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Treating desires not diseases: a pill for every ill and an ill for every pill?

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My first recollection of modern pharmaceuticals is from the winter of 1942–1943, when my younger sister, suffering from pneumonia, was treated with M&B693 from May and Baker Pharmaceuticals (http://www.may-baker.com/). The doctor and my mother sat up all night nursing her through 'the crisis', which she survived. Most families, at least in the rich world, have similar stories to tell of how medicines developed in the past half century have saved their lives, shortened their illnesses and have made previously terminal diseases, if not curable, then at least treatable. For all of this, academic medicine and science and, notably, the pharmaceutical industry are owed much. However, these positive attributes of the industry are in danger of being obscured by a pattern of business practices that places profit above patient, emphasizes marketing over medicine and exaggerates disorders to promote drug sales. These practices, which are compounded by the extensive, Washington-based, political lobbying that is carried out by pharmaceutical companies, contribute to the increasing wave of public distrust directed at these companies.

The 1 April 2006 issue of *The British Medical Journal* ran a short note by the Australian journalist Ray Moynihan describing a new disease – motivational deficiency disorder [1]. Apparently affecting one in five Australians and diagnosed by neurologist Leth Argos through both positron emission tomography scans and scoring scales, the disease was described as treatable with a new cannabinoid CB_1 receptor antagonist indolebant. Several news organizations ran with this story, accepting it as authentic presumably for two main reasons. First, the story was released on 31 March (albeit 1 April in Australia), and, second, it sounds plausible. Motivational deficiency disorder fits in with restless legs syndrome, female sexual dysfunction, social anxiety disorder, intermittent explosive disorder, irritable male syndrome and other assorted contemporary 'diseases'. It also fits well with the barrage of pharmaceutical advertising that viewers in the USA are subject to. Indeed, one knows exactly the demographics of a TV program audience by looking at the drug advertisements: advertisements for 'leaky pipes', insomnia and erectile enhancement means an audience of >50 years. Whether the motivational deficiency disorder hoax will be celebrated 30 years hence is uncertain, unlike the BBC hoax of 1 April 1957 on harvesting spaghetti bushes in Switzerland (http://news.bbc.co.uk/onthisday/hi/dates/stories/april/1/newsid_2819000/2819261.stm). However, both hoaxes sound plausible and come from authoritative sources.

All of the above disorders are described in the medical and pharmaceutical literature as increasingly prevalent and increasingly costly in both financial and emotional terms and all, of course, are treatable with expensive drugs. Neither are these issues limited to the human condition: there is, after all, canine separation anxiety and canine cognitive dysfunction syndrome for which the appropriate drugs, Clomicalm™ and Anipryl™, respectively, are available for man's best friend, even when he no longer recognizes us.

A visitor from another planet might be surprised at this emphasis on 'lifestyle' diseases, given the readily perceived contrast between the availability of drugs for these diseases and for HIV/AIDS, malaria and other diseases that dominate the poor world. They might also be surprised by the contrasts that exist in putatively the richest, most powerful country in the world, where ~50 million people do without health insurance and much health care, and where the life-expectancy gap between the best-off and the worst-off exceeds 15 years [2]. They should not be surprised: medicine has become in large part, a market and the priorities and delivery of pharmaceuticals are determined in very significant part by market imperatives (Box 1).

The market and its imperatives

Markets may be efficient mechanisms for making commercial transactions, but medicine and markets have always enjoyed an uneasy relationship, trapped between Hippocratic oaths, fee-for-service, managed care, government influence and insurance companies [3]. The pharmaceutical industry, as part of medicine, is,

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BOX 1

Janus and the pharmaceutical industry

Similar to Janus, the pharmaceutical industry presents two faces to the world. For the scientific face, there is a deserved and profound indebtedness, both singularly and collectively, to the therapeutic molecules developed by pharmaceutical companies. Few of us, at least in the rich world, are not indebted to illness cured or life saved by modern pharmaceuticals. For the business face, which too often behaves as an asocial, greedy corporate entity, there is increasing public distrust and skepticism, a distrust that is strengthened by reports of backroom deals to keep generic drugs off the market and of FBI searches of the offices of pharmaceutical company executives [52]. Recent descriptions of financial collusion between the pharmaceutical and generic drug industries to delay the introduction of generic formulations fuel public cynicism about the motives of the principal players [53]. Michael Moore's new agitprop movie entitled *Sicko* (now in production) will not help matters (http://www.free-press-release.com/news/200609/1157907489.html).

one suspects, also trapped, as suggested by the words of Hank McKinnell, the previous CEO of Pfizer (http://www.pfizer.com), 'My children, some in high school and college by then, often sided with the critics of the pharmaceutical industry. They listened to my logic, but I could tell they weren't convinced, and to tell you the truth, I wasn't either' [4].

However, medicine is part of today's market, particularly so in the USA, where the Keynesian era, which advocated a significant role for government intervention in social and economic policies, has given way to a laissez faire expression of market principles that probably would not be either recognized or acknowledged by Adam Smith [5,6], but relates more faithfully to the views of Milton Friedman and the influential Chicago School of Economics (http://economics.uchicago.edu): 'Few trends could so undermine the very foundations of our free society as the acceptance by corporate officials of a social responsibility other than to make as much money as possible for their stockholders' [7].

The pharmaceutical industry has adopted these principles and, despite current concerns of productivity, remains a profitable industry, one that has increased in the USA with the recent passage of the Medicare Part D legislation [8,9], which specifically imposed a solely market-based plan for drug availability and specifically excluded any government intervention in price negotiations. And, with ex-Congressman Billy Tauzin, former chairman of the House Energy and Commerce Committee that has oversight of the drug industry, now heading Pharmaceutical Research and Manufacturers of America (PHRMA; http://www.phrma.org/), the legislative influence of the industry is unlikely to diminish soon [10,11]. It has, however, earned a degree of public distrust that is directed more commonly at used car salesmen and similar professions [12–15].

Markets are, as Smith first described, an efficient way of satisfying demand. However, as Friedrich Hegel recognized additionally, the market also creates demand by calling 'attention to the discomfort of the consumer, in order to provide a solution to that discomfort, in the process awakening a sense of discomfort where it had not previously existed' [16]. Markets create desire that can only be satisfied through acquisition. Hegel illustrated this with fashion, but the model extends to most areas of contemporary life

BOX 2

Cures in search of disorders

'The drug industry's calculus in apportioning its resources is cold-blooded, but there's no disputing that one old, fat, bald, fungus-ridden rich old man who can't get it up counts for more than half a billion people who are vulnerable to malaria, but too poor to buy medicines they need'
Ken Silverstein, The Nation, 1999 (http://www.thenation.com/doc/19990719/silverstein).

in a consumer-led, consumption-driven culture. The marketing of drugs is no different, save only that it requires the intermediacy of a prescription between product and consumer. Hence, contemporary media advertising emphasizes the 'need to talk to your doctor' and often sweetens this with either a free trial or a US$10-off coupon for the next prescription (Box 2).

Disease classification and the Lake Wobegon phenomenon

'Where all the children are above average' [Garrison Keillor (http://prairiehome.publicradio.org)]. . .and everyone has a definable syndrome. The common link among the lifestyle diseases discussed previously is that they fall into a rapidly expanding area of medicine that is characterized by the phenomenon of 'disease-mongering': the creation and/or extension of disease terminology to identify for drug remediation what is, in essence, a normal condition [17–20]. Thus, in one estimate, female sexual dysfunction might affect up to 42% of the women between the ages of 18 and 60 [21]. With this prevalence, what is described is either normal or the criteria for definition have been drawn so broadly that the classification is without either meaning or diagnostic significance. In either event the rationale for a single, effective, drug treatment is seriously undermined. A similar case might be advanced for the other diseases already listed. In each case, the boundaries of what are either plausibly or demonstrably real (but limited) pathological conditions are extended into the normal range. These issues have been discussed recently in several articles and books [17–20] (see also a series of recent articles on pharmaceutical marketing in *PLoS Medicine* (http://www.plosmedicine.org). Few would deny the underlying pathology and need for intervention in diseases such as attention deficit hyperactivity disorder (ADHD), restless legs syndrome and female sexual dysfunction. Rather the argument is over the expansion and the inclusiveness of the classification, and the role that such over-extension has in unnecessary drug treatment, and in ignoring the role of other and, in many cases, more appropriate, non-drug treatments.

There are several underlying reasons for this apparent shift in emphasis of direction in the industry. Companies, under the constantly heightened expectations of growth and profit increases, have adopted the 'blockbuster' model of drug discovery and development. However, this is not a sustainable route – nothing can increase at 10% per annum for ever [22] – and the expected innovation and productivity increases from the new technologies of genomics, informatics, combinatorial chemistry and high-throughput screening have yet to be fully realized [10,23]. Accordingly, to sustain growth companies have embarked on a series of mergers and acquisitions, the generation of

non-innovative, follow-on drugs, the repackaging of existing drugs in combination form, the extension of patents, challenges to the generic drug industry, and the expansion of disease classifications and definitions through advertising to promote greater sales of existing drugs. Few doubt that the new, genomics-based technologies will pay off, but the path is likely to be longer and more expensive than was believed originally. Finally, although there is no shortage of diseases to be treated in both the rich and the poor worlds, the former are difficult because they are, to a significant part, diseases of aging, including neurodegenerative disorders, whereas the latter are difficult because the poor cannot pay for medicines.

Pharmaceutical advertising, which is currently permitted only in New Zealand and the USA, the latter under the eye of the Food and Drug Administration (FDA; http://www.fda.gov), fuels the demand [e.g. FDA oversight of direct-to-consumer advertising has limitations (http://www.gao.gov)] [24–26]). A recently published report from the Institute of Medicine of the US National Academy of Sciences (http://www.iom.edu) is not kind to the FDA, describing it as dysfunctional in several respects: 'Some also have serious concerns that the regulator has been ''captured'' by the industry it regulates' and 'The agency needs a more nuanced set of tools to signal uncertainties, to reduce advertising that drives rapid uptake of new drugs, or to compel additional studies in the actual patient populations who take the drug after its approval' [27].

The response of PHRMA, was, predictably, negative, preferring as it does as little government regulation as possible [28]. Unfortunately, the FDA is not the only regulatory authority that is under attack for shirking its responsibilities. The Centers for Disease Control and Management (http://www.cdc.gov) are also under attack from the media and under investigation by the General Accounting Office for complaints of personnel and financial mismanagement, and for political influence over science and public health policy [29,30] [see also GAO, HHS, OIG, Waxman launch investigations into alleged oversight, morale problems at CDC. (http://www.medicalnewstoday.com)]. It is no coincidence that these two agencies find themselves under attack because the regulation and oversight that is necessary for effective health-care delivery runs counter, in many cases, to the political ideology of the Bush administration [31]. Karl Polanyi knew the consequences of this 'Planning and control are being attacked as a denial of freedom, and the freedom that regulation creates is being denounced as unfreedom' [32].

Those familiar cautionary words used in advertising, 'See your doctor', 'between you and your doctor' and 'only your doctor can prescribe' are cop-out phrases with which to deny responsibility of fanning the flames of demand. Equally misleading are the advertisements that feature media and other public personalities who are often paid for their services. Most recently, Pfizer has featured Dr Robert Jarvik, the inventor of the artificial heart, in advertisements for Lipitor™, in which he is shown vigorously rowing a racing skiff on a lake. It says little for the integrity of this advertisement that a body double was used for this sequence ([33]; http://www.lakewashingtonrowing.com/newsletters/april2006.pdf). Nonetheless, such direct-to-consumer works, judged by the steadily escalating money dedicated to it, but for contrasting views, including a report from the late, lamented US Office of Technology Assessment, see: What goes into the cost of prescription drugs? (http://www.phrma.org); Office of Technology Assessment (2003), Pharmaceutical R&D: Costs, risks and rewards (http://www.wws.princeton.edu/ota/); and Costs of monopoly pricing under patent protection (http://www.earthinstitute.columbia.edu/cgsd/accesstomedicines_papers.html).

BOX 3

Irritable male syndrome

Based on work by Gerald Lincoln of the Medical Research Council in Edinburgh, UK (http://www.hrsu.mrc.ac.uk), irritable male syndrome is argued to derive from declining testosterone levels as a consequence of either age or stress, producing bad-tempered, irritable individuals. The syndrome is described in detail by California psychotherapist Jed Diamond [54], and his web site (http://www.theirritablemale.com) offers a 50-question quiz to aid diagnosis. I scored 50 on the test (not very difficult to do), so I am a probable candidate for irritable male syndrome. Not everyone is sympathetic to this syndrome. The British tabloid *The Daily Mirror* posed two questions in March, 2002 (http://www.worldwidewords.org/turnsofphrase/tp-irr1.htm).

- Question: What do you call a man who is always tired, miserable and irritable?

Answer: Normal.

- Question: How can you tell if a man has irritable male syndrome?

Answer: You ask him to pass the salt and he yells, 'take, take, take – that's all you ever do!'

There is, of course, both purpose and consequence to drug advertising. Pharmaceutical companies expand their market and make more money, and patients might learn about both diseases and drugs. But, too often, this is at the cost of believing increasingly that the solution to every ill is a pill, and ignoring health and mortality consequences when the use of a drug spreads beyond its appropriate patient and disease base. Few would deny that Vioxx was probably greatly over-prescribed relative to its benefits, in significant part because of the extensive advertising campaign [18,34]. Parents are now demanding prescriptions for ADHD drugs to give their children a 'boost' in school or college. This is a form of 'academic doping', in part to cope with an academic environment that is increasingly stressed by the testing demands of the 'no child left behind act' [35]. Advertising has almost certainly had a major role in the fivefold increase in atypical antipsychotic prescribing to children and adolescents from 1993 to 2002 [36] [E. Pringle, E. (2006) Drug companies still peddling risperdal & zyprexa. Scoop Independent News (http://www.scoop.co.nz)]. Similarly, food advertising to children is, according to an Institute of Medicine study, a significant contributor to the current epidemic of childhood obesity [37,38]. Such advertising plays to people's desires, in this case young and adolescent children, with the familiar results of over-consumption, with the profit going to industry and the attendant economic and social costs being externalized to the community at large (Box 3).

Restless legs syndrome: an ill looking for a pill?

In 2003, GlaxoSmithKline (http://www.gsk.com) had two press releases concerning restless legs syndrome, which they described as 'a little known and often misdiagnosed disorder. . .can have as great an impact on the quality of life as type 2 diabetes, hypertension and acute myocardial infarction' and 'is keeping America

BOX 4

Lady Hillingdon's lament: lie back and think of England

The phrase 'lie back and think of England' is attributed to Lady Hillingdon, wife of the 2nd Baron Hillingdon, who is reported to have said about her husband 'I now endure but two calls a week, and when I hear his steps outside my door I lie down on my bed, close my eyes, open my legs and think of England.' Others have attributed the phrase as advice given by Queen Victoria to her daughter on her wedding night. Generally, however, the phrase stems from the reported Victorian prudery of that age. The Victorians might have been sexually ignorant, but the abundant, well-read pornographic literature of that time indicates that they were, as a class, probably not sexually dysfunctional [55].

awake at night', (http://www.gsk.com/ControllerServlet?appId=4&pageId=402&newsid=175; http://gsk.com/press_archive/press2003/press_06102003.htm). Ropinirole was approved for use subsequently by the FDA in May 2005, noting that this condition affects 10% of the population. A subsequent study revealed a prevalence of 2.7% [39]. Woloshin and Schwartz have analyzed the literature and the media reporting around restless legs syndrome [40]. Although they do not disagree that the syndrome exists, they argue that the prevalence and seriousness have been exaggerated significantly, and that the media have accepted uncritically the claims advanced in the press releases, have generally described the syndrome and the drug in overly dramatic terms and have failed to note that the effects of ropinirole are relatively modest and that the trials concerned relatively short-term use. They conclude that, '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 over-diagnosis. In essence, the media seemed to have been co-opted into the disease mongering process'.

Female sexual dysfunction? A pill looking for an ill?

Subsequent to the introduction of Viagra™, there have been major efforts to expand the market for selective phosphodiesterase 5 (PDE5) inhibitors by expanding the definition of erectile dysfunction to include conditions that do not stem from organic causes, such as prostate surgery and diabetes [41]. Judged by TV advertising and sales, this has been successful. Additionally, there has been an extensive campaign for 'pink viagra' for the condition of female sexual dysfunction, which is reported to affect 33–43% of women [21,42]. This has not been successful to date [43]. Critical commentaries on this campaign have argued that this epidemiology has been inflated and exaggerated by a lack of understanding of the multiple causes that might lead to an unsatisfactory sex life and, that it reflects little more than an attempt to commodify female sexual behavior [44–47]. An understanding of female sexual behavior requires more than measurements of pelvic blood flow (Box 4).

Toenail fungus: a global threat?

One of the most entertaining, and revolting, advertisements on television today is for Digger, a cute little dermatophyte who loves to live under your toenails and proclaims 'I'm not leaving'. Entertaining because it gets your attention for the underlying message that Lamisil™, the fourth best-selling drug from Novartis (http://www.novartis.com), is bad for Digger and good for you, but not revolting enough to make you change the channel [http://www.pharma.us.novartis.com/newsroom/pressReleases/index.jsp; Walker, R., The beast under your toe nail (http://www.slate.com)]. And that, of course, is the intention of Novartis, who have reportedly spent over US$200 million on Lamisil ads over the past 3 years [see Langreth, R. and Herper, M. (2006) Wired Magazine Pill pushers go into overdrive (http://wired.com)]. A previous version of the advertisement was banned by the FDA on the grounds that it overstated the efficacy of the drug (only 38% of patients achieve cure), minimized the risk and made claims of unsubstantiated superiority (http://www.pharmcast.com/WarningLetters/Yr2003/August2003/Novartis0803.htm). Regardless of this, advertising works and sales of Lamisil now exceed US$1 billion y^{-1}.

Conclusions

The pharmaceutical industry faces a set of difficult choices over the next decade. Although few doubt that the scientific advances in genomics, screening and informatics technologies in which so much has been invested will pay off, it is also clear that both the timescale and the costs are greater than anticipated. It is also clear that, ultimately, there are limits to the affordability and the extent of health care that can be provided either privately or publicly. These limits need to be dealt with, and with some urgency, particularly in the USA, where expenditure already exceeds 16% of GDP. This expenditure has not, however, made the USA the healthiest nation on Earth. On the contrary, in two key areas, infant mortality and longevity, the USA lags behind many other nations, including every country in the Organisation for Economic Co-operation and Development (OECD), see US Census Bureau International database (http://www.census.gov/ipc/wwwidbnew.html). At the other extreme of global wealth and power, the diseases of the poor world must also receive far greater attention, on pragmatic, if not, moral grounds, because a healthier, more prosperous poor world is a partner in solving the global problems of the 21st century.

The pharmaceutical industry, thus, has two extreme alternatives. It can continue its market-based approach, relying on a progressively more difficult to maintain, 'blockbuster' model of drug discovery and delivery to generate its profits, afflicting the poor by continuing to ignore the tropical and infectious diseases that plague them, and by hoarding and defending its intellectual property, and comforting the rich by defining more life-style diseases that afflict them and that are treatable by its products rather than by exercise, diet, public health and acceptance that we can grow old gracefully. We can, in fact, anticipate Aldous Huxley's predicted future in his Brave New World: '''Fortunate boys!'' said the Controller. ''No pains have been spared to make your lives emotionally easy – to preserve you, as far as possible, from having any emotions at all.''' Perhaps the ultimate (and most cynical) extension of Huxley's vision will be a merger between McDonalds and pharma to create McPharma selling both 'happy pills' and 'happy meals' (Box 5).

There are alternative approaches that recognize both the remarkable scientific achievements and organization of the pharmaceutical industry and marries these with the need for a more equitable, efficient delivery of pharmaceutical care. Thus, the

BOX 5

Tranquilax™: the ultimate pharmaceutical?

Tranquilax™, a combination of a sedative, tranquilizer and laxative, featured prominently in the 1963 film, 'Heaven's Above', starring Peter Sellers as the Reverend John Smallwood. After its market failure, which was precipitated by Sellers's Christian good works, Tranquilax was repackaged as Triple Unction™ as the guarantee of inner cleanliness to 'Build you up and clean you out.' Either way, it would probably sell today.

Nobel prize-winning economist Joseph Stiglitz has argued that the current patent system and business model of the pharmaceutical industry fails to reward innovation in crucial areas of medicine that affect the poor world. Rather than using patents as a reward for innovation, he suggests that a system of prizes might be an alternative that would give very large financial rewards for major innovative advances and small rewards only for negligible advances [48,49]. An alternative model, which has been discussed recently, is to implement open-source research using the software developments that led to open-source Linux as a model [50]. There are well-recognized differences between software development and molecule development, but there is one element in common, at least – many scientists will work for recognition according to the scientific ethos described by Robert Merton [51].

Finally, there is a global responsibility. Despite my harsh words, the pharmaceutical industry should not be the only, or even the major, whipping boy: the rich world in general carries major responsibility when we favor tax cuts and wars over aid and assistance, and promote abstinence over medicines. We are, ultimately, whether we want to be or not, our brothers' keeper.

Conflicts

David J. Triggle has no current research support from any private source. He serves on the Science Advisory Boards of three small biotechnology companies for which he receives travel reimbursement and honoraria (none in either 2005 or 2006). He gives scientific seminars at US universities and elsewhere for which he accepts local travel expenses only and declines honoraria. He has served as an expert witness in several litigation issues for which he receives personally travel expenses only (and, in one case, a fee for preparing a written document in 2005). He receives royalties from several academic publishers, including Elsevier, for writing and editing activities. He is the Senior Editor, with John Taylor, of the forthcoming 2nd edition of *Comprehensive Medicinal Chemistry* (Elsevier). Parenthetically, all but one of his many graduate students and post-doctoral fellows work in the pharmaceutical and biotechnology industries, to which they have made many significant contributions.

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