

## Disease Mongering\_Conference / PLoS Special Issue

Monday, 10 April 2006

"Are we becoming patients for profit? That is the question knowledgeable observers are asking.

An Inaugural Conference on Disease-Mongering, April, 11 to 13, is being hosted by the Newcastle Institute of Public Health and School of Medicine and Public Health at the University of Newcastle, Australia. Dr. David Henry, professor of clinical pharmacology, is the spokesperson for this Conference.

An international group of experts will address the commercialization of disease and medical conditions, and such public policy issues as: When does legitimate promotion of public health become mongering of disease for profit?&rdquo;

Speakers will also discuss non-medical implications&mdash;such as economic and social ramifications of medicating developmental &ldquo;conditions&rdquo; and medicalizing normal life experiences. Drug manufacturers have been hugely successful in expanding the market for lifestyle drugs by playing on peoples fears, fantasies and cravings to be forever young and sexually better than well. See, conference program and speaker roster at: <http://www.diseasemongering.org/downloads/program.pdf>

We would add several important overarching issues that were left out of the discussion:

Big Pharma money and advertising not only influence the perception of illness, the demand for drugs, and the practice of medicine, but government budgets, including health service and oversight agencies have become dependent on Big Pharma money. An out of the box analysis opened our eyes to a fundamental conflict of interest that has never been discussed. Public health policies are not merely influenced by Big Pharma; they are formulated so as to increase industry&rsquo;s profits because GOVERNMENT BUDGETS are tied to this industry&rsquo;s profits.

It happened when Congress passed the Prescription Drug Users Fees Act (PDUFA) in 1992 which ushered in a "fast track" drug approval process. In the first ten years following the passage of PDUFA the FDA has received \$825 million in industry &ldquo;user fees.&rdquo; Other government agencies have similarly become financially dependent on Big Pharma and its marketing gimmicks such as the government approved TMAP prescribing guidelines.

With increased use of patented prescription drugs&mdash;more than 50% of Americans are taking at least one drug&mdash;and increased speed with which these drugs are being approved and marketed, the number of people killed or harmed from adverse drug reactions (ADRs) has skyrocketed. More than two million hospitalized patients in the U.S. suffered a serious ADR within a 12-month period and, of these, 106,000 died as a result of non-error ADR. &ldquo;The researchers found that over 75 per cent of these ADRs were dose-dependent, which suggests they were due to the inherent toxicity of the drugs rather than to allergic reactions [1] [2].

Prescription drug abuse&mdash;the federal Substance Abuse and Mental Health Services Administration reports that prescription medication has become the fastest-growing category of drugs being abused, with the biggest growth of abuse among people ages 12 to 24. According to SAMHSA, after marijuana, prescription drugs are the drugs most commonly abused by teenagers. Nationally, an estimated 14% of high school seniors have used prescription drugs for non-medical reasons according to a 2004 University of Michigan survey.

But in a brilliant original analysis, Jim Amrhein shows what the crass brass knuckle economic facts are behind FDA's inaction in "Buying The Parma:"

"It would make no fiscal sense for the FDA to derail the money train by blowing the whistle about some drugs' dangers -- even if it costs a few hundred thousand American lives each year to look the other way&hellip;" [Stay tuned]

Underscoring the importance of the issues addressed at this conference&mdash;and the fact that most of us could not attend&mdash;PLoS Medicine has published a special issue in conjunction with the conference devoted to Disease Mongering. Eleven articles presented at the conference are accessible free at:

<http://collections.plos.org/diseasemongering-2006.php>

### References:

Medical Errors - A Leading Cause of Death by Dr Barbara Starfield, MD, MPH, of the Johns Hopkins University, Journal of the American Medical Association (JAMA) July 26th 2000, Vol 284, No 4.; See also, Jason, et al. (Lazarou et al), Incidence of Adverse Drug Reactions in Hospitalized Patients, JAMA, Vol. 279. April 15, 1998, pp. 1200-05. Also Bates, David W., Drugs and Adverse Drug Reactions: How Worried Should We Be? JAMA, Vol. 279. April 15, 1998, pp. 1216-17.

See also, Death by Medicine By Gary Null, PhD; Carolyn Dean MD, ND; Martin Feldman, MD; Debora Rasio, MD; and Dorothy Smith, PhD, 2004 [http://www.lef.org/magazine/mag2004/mar2004\\_aws\\_i\\_death\\_02.htm](http://www.lef.org/magazine/mag2004/mar2004_aws_i_death_02.htm)

Extracts from the PLoS compilation of provocative and timely articles follow:

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### 1. Bigger and Better: How Pfizer Redefined Erectile Dysfunction by Joel Lexchin

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?

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.

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### 2. Medicine Goes to School: Teachers as Sickness Brokers for ADHD by Christine B. Phillips

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 the roles of teachers as brokers for ADHD and its treatment, and the strategies used by the pharmaceutical industry to frame educators's responses to ADHD.

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. Teachers often agree to administer 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 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.

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### 3. Female Sexual Dysfunction: A Case Study of Disease Mongering and Activist Resistance by Leonore Tiefer

&hellip;&ldquo;The pharmaceutical industry has taken an aggressive interest in sex&rdquo;&hellip;..

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." False expectations set the stage for disease mongering, a process that

encourages the conversion of socially created anxiety into medical diagnoses suitable for pharmacological treatment.

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. 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].

### 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. 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://www.jsm.issir.org>)—which has already published an industry-supported supplement on FSD [12].

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

### 4. The Latest Mania: Selling Bipolar Disorder by David Healy

"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."

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.

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". 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.

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."

#### 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].

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].

The 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.

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 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). Based on these absolute numbers I have calculated 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).

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.

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.

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.

## 5. Disease Mongering in Drug Promotion: Do Governments Have a Regulatory Role? By Barbara Mintzes

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. 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. 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].

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. 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].

### 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. 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 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].

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. 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&hellip;&hellip;&hellip;.

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## 6. Combating Disease Mongering: Daunting but Nonetheless Essential Iona Heath

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].

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.

For complete text of all 11 articles see: <http://collections.plos.org/diseasemongering-2006.php>

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