" (http://www.fda.gov/cder/warn/2005/12560-letter.pdf)
Effexor[a]	Venlafaxine	Depression	False and misleading effectiveness and safety claims	Radio advert "fails to communicate important characteristics necessary to distinguish between major depressive disorder and variations of normal daily functioning" (http://www.fda.gov/cder/warn/2004/Effexor.pdf)
Enbrel	Etanercept	Plaque psoriasis	Broadens indication; overstates effectiveness	Television advert gives impression that "Enbrel completely clears skin with psoriasis…To our knowledge, Enbrel has not been shown to provide complete clearing of psoriatic skin" (http://www.fda.gov/cder/warn/2005/Enbrelwl.pdf)
Kaletra	Lopinavir/ritonavir	HIV/AIDS	Overstates effectiveness; omits indications and risk information	Advert gives a "misleading impression concerning the effectiveness of Kaletra" (http://www.fda.gov/cder/warn/2004/12810Kaletra.pdf)
Levitra	Vardenafil	Impotence	Unsubstantiated implied superiority	Adverts "suggest that Levitra is superior to other treatments for ED [erectile dysfunction]…FDA is not aware of substantial evidence or substantial clinical experience demonstrating that Levitra is superior to other ED treatments" (http://www.fda.gov/cder/warn/2005/Levitra.pdf)
Muse	Alprostadil	Impotence	Omits and minimizes risks; fails to mention urethral insertion	"it is misleading to claim that MUSE will provide a 'more normal and spontaneous sexual lifestyle' or 'allow the spontaneity that you and your sexual partner desire,' when patients must follow at least 12 distinct steps to administer MUSE correctly" (http://www.fda.gov/cder/warn/2004/Macmis12039.pdf)
Pamine[a]	Methscopolamine	Peptic ulcer (adjunct)	Omits risks, misrepresents safety, and promotes off-label use	Patient brochure and Web site contain "unsubstantiated effectiveness claims" (http://www.fda.gov/cder/warn/2004/12413.pdf)
Paxil	Paroxetine	Social anxiety disorder	Broadens indication; minimizes serious risks	Advert misleads because it "suggests that *anyone* experiencing anxiety, fear, or self-consciousness in social or work situations is an appropriate candidate for Paxil CR" (http://www.fda.gov/cder/warn/2004/MACMIS12439.pdf)
Quadramet	Samarium lexidronam	Osteoblastic metastic bone lesions (pain)	Overstates effectiveness; omits or minimizes risks	Adverts "imply that Quadramet is more effective in treating cancer pain and more beneficial to patients receiving the drug than has been demonstrated by substantial evidence or substantial clinical experience" (http://www.fda.gov/cder/warn/2005/Quardramet_wl.pdf)
Seasonale	Levonorgestrel/ethinyl estradiol	Contraception	Omits and minimizes risks	TV advert "fails to reveal that (a) patients using Seasonale may experience breakthrough bleeding or spotting for up to a year, (b) the breakthrough bleeding may be up to the amount similar to a regular period" (http://www.fda.gov/cder/warn/2004/12748.pdf)
Strattera	Atomoxetine	Attention deficit disorder	Broadens indication; minimizes risks	"This ad is concerning from a public health perspective because by failing to adequately communicate the Attention-Deficit Disorder (ADD) indication for Strattera, it potentially broadens the use of the drug beyond the indicated patient population, while also minimizing the serious risks associated with the drug" (http://www.fda.gov/cder/warn/2005/strattera.pdf)
Tracleer[a]	Bosentan	Pulmonary arterial hypertension	Unsubstantiated superiority claims; broadens indication	"…the statement that PAH [pulmonary arterial hypertension] was 'invariably fatal' before Tracleer implies that a survival benefit has been shown for PAH patients who receive Tracleer therapy…FDA is not aware of substantial evidence or substantial clinical experience demonstrating a survival benefit for Tracleer" (http://www.fda.gov/cder/warn/2005/Tracleer_wl.pdf)
Viagra	Sildenafil	Impotence	Broadens indication; fails to disclose indication and risks	TV advert contains "unsubstantiated effectiveness claims" (http://www.fda.gov/cder/warn/2004/12726.pdf)
Viramune	Nevirapine	HIV/AIDS	Fails to disclose limits on indication; minimizes risks	"print ad is misleading because it fails to present risk information with…prominence and readability"(http://www.fda.gov/cder/warn/2004/12717.pdf)

[a]Violations involved materials targeting consumers and health professionals.

DOI: 10.1371/journal.pmed.0030198.t001

Promotion states that advertisements, "…should not take undue advantage of people's concern for their health" [36].

Disease mongering by definition creates erroneous impressions of the condition a product aims to treat and the merit and safety of treatment, and frequently provokes undue anxiety or exaggerates prevalence rates. Many of the activities in Box 1 are off-label promotions.

The prohibition of DTCA is consistent with regulatory aims to protect health and encourage appropriate medicine use. Unbranded disease-awareness campaigns for the condition a manufacturer's drug aims to treat are a form of DTCA. If these adverts are allowed under laws guaranteeing commercial freedom of expression, a regulatory rationale remains to (1) de-link them from suggestions to "ask your doctor" for a treatment and (2) to insist on prescreening of adverts by a government agency to ensure conformity with the law before they are broadcast or printed. Similarly, drug company funding of media promotions aiming to stimulate sales should be subject to the same regulatory control as direct advertising.

Better definitions are needed of the indications drugs are approved to treat, to ensure consistency with assessed outcomes in premarket trials. Evidence of benefit should be based on clinical outcomes, and greater caution is needed in introducing new diagnoses.

A key question is whether there is sufficient political will among government regulatory agencies to better enforce existing regulations governing drug promotion or to introduce new solutions. Most regulatory agencies fail to treat regulation of drug promotion as a public health concern. Unless this changes, the public can expect more unfettered disease mongering warning them that without the latest treatment, life will be grim indeed. ■

References

1. Moynihan R, Heath I, Henry D (2002) Selling sickness: The pharmaceutical industry and disease mongering. BMJ 324: 886–891.
2. World Health Organization (2004) World medicines situation. Geneva: World Health Organization. Available: http://w3.whosea.org/LinkFiles/Reports_World_Medicines_Situation.pdf. Accessed 7 March 2006.
3. Brown B, Standing Committee on Health (2004) Opening the medicine cabinet: First report on health aspects of prescription drugs. Ottawa (Ontario): House of Commons. Available: http://www.parl.gc.ca/InfocomDoc/Documents/37/3/parlbus/commbus/house/reports/healrp01-e.htm. Accessed 7 March 2006.
4. Van Egmond-Vettenburg JS, ter Steege H (2001) Marketing plans for medicinal products available on prescription only: The current situation. Health Care Inspectorate. Amsterdam: The Hague. Available: http://healthyskepticism.org/publications/editions/2002/IN04.htm. Accessed 7 March 2006.
5. Parmar H (2005 December) The communication gap: Pharmaceutical direct-to-consumer advertising in Europe. Pharmaceutical Field. Available: http://www.inpharm.com/static/intelligence/pdf/MAG_394184.pdf. Accessed 7 March 2006.
6. Outterson K (2005) Agony in the antipodes: The generic drug provisions of the Australia–USA free trade agreement. J Gen Med 2: 316–326.
7. Gardner D, Mintzes B, Ostry A (2003) Direct-to-consumer prescription drug advertising in Canada: Permission by default? CMAJ 169: 425–427.
8. Berndt ER (2005) To inform or persuade? Direct-to-consumer advertising of prescription drugs. N Engl J Med 352: 325–328.
9. Division of Drug Marketing, Advertising, and Communication; US Food and Drug Administration (2004) Guidance for industry. "Help-seeking" and other disease awareness communications by or on behalf of drug and device firms. Rockville (Maryland): US Food and Drug Administration. Available: http://www.fda.gov/cder/guidance/6019dft.pdf. Accessed 7 March 2006.
10. Jackson T (2003) Regulator spells out rules on disease awareness campaigns. BMJ 326: 1219.
11. Sheldon T (2002) Dutch GPs call for a ban on Novartis products. BMJ 325: 355.
12. 't Jong GW, Stricker BWH, Sturkenboom MCJM (2004) Marketing in the lay media and prescriptions of terbinafine in primary care. BMJ 328: 931.
13. Therapeutics Initiative (2003) Do statins have a role in primary prevention? Ther Lett 48. Available: http://www.ti.ubc.ca/PDF/48.pdf. Accessed 7 March 2006.
14. Quick JD, Hogerzeil HV, Rago L, Reggi V, de Joncheere K (2003) Ensuring ethical drug promotion—Whose responsibility? Lancet 362: 747.
15. Pettigrew P (2005) Minister of health. Letter to Anne Rochon Ford, June 16, 2004. Toronto (Ontario): Women and Health Protection. Available: http://www.whp-apsf.ca/pdf/Pfizer_adRresponse.pdf. Accessed 7 March 2006.
16. Lenzer J (2004) US consumer body calls for review of cholesterol guidelines. BMJ 329: 759.
17. Pfizer (2006) Form 10-Q for Pfizer Inc. Quarterly report. May 6, 2005. Item 2. Management's discussion and analysis of financial condition and results of operations. New York: Pfizer. Available: http://biz.yahoo.com/e/050506/pfe10-q.html. Accessed 7 March 2006.
18. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, et al. (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA 288: 321–333.
19. Fem 7 (1998–1999) Menopausal complaints—Estrogen deficiency. Darmstadt (Germany): Merck KGaA. Available: http://www.fem7.com/estrogen.htm. Accessed 7 March 2007.
20. The Society of Obstetricians and Gynaecologists of Canada (2006) The journalist's menopause handbook. Ottawa (Ontario): The Society of Obstetricians and Gynaecologists of Canada. Available: http://www.sogc.org/media/pdf/advisories/Menopause-journalists-guide_e.pdf. Accessed 7 March 2006.
21. Mamdani M, Juurlink DN, Kopp A, Naglie G, Austin PC, et al. (2004) Gastrointestinal bleeding after the introduction of Cox-2 inhibitors: Ecological study. BMJ 328: 1415–1416.
22. Bashford JNR, Norwood J, Chapman SR (1998) Why are patients prescribed proton pump inhibitors? Retrospective analysis of link between morbidity and prescribing in the General Practice Research Database. BMJ 317: 452–456.
23. Dial S, Alrasadi K, Manoukian C, Huang A, Menzies D (2004) Risk of *clostridium difficile* among hospital inpatients prescribed proton pump inhibitors: Cohort and case-control studies. CMAJ 171: 33–38.
24. Class S (2002) Pharma overview. Chem Eng News 80: 39–49. Available: http://pubs.acs.org/cen/coverstory/8048/8048pharmaceutical.html. Accessed 7 March 2006.
25. European Agency for the Evaluation of Medicinal Products [EMEA], Committee for Proprietary Medicinal Products [CPMP] (2003) Summary information on referral opinion following arbitration pursuant to article 30 of council directive 2001/83/EC for Prozac and associated names. London: EMEA. Available: http://www.emea.eu.int/pdfs/human/referral/326303en.pdf. Accessed 7 March 2006.
26. National Prescribing Service (2004) Sertraline (Zoloft), fluoxetine (Lovan, Prozac) for premenstrual dysphoric disorder. Surry Hills (New South Wales): National Prescribing Service. Available: http://www.npsradar.org.au/site.php?page=1&content=/npsradar/content/sertraline.html#Reason_for_PBS_listing. Accessed 7 March 2006.
27. Stockbridge LL (2002) Untitled letter to G Brophy, Director U.S. Regulatory Affairs, Eli Lilly. Rockville (Maryland): US Food and Drug Administration. Available: http://www.fda.gov/cder/warn/nov2000/dd9523.pdf. Accessed 7 March 2006.
28. Wittchen HU, Becker E, Lieb R, Krause P (2002) Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. Psychol Med 32: 119–132.
29. Moynihan R, Cassels A (2005) Selling sickness: How the worlds biggest pharmaceutical companies are turning us all into patients. New York: Nation Books. 254 p.
30. US Food and Drug Administration (2005) Warning letters and untitled letters to pharmaceutical companies. Rockville (Maryland): US Food and Drug Administration. Available: http://www.fda.gov/cder/warn. Accessed 7 March 2006.
31. Lacasse J, Leo J (2005) Serotonin and depression: A disconnect between the advertisements and the scientific literature. PLoS Med 2: e392. DOI: 10.1371/journal.pmed.0020392
32. O'Brien C (2003 October 5) Drug firm to drop non-addiction claim. Irish Times.
33. Kravitz RL, Epstein RM, Feldman MD, Franz CE, Azari R, et al. (2005) Influence of patients' requests for direct-to-consumer advertised antidepressants: A randomised controlled trial. JAMA 293: 1995–2002.
34. European Commission (2003) Community code relating to medicinal products for human use. Brussels: European Commission. Available: http://europa.eu.int/scadplus/leg/en/lvb/l21230.htm. Accessed 7 March 2006.
35. Department of Justice [Canada]. Food and Drugs Act. Chapter F-27. Ottawa (Ontario). Available: http://laws.justice.gc.ca/en/F-27/191368.html. Accessed 7 March 2006
36. World Health Organization (1988) Ethical criteria for medicinal drug promotion. Geneva: World Health Organization. Available: http://mednet2.who.int/tbs/promo/whozip08e.pdf. Accessed 7 March 2006.

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

Found at DOI: 10.1371/journal.pmed.0030213.sd001 (25 KB DOC).

Acknowledgments

I would like to acknowledge the support of P. Sulochana, Correspondent, Sai Padmavathi School of Pharmacy, Tirupathi

C. Jairaj Kumar (jairaj81in@yahoo.co.in)

Abhizith Deoker

Ashwini Kumar

Arunachalam Kumar
Kasturba Medical College
Mangalore, Karnataka, India

B. M. Hegde
Manipal Academy of Higher Education
Manipal, Karnataka, India

References

1. Lal A (2001) Pharmaceutical drug promotion: How it is being practiced in India? J Assoc Physicians India 49: 266–273.
2. Kumar CJ, Kumar A (2005) Is prescription necessary to buy drugs in India [abstract]? Regional Conference on Medical Ethics; 2005 7–8 March; Tirupati, India. Padmavathi School of Nursing. pp. 3–5.
3. Kohn L, Corrigan J, Donaldson M, editors (2000) To err is human: Building a safer health system. Washington (D. C.): National Academy Press. 287 p.
4. Starfield B (2000) Is US health really best in the world? JAMA 284: 483–485.
5. Hegde BM (2001) Is academic medicine for sale? J Assoc Physicians India 49: 831–832.
6. Angell M (1997) Anti-polymer antibodies, silicone breast implants, and fibromyalgia. Lancet 349: 1171–1172.
7. Smith R (2003) The screening industry. BMJ 326. Available: http://bmj.bmjjournals.com/cgi/content/full/326/7395/0/f. Accessed 8 March 2006.
8. [Anonymous] (2000) Drug company influence on medical education in USA. Lancet 356: 781–783.

Citation: Kumar CJ, Deoker A, Kumar A, Kumar A, Hegde BM (2006) Awareness and attitudes about disease mongering among medical and pharmaceutical students. PLoS Med 3(4): e213.

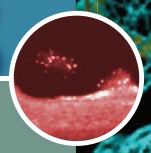
Funding: The authors received no specific funding for this article.

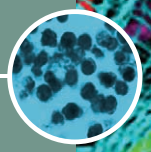
Competing Interests: The authors have declared that no competing interests exist.

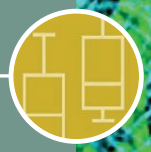
DOI: 10.1371/journal.pmed.0030213

PLoS PATHOGENS

Understanding how pathogens affect living systems







On September 30th 2005, the Public Library of Science (PLoS), a leading international online provider of freely accessible, peer-reviewed and highly cited scientific research, launched PLoS Pathogens, a new title in the PLoS community journal series.

Registering for a regular table of contents e-mail alert is the convenient way to keep this quality content at your fingertips.

Each month, quality peer-reviewed research is instantly and freely available online for you to read, copy, distribute and use without limits. We simply ask that you credit the author and original source. **This is the beauty of true open access.**

Want some even better news? **Readers will pay nothing for this first rate content.**

Covering all aspects of pathogen research, from molecules to physiology, the focus of *PLoS Pathogens* is broad, deep and international. Combine this with speed—once papers have completed review we publish them online without delay—and we have a recipe for an outstanding publication. **We invite you to submit your next great paper to *PLoS Pathogens*.**

The pathogen research community has a new home, *visit* ***www.plospathogens.org*** *today.*

Main image: Robertson M, *PLoS Biology*. Small images: Weiser J, *PLoS Pathogens Preview*.
Cover image: Hultgren S, Hung C, Salk Institute for Biological Studies.

Imagine what we could do with free global access to medical research.

Since its launch one year ago, *PLoS Medicine* has shaken up medical publishing, liberating communication and empowering researchers. World-class peer-reviewed research and comment are now instantly and freely accessible online to read, copy, translate and distribute without limits. To join the open access community, you can:

- Read the journal at http://www.plosmedicine.org
- Sign up for email alerts at http://www.plos.org/medetoc
- Submit your next paper to http://medicine.plosjms.org

www.plosmedicine.org

PLoS MEDICINE

Expanding access to health research