INTRODUCTION

The Journal of Ethics in Mental Health would like to warmly thank Dr. Richard Warner for inviting authors to contribute to this special supplement on the relationship between psychiatry and the pharmaceutical industry. We are also very grateful to Dr. Warner for contributing his guest editorial. Dr. Warner is Professor of Psychiatry and Adjunct Professor of Anthropology at the University of Colorado and an internationally recognized authority in a number of areas, including recovery from schizophrenia and social inclusion. He is well known for his comprehensive views of treatment and recovery and the range of issues that affect it, including the role of medications.

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Ethical Problems in the Relationship of Psychiatry to the Pharmaceutical Industry

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Psychiatry and the pharmaceutical industry have been embarrassed by U.S. senate hearings and a series of articles in the New York Times revealing that a number of prominent psychiatrists have failed to report significant financial conflicts of interest. Harvard research psychiatrists, whose work has encouraged the use of antipsychotic medication in children, failed to report to the university most of their consulting income from pharmaceutical companies, skirting a requirement that involvement in human subjects' research be free of significant personal industry remuneration. Another research psychiatrist at Emory University did not declare $1.2 million of $2.8 million in industry earnings to his university. An influential psychiatrist who hosted a popular National Public Radio program failed to report $1.3 million in drug company earnings: when the network learned of this conflict, they removed the program from its satellite service (Harris, 2008a).

The close ties between academic psychiatry and industry that spawned the concerns raised by the U.S. senate hearings have become more prominent since the passage of the Bayh-Dole Act in 1980. The intent of that act was to speed the commercialization of government-funded research discoveries and create new markets and industries. An unintended consequence has been decreased public trust in biomedical research. The conflicts between serving patients and marketing products have led to the formulation by the American Association of Medical Colleges of new standards to restrict the participation of investigators with financial conflicts of interest in human subjects' research. Some observers fear that expanded academic-industry partnerships have led to a credibility crisis for medicine fostered by such practices as increases in the "off-label" promotion of medication use, industry control of research priorities, bias in reporting research results, the "ghostwriting" of research articles and the involvement of industry in the ongoing education of physicians. (See McHenry and Jureidini in this issue.)

The off-label promotion of pharmaceuticals by key psychiatric opinion leaders has been considered by some observers, including Moncreiff in this issue, to spill over into "disease-mongering," as it seeks to find new uses for approved drugs. An example would be the 40-fold increase in the diagnosis of bipolar disorder in the U.S. between 1994 and 2003 based on the work of the Harvard psychiatrists targeted by the senate hearings. The work of these researchers in identifying bipolar disorder in children has stimulated a greatly expanded use of antipsychotic medications in this age group. More than a quarter of the prescriptions for Johnson and Johnson's antipsychotic, Risperdal, is now for children and adolescents, although only a small fraction of those with a psychotic illness would be expected in this population. The close links between the drug company and the research team is illustrated by the three research goals of the Harvard center for the study of pediatric psychopathology in their 2002 annual report – "improve psychiatric care for children, have high standards and 'move forward the commercial goals of J.&J.'"(Harris, 2008b). A similar concern about "disease-mongering" has been raised by the broad international interest in the "prevention" of psychosis through the use of medications and other interventions before the condition is fully apparent. This interest persists despite the observation that the best screening instruments for the prediction of psychosis have a 98% false-positive rate in the general population

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and a 66% false-positive rate in highly selected groups of disturbed young people in two intervention studies funded by the makers of the antipsychotic medications Risperdal and Zyprexa. The use of medications in these prevention trials was associated with a significant risk of side effects (Warner, 2005).

Concern about industry influence in creating bias in the reporting of research results, emphasized by Fava in this issue, has been heightened by a survey which reveals that a majority of medical school research departments do not prohibit the common practices of ghostwriting articles or of industry sponsors inserting their own statistical analyses. Two-thirds of these departments would allow sponsors to prohibit researchers from sharing their data upon conclusion of the study (Mello et al., 2005). Financial conflict of interest has been shown to be frequent, and declaration of this conflict close to zero, among lead authors in medical articles (Krimsky et al., 1998), Diagnostic and Statistical Manual panel members (Cosgrove et al., 2006) and authors of clinical practice guidelines (Choudhry et al., 2002). Selective reporting of research results distorts the data available to practitioners. When published studies of SSRIs were compared to study data submitted to the Swedish drug approval authority, it was found that studies showing positive effects were more likely to be published multiple times and that many articles ignored less favorable data. These biases varied from product to product, making it impossible to form an accurate impression of the effectiveness of any one SSRI (Melander et al., 2003). A review of all the clinical trials in four major psychiatric journals between 2001 and 2003 found that nearly half of the authors reported financial conflict of interest, and that these clinical trials were five times more likely to report a positive result for the test product (Perlis et al., 2006). Pharmaceutical companies hire medical communications companies to write journal articles favorable to their product and pay a well-known academic to publish it under his or her name. At least 10% of medical articles are ghostwritten in this fashion, including 50% of industry-sponsored drug trials (Moffatt & Elliott, 2007).

More than three-quarters of industry spending on marketing is for free samples and detailing physicians. Since samples assist pharmaceutical representatives in getting appointments with doctors, we may assume that the industry believes that their investment in detailing is productive. The industry hires one representative for every six physicians in the U.S. (See Pollack et al. in this issue.) Teaching hospital physicians meet with representatives once or twice a month on average and, prior to the imposition of recent restrictions, accepted industry funded meals at least once a month (Lurie et al., 1990). Industry also contracts with companies that provide continuing medical education (CME) to physicians. To what extent is the practice of physicians compromised by these efforts? Industry sponsored CME presentations have been shown to preferentially highlight the sponsor's drugs (Wazana, 2000). Meeting with drug representatives, accepting free meals and attending company-sponsored CME events have been shown to be associated with increased prescribing of the sponsor's drugs and non-rational prescribing practices (Lurie et al., 1990; Chren & Landefeld, 1994; Wazana, 2000). Sometimes this marketing is clearly not in the patient's interest. When the anticonvulsant gabapentin was released, the off-label promotion of the drug as a mood-stabilizer for people with bipolar disorder, based on low-quality review articles distributed by industry representatives, led to a surge in its use. The subsequent randomized controlled trials, however, found it to be ineffective for this purpose (Williams et al., 2009). Physicians are at risk of branding themselves as collaborators with the pharmaceutical industry. Although, in a study of resident physicians in Virginia, only a small percentage were willing to wear a pharmaceutical company logo on the breast pocket of their white coat, virtually all were carrying industry-branded equipment, including 95% who were sporting a drug company logo on their stethoscopes – all gifts from company representatives (Sigworth et al., 2001). The physicians' behavior met AMA standards, that industry gifts should be of negligible value, but is that standard adequate? Does carrying company branded equipment constitute product endorsement or, more broadly, an endorsement for the use of medications in general, to the exclusion of other approaches?

A relationship which has been profitable to both pharmaceutical companies and physicians has become an embarrassment. New regulations are being promulgated to restrict gift-taking, funding for educational travel and conflicts of interest in research. Will they be enough to

restore public confidence in the bias-free practice of psychiatry? Equally important, where will psychiatrists learn of advances in psychiatry – from meetings with drug representatives and industry sponsored symposia or from publications that are tainted by selective reporting of industry-sponsored research? Medicine needs the pharmaceutical industry to produce effective treatments and the industry must have a partnership with medicine to be able to conduct human subjects' research on its products. But it is not necessary for the industry to have control over the conduct of the research and its publication. Society should take the opportunity presented by the current crisis of confidence to evaluate whether our present methods of industry funding of medical research and education is in the public interest or whether we should redesign the system so that industry can, instead, contribute to research funding through independent bodies such as the National Institutes of Health.

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ARTICLE
Special Theme issue article

Pharmacists, the Pharmaceutical Industry, and Ethics

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Abstract

Considerable ethics-related focus has been directed to the pharmaceutical industry's relationship with physicians, in part because physicians have the only profession able to prescribe much of what the industry manufactures. In Alberta, however, pharmacists have recently been permitted to modify physician prescriptions for a patient and even to prescribe without physician involvement. This paper will examine how this change in responsibilities could change pharmacists' relationships with the industry.

Key words: pharmacist, pharmaceutical inductry, ethics, prescribing, conflicts of interest.

Ethical concerns about the pharmaceutical industry have prompted numerous media stories, academic articles, conference presentations, books and television storylines. However few people would applaud the demise of commercial pharmaceutical manufacturers -- whether of branded or generic products -- because many of their products help prevent or forestall death, restore diminished or lost functions and recover lives of meaning and connection. Since product development and manufacture occurs in an exceedingly competitive marketplace, many corporate activities can be ethically justified as per business ethics. But perfect competition requires many buyers and sellers, full and timely information, freedom of entry and exit and a uniform item. These qualities are absent or minimal within healthcare and so the marketplace alone cannot be relied on for quality, efficiency, fairness or met needs. Various pharmaceutical company activities seem not just questionable, but far beyond the pale of such business-related virtues as integrity, fair reciprocity and respect. Substantial suspicion about the industry is the result. Multimillion-dollar legal settlements for deceptive advertising, holding back negative research findings, and unfair business practices stoke such cynicism. Likewise for misleading patent extensions[1], "ghost written"[2] academic articles, lavish professional conferences, and statistics correlating researcher and physician honorariums and grants with disproportionately favourable conclusions about their products.

Much attention, appropriately so, has been devoted to conflicts of interest among industry, physicians and university-college medical programs (Davar 2008, Streiffer 2006, Perlis et al 2005, Wazana 2000, Bodenheimer 2000, Schwartz 1987). As fiduciaries, physicians must put patients' well being before all else and serve as their advocates. Universities and colleges' purposes are to develop and share knowledge and to promote open inquiry. As private health-related businesses, pharmaceutical companies are expected to "provide a societal benefit which helps generate… profit" (Schwartz, 83). These objectives often compete and clash with each other. This paper, however, will examine the ethical implications of pharmacists' relationships with the pharmaceutical industry. Impetus for this examination comes from a recent change in pharmacist responsibilities in Alberta. The province's *Health Profession Act* was amended to include the *Pharmacists Profession Regulation* in 2006. This amendment permits licensed pharmacists to alter physician-written prescriptions as well as to prescribe independently of physicians. This change is important because pharmacist responsibilities are becoming progressively similar to those of physicians. Moreover this is a substantive issue in mental health and addiction care because many therapies are pharmacological. Just as significant ethical worries about the relationships between physicians and the pharmaceutical industry have and continue to exist, what worries about pharmacist-industry relationship need analysis and resolution?

Pharmacy's Evolution:

Around 1080 A.D., infirmaries built by the Knights Hospitallers to care for ailing pilgrims to the Holy Land included the first pharmacists qua chemists (Jonsen 2000). "Apothecary" appears in the English language around 1350 A.D. and *apotheca* is Latin for storehouse for such things as herbs and spices (*Webster's* 1983). Specialized knowledge about natural products and chemicals and mixing them into therapeutic compounds defined the pharmacist role into the 1900s. Large scale, assembly line manufacturing began to emerge in the 1950s in North America when immense research efforts produced substantive health benefits for many common illnesses and conditions. Yet knowledge of clinical diagnoses and prognoses as well as drug benefits, burdens and risks rested with physicians. Physician-written prescriptions were therefore a necessary condition for access to pharmacotherapies.

Although mixing and selling products from manufacturers remained primary responsibilities, pharmacists were recognized as health professionals in various provincial regulations during the 1960s. The concept of "clinical pharmacy" subsequently arose,

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indicative of closer interactions with individual patients and with their healthcare practitioners. As Pearson notes, pharmacists' role in "'the responsible provision of drug therapy for the purpose of achieving definitive outcomes that improve a patient's quality of life'" helps explain why they are often considered important members of someone's in-hospital or community-based health team (2007, 1295).

Since 2000, provincial legislatures have gradually permitted pharmacists to provide emergency contraception without a physician's prescription (all other Schedule II drugs must be prescribed by a physician). Related to the aforementioned change to Alberta's professional legislation, Saskatchewan's College of Pharmacy has published a paper supportive of pharmacist prescribing (*Position Statement on Enhanced Authority 2007*). In 2006, Manitoba passed *Bill 41 Pharmacist Act*, which permits independent prescribing and administering of certain drugs plus independent ordering and interpreting certain diagnostic tests (the Bill has not been enacted yet; Pearson 2007). And British Columbia's Pharmacy Association has recently expressed support for independent prescribing (*Pharmacist Prescribing Position Statement 2007*).

Evolution of the pharmacist role mirrors the evolution of the physician's role. The Hippocratic Oath, written in the fourth or fifth century A.D., portrays physicians as a guild-like group who helped alleviate suffering and injury through non-surgical techniques and medicinal compounds. The reliability and effectiveness of medical interventions themselves -- as opposed to public health measures and comfort care -- became significant with the discovery of antibiotics in the early 1900s. The technological boom began in the 1950s when large public institutions (e.g., the U.S. National Institutes of Health, the Canadian Institutes of Health Research) and private corporations funded research studies and companies invested in patenting, production and distribution. In terms of mental health treatments, in the late 1950s and 1960s, psychotherapies and rehabilitative or protective institutionalization were augmented or replaced by the first generation antipsychotic medications (e.g., thorazine, stelazine and haldol). Atypical or second-generation antipsychotic medications, such as olanzapine, quietiapine and risperidone, appeared in the 1990s. Sales of these drugs alone now total approximately 3% of the industry sales or $20 billion (*Antipsychotics Market Insight & Analysis 2008*).

Distress of Pharmacists:

Surveys of pharmacists who face ethical quandaries and feel moral distress are illuminating. Moral distress has been defined as "incoherence between… what one sincerely believes to be right, what one actually does, and what actually transpires" (Webster & Baylis 2000, 218). Sporrong et al describe it as "'traditional negative stress symptoms that occur due to situations that involve ethical dimensions and where the health care provider feels she or he is not able to preserve all interests and values at stake'" (2006, 418). Mott found that 70% of the pharmacists he studied admitted to being morally distressed in their work (Sporrong et al 2005). In 2006, Sporrong et al surveyed 259 staff working either in a pharmacy or a pharmacy department. While the departments' physicians and nurses experienced somewhat more distress than the pharmacists (59% to 51%), their openness to ethical concerns was also higher (34% to 28%).

In a study of 377 pharmacists, 32% identified ethical conflicts with customers, 27% with gifts and kickbacks, 23% with pricing practices and 23% with honesty of business agreements (Vitell et al 1991). Moreover 38% of the respondents stated that ethical standards had declined over the past ten years. Latif (2000) compared 130 community pharmacists' ethical reasoning to that of first-year pharmacy students and other healthcare professionals. His finding: the pharmacists scored lower than the students and other professionals plus the length of practice inversely correlated with reasoning abilities. Smith et al (2006) examined the industry's impact on academic pharmacy programs. Respondents were asked to indicate whether a variety of ethically questionable and unacceptable practices in program planning had occurred. Incidence of eight ethically questionable practices ranged from 3 to 37% while incidence of six unacceptable practices ranged from 2 to 11%.

Worrisomely, several writers note that focused, sustained teaching of ethics in many pharmacy academic programs remains absent (Banks 2005, Resnik et al 2000, Latif 2000). An important rejoinder to this absence comes from Murawski (2007). A pharmacy professor himself, he finds that students usually hold unjustified, distorted viewpoints about the industry because instructors tend to teach from a "Zeitgeist[3] of the industry… [being] unrepentantly evil" (36). If a university's purpose includes facilitating open inquiry, reified and absolutist positions qualify as anathemas just as naïve and superficial positions so qualify.

Hospital Pharmacists:

Many people living with a substance use and/or psychiatric problem include pharmaceuticals in their recovery and health regimens. The patient- or client-pharmacist relationship typically occurs in two settings: hospitals and in the community.

Hospital pharmacists work in a somewhat more insular environment compared to community pharmacists (Wilson 2007). Snead (2007) and Wilson both note that the industry has paid less attention to hospital-based pharmacists. Fewer financial incentives exist. Nonetheless Latif insightfully argues that "most workplace settings are strong settings… that exert significant influences on individual attitudes and behaviors" (344). And moral distress exists:

> Hospital pharmacies find themselves in the uncomfortable position of having to choose between achieving cost savings for their cash-strapped institutions by accepting less than definitive data as the basis for P & T and bedside therapy decisions and making a more conservative data-based decision. (Wilson, 58).

When first developed, hospital drug formularies were simply lists of available products (Helling 2000). However as the variety and cost of drugs increased dramatically, "formulary decisions [came to be] decisions about rationing" (Haddad 2000, 857). Formularies have become focal points for competing professional, organizational and industry interests. For instance, as presented in Carroll's

description of pharmacy-industry evolution, during the 1950s the job description of the Director of Hospital Relations for the U.S. National Pharmaceutical Council included the goal to "slow up, if not stop, the trend of more hospitals adopting a compulsory formulary" (2007, 28). In terms of pharmacy associations, for many years pharmacists employed by pharmaceutical companies could not belong to the Society for Health-System Pharmacists in the United States because indefensible conflicts of interest were presumed inescapable. Only recently has the Society changed its position by requiring transparent, proactive management of such conflicts by every pharmacist, irrespective of his or her workplace (Frye & Witmer 2002). Pharmacy and Therapeutics (P & T) committees are commonplace in hospitals now, given the complexity and number of available pharmaceutical and mechanical products.

Drug formularies have been characterized as "an instrument of management" (Jonsen 2000, 485) and as a "safe haven… of sorts that minimizes organizational conflicts and the potential influences of individuals" (McAllister 2000, 860). Formularies are hoped-for outcomes of defensible compromises among patient needs and wants, clinicians' preferences, pharmacists' expertise and hospital budgets. Various writers however worry that hospitals' bottom-line pressures erode quality care and patient health outcomes (Wilson, Wertheimer, Carroll, Snead, Maine, O'Brien, Peck, Haines & Dumo, all 2007; Lisi 1997). They recommend that pharmacists act as patient advocates in cost-effectiveness and budget discussions. Furthermore hospital pharmacists must understand the types and forms of messaging the industry directs to physicians qua prescribers and to patients qua customers. They can then counter incomplete and skewed information and interpretations. Helling holds that, in the end, pharmacists must stay focused on patients first and be "good fiscal stewards" (2000, 859). Stewardship involves such ethical values as fairness, dependability and duties to future as well as immediate patients.

Community Pharmacists:

The major difference between hospital and community pharmacists is the latter works in a market place setting. According to sociologists Denzin and Mettlin, "'retail pharmacists represent the most non-professional aspects of the profession'" (Latif 2000, 346). Maine (2007) and Carroll (2007) characterize community pharmacists as a channel of distribution from manufacturer to patient. Not surprisingly, the goals of manufacturers and pharmacists differ: profits and control of prescribing and information flow versus provision of effective medicines and individualized information. Yet the history of the industry, community pharmacists, and state associations' rift is revealing, as described by articles in a recent issue of the *Journal of Pharmaceutical Marketing and Management*. Carroll explains that in the 1950s, different brand manufacturers typically produced identical items, which meant increased pharmacy inventories. Pharmacists subsequently stocked only one brand of an item and/or stocked generic products. In response, the industry canvassed the Federal Drug Administration, initiated legal action against pharmacists, and lobbied state associations in order to ban generic substitutions. These efforts proved successful in that forty-four states had non-substitution legislation by the late 1950s. Yet by the 1970s, all such legislation had been repealed. In 1984, the U.S. Congress passed the *Waxman-Hatch Health Act* (or *Drug Price Competition and Patent Term Restoration Act*), which sanctioned generic prescribing and substitutions. The pharmaceutical industry, according to Carroll, then countered with inaccurate messages that generic drugs were of inferior quality, but these efforts were ultimately unsuccessful.

Because the pharmaceutical industry is a business and pharmacy is a profession, goals vary. However community pharmacists are often offered financial incentives to dispense branded medications or receive volume rebates. The American College of Clinical Pharmacists has tried to promote a collaborative drug therapy management approach to strengthen and regularize interactions between patients and pharmacists in hopes of achieving better health outcomes and improved access. As of 2002, thirty-eight U.S. states permit CDTM practices wherein pharmacists can adapt prescriptions to better fit a patient's circumstances (Carroll).

Just as ethical concerns exist over industry's marketing to physicians and medical schools, concerns exist over the dubious marking tactics to pharmacists. Sales representatives try to have their branded drugs become pharmacist's "default choice." Moreover there are roughly 800,000 sales reps in the U.S., which translates into one full time rep for every ten physicians, according to Wright et al (2007). Not surprisingly, their marketing tactics have had to be creative and aggressive.

Yet to be fair, the reps themselves have worried about increasing pressures to achieve monthly sales targets. Because it is a "prescribers markets," many reps came to feel they were "prostituting themselves or their products… or began to approach outright bribery to capture physician time and attention" (Wright et al, 49). As Maine aptly cautions, unfortunately "pharmacists and the industry both suffer if the buyer of medications simply thinks of a drug as a commodity to be acquired at the lowest possible price" (2007, 73).

Conclusions:

"The best future for all concerned depends upon strong alignment between interests for pharmacy and pharma in transcending pills and adding capabilities to improve health" (Peck 2007, 92). As reflected by the *Journal of Pharmaceutical Marketing and Management's* issue about the pharmacy-industry rift, various initiatives reflect increased collaboration that should help serve the public better. In 2002, the Pharmaceutical Research and Manufacturers Association (PhRMA) finally developed a policy for its members regarding gift gifting. In 2003 a working document titled "Guiding Principles for a Pharmacy Benefit: A Call for Pharmacy Provider Services and Access to Pharmaceuticals" was developed by American state pharmacy associations and PhRMA to help counter mistrust, imbalance, and reduced patient outcomes (Snead 2007).

"Professional" has two connotations: someone whose work meets formal standard of social exchange or someone who belongs to a socially regulated profession. In the context of healthcare, nurses and physicians' professional standards require that a patient's welfare come before their own interests and serious conflicts of

interest must be avoided. These standards are especially high and unyielding because patients are so vulnerable and in need of others' specialized resources, skills and knowledge.

Business interests must come far after patient well being, regardless of whether a pharmacists' work is in a hospital or community drug store. Community pharmacists can choose one of two paths: one focused on the business of mixing and selling pharmaceuticals only and one that includes individual counselling and prescribing. The former is typified by the emergence of drive-through pharmacies, mail order pharmacies and mass merchandising chains that promise convenience and lower costs. These pharmacists' relationship with the pharmaceutical industry must be guided by principles and practices reflective of sound and thoroughgoing business ethics. On the other hand, the relationship between pharmacists who counsel and prescribe and the industry must be guided by robust business ethics and a thoroughgoing professional ethic akin to that of physicians and nurses. Without these ethical paradigms informing their work, pharmacists, their associations and their academic programs will be among those who harm, exploit and disrespect people who are living with a psychiatric and/or addiction problem and their families.

Footnotes:

1. A patent extension is misleading if the reason for the extension is to financially benefit the manufacturer, but it is marketed as if the primary reason was to benefit patients in a meaningful way.

2. The classic example of ghost writing is a company employee researches and writes an article and it is subsequently reviewed by a healthcare professional. When published, though, the professional is listed as the only author or the professional is listed first, implying he or she is the primary contributor. Both options are inaccurate and misleading.

3. "Zeitgeist" is a German word meaning the spirit of an age or time. In other words, the overall moral, social, and intellectual outlook of a particular time period.

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ARTICLE
Special Theme issue article

The Pharmaceutical Industry and the Construction of Psychiatric Diagnoses

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Abstract

Psychiatry is fertile ground for the disease mongering activities of the pharmaceutical industry. Over the last few decades, industry influence has helped to create new psychiatric conditions and transform old ones. The modern concept of depression, for example, was established alongside the marketing of antidepressants in the 1950s and 1960s. More recently the label of depression has been applied to an even wider section of the population, associated with intense marketing of SSRIs. Bipolar disorder has also been transformed from a very rare to a relatively common condition in parallel with the promotion of antipsychotic drugs for its treatment. Schizophrenia has also been expanded into the more vague concept of psychosis, and concepts such as "early intervention" and preventive treatment allow more people to be started on potentially life-long antipsychotic drug treatment. Thus marketing has shaped the very nature of psychiatric concepts and psychiatric knowledge. It also distorts service priorities and focuses attention on mass markets in the general population rather than people with the most severe disorders and the greatest needs.

Key Words: pharmaceutical industry; pharmaceutical marketing; medicalisation; disease mongering; antidepressants; antipsychotics; bipolar disorder; early intervention in psychosis

People have always hoped to find a quick fix to difficult social and personal problems. Quacks of past centuries sold potions that promised success, love and happiness as well as ones that were supposed to help physical ailments. Alternative medicines still offer hopes of improving creativity and concentration and reducing depression, stress and troublesome behaviours. But until recently these activities lay at the fringes of medicine and commanded no real legitimacy. Over the last few decades this has changed. The pharmaceutical industry, have spied a market in persuading people to see all sorts of troubles as medical illnesses in need of a chemical remedy. The rising tide of prescriptions of psychiatric drugs confirms that the message has been thoroughly absorbed. In the process the industry has changed perceptions about what it is to be human, with people increasingly likely to view their behaviour as chemically driven (Rose, 2004). It has also shaped our understanding of what psychiatric disorders are and how they should be treated.

Several recent commentators have drawn attention to this process of disease mongering (Moynihan *et al*, 2002). Sexual dysfunction, osteoporosis and irritable bowl syndrome have also been targets of such marketing, but psychiatry represents by far the most lucrative area. In recent years, it has been shown that pharmaceutical companies orchestrated the promotion of previously little known disorders such as panic disorder (Healy, 2004) and social anxiety disorder (Koerner, 2002), such that they are now household names. But the role of the industry goes back much further and has shaped the nature of conditions that are viewed as fundamental psychiatric disorders. Depression, for example, now an undisputed psychiatric disorder, barely existed prior to the appearance of drugs designated as antidepressants (Moncrieff, 2008a) and in recent years conditions like manic depression have been changed beyond recognition (Healy, 2006).

In this paper, I will argue that psychiatrists need to be aware of the commercial influences on the development of psychiatric classification, and should be prepared to resist the direction in which the pharmaceutical industry is driving psychiatry. Otherwise, psychiatrists risk becoming lackeys of an industry whose motivation is to persuade almost everyone to view themselves as sick. Not only do industry activities expose many people to unnecessary, unhelpful and potentially harmful chemicals, they distort health care priorities, leading to neglect of the needs of those with the most severe forms of mental disturbance.

The construction of depression

In the 19th century and early part of the 20th century, psychiatry was mostly concerned with severe psychiatric disorders that required hospitalisation. Indeed, up until 1930 in the United Kingdom, it was impossible for someone to be admitted to a psychiatric hospital on a voluntary basis. Psychiatric classification, following Kraeplin, divided these severe conditions up into schizophrenia and manic

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depression, the latter category including cases of "involutional melancholia." Descriptions of depressive conditions were brief, and they were considered rare and not particularly important in their own right. There was a further category of disorders referred to as "neuroses" which commonly included alcohol disorders, anxiety and neuraesthenia, but not depression (Braude, 1937;Henderson and Gillespie, 1927;Mayer-Gross *et al*, 1954).

Depression as a category of psychiatric disorder, was only introduced into psychiatric textbooks after the acceptance of the idea that some drugs could be considered as "antidepressants". The principle British textbook of the 20th century introduced a general category of disorder called depression in 1962 (Henderson and Gillespie, 1962). Depression differed from previous diagnoses in that it covered a range of problems in a variety of settings, from the mute, psychotic or stuporous hospitalised "melancholic" to the private practice office patient. Although the first reports of the antidepressant properties of imipramine emphasised that it was most effective in severe forms of melancholic depression (Kuhn, 1958), the idea that depression might be a common disorder was soon proposed. An eminent American psychopharmacologist, Frank Ayd wrote a book called "Recognising the depressed patient", which suggested that a much higher proportion of the general population suffered from depression than was previously thought, and recommending ways for General Practitioners and general hospital physicians to identify the condition (Ayd, Jr., 1961). Millions of copies of this book were bought by Merck, the makers of one patented form of the antidepressant amitripyline, and distributed to medical practitioners worldwide (Healy, 1997).

In recent years the transformation of the concept for commercial ends has become even more apparent. From the late 1980s, Prozac and other SSRIs were marketed again alongside the notion that depression was a widely under-recognised condition. Campaigns such as the Defeat Depression Campaign in the UK and the Depression Awareness Recognition and Treatment (DART) campaign in the US were run by the psychiatric profession, but part funded by pharmaceutical companies (Healy, 2003). Their message aimed to encourage GPs to diagnose people as depressed and to persuade the general population not to be concerned about receiving the diagnosis or taking antidepressants.

Hence the emergence of the modern concept of depression was linked with the introduction of a drug that could be marketed to treat it. The pharmaceutical industry was not solely responsible for the construction and promotion of depression. The psychiatric profession undoubtedly also saw advantages in the promotion of a disorder linked to a simple medical remedy, that allowed it to claim supremacy over other professions in the treatment of people outside the hospital setting (Moncrieff, 2008b;Moncrieff, J., 2008a). However, in recent years at least, the industry has been the main driving force in the expansion of the diagnosis to cover a significant proportion of the population. During 2002 for example, 11% of women and almost 5% of men in the United States were prescribed antidepressants (Stagnitti, 2005).

The influence of the pharmaceutical industry does not necessarily mean that the concept of depression itself is problematic. It is possible that commercial motivations have helped to identify real problems that would otherwise have languished unrecognised and untreated. However, revealing the involvement of the industry should make us wary of accepting the modern notion of "depression" at face value. Probing scientific research on depression makes it apparent that there is little support for the premise that people who are currently labelled as depressed suffer from a specific biological abnormality that gives rise to their symptoms and that can be rectified by the use of antidepressants (Moncrieff and Cohen, 2006). Instead it appears that the diagnosis of depression may simply follow from the decision to prescribe antidepressants. This is supported by the recent transition from depression to bipolar disorder as antidepressants have gone off patent and atpyical antipsychotics have become the main focus of drug company marketing for psychiatric disorders.

The transformation of bipolar disorder

David Healy and colleagues have charted the rise and transformation of bipolar disorder over recent years (Healy, D., 2006; Healy, 2008). The well characterised but rare condition known as "manic depression" has somehow metamorphosed into a vaguely defined, supposedly common disorder, which is being applied to ever greater numbers of people. These changes co-incide with the marketing of the highly profitable atypical antipsychotics, such as Zyprexa (olanzapine). Healy has shown how Abbot laboratories, the makers of semi-sodium valproate (Depakote) popularised the concept of a "mood stabiliser" in the mid 1990s and the rapidly increasing use of Depakote seemed to confirm that there was a large potential market for such a product (Harris *et al*, 2003). In the last 10 years Eli Lilly have conducted a small number of trials of olanzapine in people with classical manic depression or bipolar 1 disorder, including just one placebo controlled trial which appeared to show that olanzapine is superior to placebo in prevention of relapse (Tohen *et al*, 2006). Although there were obvious methodological problems with this trial, which make it likely that the results reflect a discontinuation effect rather than a genuine prophylactic effect, olanzapine was recommended as one of the first choices for prophylaxis and acute treatment of bipolar disorder in the UK's National Institute of Clinical Excellence (NICE) Bipolar Disorder treatment guidelines published in 2006 (National Institute for Clinical Excellence, 2006).

Prior to the publication of this trial, Eli Lilly launched an advertising campaign designed to persuade people to diagnose themselves as bipolar and seek treatment from their doctors. In one advertisement, a young woman is portrayed one minute dancing at a nightclub, or shopping to excess, the next minute looking glum and depressed. The voice over says: "That fast talking, energetic, quick tempered, up all night you never shows up in the doctors office" and it concludes "That is why so many people with bipolar disorder are being treated for depression and aren't getting any better- because depression is only half the story" (Lilly 2002, cited Healy, 2008, P 190). The advert goes on to advise people to complete a mood disorder questionnaire, offered on a Lilly sponsored website. Several other company websites offer questionnaires that encourage people to assess themselves and monitor their moods, and advise people to visit their doctor if they score above a certain level.

Not only has bipolar disorder come to rival depression as a label

for the discontent and disaffection felt by adults, it has also come to be applied increasingly frequently to children. Until recently manic depression was not thought to occur in children at all and only very rarely in adolescents. Over recent years, however, certain prominent academics have sanctioned the idea that bipolar disorder occurs in children, even though the supposedly characteristic behaviour patterns are non specific and occur in other childhood disorders (Biederman *et al*, 2003). Although the concept of childhood bipolar disorder has yet to have official approval in diagnostic manuals like the DSM, it has helped to justify a massive increase in prescribing of antipsychotic drugs to children.

The case of paediatric bipolar disorder illustrates how disorders can be constructed without direct marketing campaigns, through the activities and influence of academic psychiatrists. The role of the drug industry in this case is to promote the views of those psychiatrists who are telling a story that suits its purposes. The industry does this by funding research studies and whole research centres, by setting up and funding symposia at academic conferences and through payments to the academics concerned for consultation and other activities. Healy reports that 30% of symposia at the 2003 annual meeting of the American Psychiatric Association, the largest psychiatric event in the United States, concerned bipolar disorder, almost all of which were funded by drug companies (Healy, D., 2008). The research group in Boston who have have promoted the concept of childhood bipolar disorder and its treatment with drugs were funded to set up a research centre by Janssen-Cilag, makers of risperidone. Moreover, some of these researchers recently revealed that they had received income of over a million dollars each from drug companies over the last few years (Harris and Carey, 2008).

From schizophrenia to psychosis

There has been a subtle change in perceptions of the most severe psychiatric disorders over recent years, in which the pharmaceutical industry have also had a hand. Like the transformation of manic depression into bipolar disorder, the vague concept of psychosis has increasingly replaced the more clearly defined disorder called schizophrenia. Although the concept of psychosis has gained popularity partly because it avoids the stigma associated with schizophrenia, it also helps to pave the way for the extension of drug treatment normally reserved for schizophrenia. Twenty years ago, the grave implications of labelling someone with schizophrenia, with its association with life-long disability, made professionals cautious about making the diagnosis. The normal procedure for anyone thought to be displaying psychotic symptoms for the first time was to wait and observe, in order to be certain of the nature of the symptoms and to give them time to resolve spontaneously. Drug treatment would not be started until after this observation period.

Since then, a concerted campaign to promote Early Intervention in Psychosis has changed this approach completely. Early intervention undoubtedly brings benefits such as support for the family, and yet there is little evidence that it alters the long-term outcome of schizophrenia or a psychotic episode (Marshall and Rathbone, 2006). Claims for the benefits of Early Intervention rest on the observation that people who are ill for a longer prior to receiving treatment have a worse outcome (Marshall *et al*, 2005). However, it has long been known that a gradual onset of psychotic symptoms was a characteristic of a more severe disorder, and conversely that people whose symptoms came on suddenly were more likely to make a full recovery, regardless of treatment. However, this knowledge has been ignored in the burgeoning literature on "duration of untreated psychosis," or DUP as it is often referred to. The small number of trials that have evaluated early intervention services have not found positve results on long-term outcome and have not addressed the particular impact of early drug treatment (Marshall, M. and Rathbone, J., 2006).

Despite the dearth of evidence for its benefits, information about early intervention makes repeated claims that "the evidence for early intervention in psychosis is overwhelming" (Care Services Improvement Partnership North West and Care Services Improvement Partnership, 2007) and Early Intervention services have been introduced throughout the western world. Much of the literature on Early Intervention from the UK has been produced by the National Institute for Mental Health in England, which is a partnership between the government and private companies. Drug companies have also funded conferences on early intervention and sponsored the publication of journal supplements on the topic. Two randomised trials of drug treatment for young people thought to be at risk of developing psychosis have been funded by drug companies (McGorry *et al*, 2002;McGlashan *et al*, 2006).

The result of the publicity on Early Intervention is that there is greater proclivity to start prescribing antipsychotics to people who exhibit strange or difficult behaviours, including young people and children. The emphasis placed on the notion that treatment can help prevent deterioration more or less demands that practitioners start prescribing at the earliest signs of a possible problem. The knowledge that many people can recover from psychosis without antipsychotics has been forgotten (Bola and Mosher, 2003). Therefore, many people are being exposed to these drugs who would never have had a full blown episode of psychosis, or who would have recovered without drug treatment. Moreover, once started these drugs are often continued for years, as professionals are often reluctant to stop them.

Psychiatric diagnosis and commercial interests

Despite the seemingly objective appearance of systems like the current Diagnostic and Statistical Manual, diagnosis in psychiatry has always been a movable feast. Conditions like hysteria, neurasthenia and neurotic depression have gone in and out of fashion. This is why psychiatry represents a soft target for disease mongering activities.

The pharmaceutical industry is not the only interest group to shape psychiatric classification to further its own ends. As described earlier, the psychiatric profession has had its own reasons for wanting to promote disorders that can be treated outside the asylum. Similarly, psychologists may have interests in promoting the existence of disorders that appear to be amenable to psychological interventions. However, the resources at the disposal

of drug companies, and the intense competition they are now engaged in, mean their level and sphere of influence goes well beyond the means of professional groups.

The commercial influence on psychiatric diagnosis is important for several reasons. The levels of prescribing we are currently witnessing provoked an outcry in the 1980s when it was revealed that benzodiazepines were being doled out indiscriminately and used to drug millions of women who had genuine complaints about their lives. However, if complaints are framed in terms of a diagnosis, which automatically implies the presence of an underlying neurological disease or dysfunction, and if drug treatment is presented as being able to rectify the underlying abnormality, then it is more difficult to oppose the mass prescription of psychotropic drugs. Many people currently diagnosed as having depression, bipolar disorder, psychosis and other conditions are almost certainly taking toxic psychoactive drugs for no proven benefit, with all the harms that may entail. But to challenge that situation is to risk being accused of denying the reality of emotional suffering and abandoning the mentally ill.

Diagnoses take on lives of their own. Once a diagnosis is established, or even suggested, it is difficult to challenge its validity, and such challenges are usually ignored. Adult Attention Deficit Hyperactivity disorder (ADHD), for example, which barely existed a few years ago, and is still regarded with scepticism by many, is now routinely employed to justify the prescription of stimulant drugs to adults. The United Kingdom National Institute for Clinical Excellence (NICE) guidelines endorsed the diagnosis of adult ADHD, with little consideration of evidence for its validity (National Institute for Health and Clinical Excellence, 2008). In this way, the interests that produce a diagnosis are buried within it, and become invisible in the process. The whole system of psychiatric knowledge and the practices that flow from it both embody and obscure the influences that formed them. Most practising psychiatrists and general practitioners are unaware that many of the concepts they use to denominate problems and to justify treatment have been constructed for them with commercial interests in mind.

Diagnosis has also become an important tool in resource allocation, especially in countries with managed care systems like the United States, but increasingly in other countries as well. The designation of a particular diagnosis determines the amount of specialist care that the state will fund, it gives access to sickness benefits and justifies sickness absence from work. Apart from the costs of drug treatment, inappropriately labelling people as mentally ill uses scarce resources that may be better employed elsewhere. People who suffer from the most severe and long-lasting mental disorders are some of those who are losing out from this distortion of priorities. In the United Kingdom, policy makers have been persuaded to fund large increases in psychological treatments in primary care (Layard, 2008) while at the same time endorsing the contraction of specialised rehabilitation services for the severely mentally ill.

The debate around the nature of psychiatric diagnosis stimulated by the development of DSM V represents an opportunity to refocus psychiatry back on severe mental disorder and to curb the disease mongering activities of the pharmaceutical industry. However, this is not possible until the financial relations between the profession and the industry are severed. At present the psychiatric profession is far too ready to accept diagnostic justifications for prescribing potentially toxic drugs to adults and children on a mass scale. The profession must disentangle itself from the clutches of the industry to salvage its own credibility and in order to represent the real interests of its patients.

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ARTICLE
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Direct-to-Consumer Advertising and the Internet: Implications and Imperatives

Hugh Schulze, president of c|change inc. and

co-author of *Reducing the Stigma of Mental Illness*, Cambridge University Press, 2005

Abstract

In 1996, the U.S. Food and Drug Administration eased restrictions on Direct-to-Consumer (DTC) advertising, opening the way to additional promotion in broadcast media. At the same time, globally, internet usage began expanding at an exponential rate. In this article, we examine what has been learned after a decade of DTC advertising in the U.S. and the ethical implications for communicating about prescription drugs on the Worldwide Web, in an era where government regulation is problematic.

Key Words: marketing, worldwide web, direct-to-consumer, internet, FDA guidelines, DTC, convergence, collaboration

Introduction

In the last half of the last decade of the twentieth century, two developments in the field of communication dramatically changed the field of pharmaceutical marketing: a) in the United States, the Food and Drug Administration (FDA) eased restrictions on the advertising of pharmaceutical products to consumers; and b) globally, the introduction of web browsers such as Explorer and

Figure 1: World Internet Usage and Population Statistics

World Regions	Population (2008 Est.)	Internet Users 12/31/2000	Internet Usage, Latest Data	% Population (Penetration)	Usage % of World	Usage Growth 2000-2008
Africa	955,206,348	4,514,400	51,065,630	5.3%	3.5%	1,031.2%
Asia	3,776,181,949	114,304,000	578,538,257	15.3%	39.5%	406.1%
Europe	800,401,065	105,096,093	384,633,765	48.1%	26.3%	266.0%
Middle East	197,090,443	3,284,800	41,939,200	21.3%	2.9%	1,176.8%
North America	337,167,248	108,096,800	248,241,969	73.6%	17.0%	129.6%
Latin America/ Caribbean	576,091,673	18,068,919	139,009,209	24.1%	9.5%	669.3%
Oceania/ Australia	33,981,562	7,620,480	20,204,331	59.5%	1.4%	165.1%
WORLD TOTAL	6,676,120,288	360,985,492	1,463,632,361	21.9%	100.0%	305.5%

NOTES: (1) Internet Usage and World Population Statistics are for June 30, 2008. (2) Demographic (Population) numbers are based on data from the US Census Bureau. (3) Internet usage information comes from data published by Nielsen//NetRatings, by the International Telecommunications Union, by local NIC, and other reliable sources. (4) Information in this site may be cited, giving the due credit to www.internetworldstats.com. Copyright © 2001-2008, Miniwatts Marketing Group. All rights reserved worldwide.

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Netscape gave physicians and the general public alike unprecedented access to information on the Worldwide Web.

While, at present, DTC advertising is limited to the U.S. and New Zealand, three aspects of the global business environment have implications for marketing to both physicians and the general public:

a) FDA Guidelines for advertising products direct-to-consumers on the Internet are the same as those for other broadcast media (i.e., television and radio), thus what can be seen on U.S. television can, in theory, be seen globally on-line through websites such as YouTube.com or Blinkx.com.

b) Internet usage continues to grow at an astonishing rate. Figure 1 shows the usage statistics for the last eight years, though defining statistics by region can be slightly misleading. [(1)]

   For example, while North America shows "penetration," or the percentage of the population accessing the internet, as the highest at 73.6%; in 2008, eight countries had greater access to broadband and cellular networks than the U.S. – with Sweden #1, followed by Iceland, Switzerland, Netherlands, Denmark, Hong Kong, South Korea and Norway respectively.[(2)]

c) Finally, the largest pharmaceutical companies are global companies and while guidelines on marketing to physicians and the general public may vary from country-to-country, these companies operate in a competitive environment in which they actively work to maximize reach and impact of their advertising, as well as amortize costs.

In this paper, we explore ethical implications for both DTC advertising and the internet that have relevance for how pharmaceutical companies market to physicians and the general public, as well as how the dialog is changing between physicians and their patients.

Methodology:

This study relies upon secondary research from medical journals and business publications from both the pharmaceutical and advertising industries. Providing specific numbers – whether that might be viewers of an advertisement or money spent – can be difficult for a number of reasons:

1. Measures vary from medium to medium. Television and radio are what are known as "push" media; that is, they are broadcast at specific times of day, often as part of specific programming which has allowed the industry to monitor performance using methods developed over the last five to six decades. The internet, a medium that has evolved most dramatically in the last 10 years, has become more of a hybrid medium. While content is largely chosen ("pulled") by consumers, advertising through pop-up and banner ads have blurred the line. At present, just as traditional broadcast television and radio are challenged by cable and satellite, marketers are refining better tools to measure advertising effectiveness on the Internet.

2. The definition of "marketing expenditures" can be difficult to define and quantify. A company's report on its marketing mix may capture visits by pharmaceutical sales reps or radio advertising, it may not capture expenditures on event sponsorships or the cost

FIGURE 2: 2006/2007 TOP THERAPEUTIC CLASSES BY US DISPENSED PRESCRIPTION (5)

Rank	Therapeutic Class	2006 Total Scripts (Millions USD)	2007 Total Scripts (Millions USD)	% Increase
1	Anti-Depressants	227.4	232.7	2.3%
2	Lipid Regulators	203.1	220.9	8.1%
3	Codeine & Comb	177.2	186.1	4.8%
4	ACE Inhibitors	154.2	157.9	2.4%
5	Beta Blockers	130.5	132.5	1.5%
6	Proton Pump Inhibitors	101.7	108.4	6.8%
7	Seizure Disorders	94.9	101.8	6.8%
8	Thyroid Hormone, synth.	97.7	101.4	3.7%
9	Calcium Blockers	87.0	87.4	0.5%
10	Benzodiazepines	80.2	82.9	3.3%
	All	3,706.4	3,809.3	2.7%

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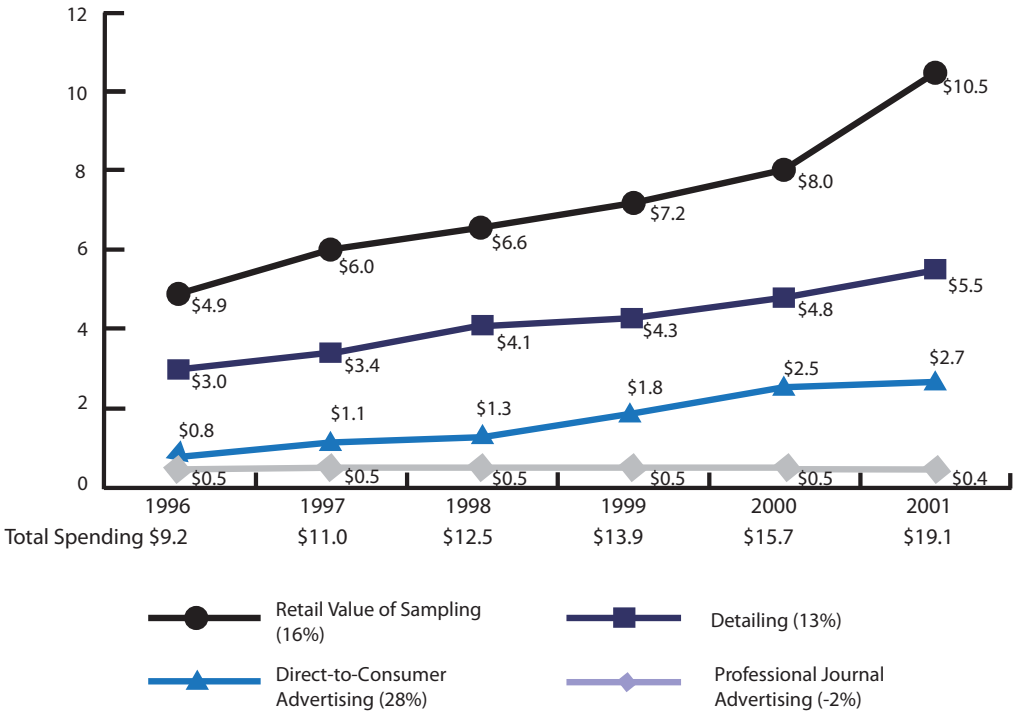
Figure 3. Trends in Promotional Spending for Prescription Drugs, 1996-2001 ($ in Billions)



NOTE: May not add to totals due to rounding. Percents in parentheses are average annual increases from 1996-2001. Excludes promotional spending for professional meetings and events.

Source: Kaiser Family Foundation and Sonderegger Rsearch Center, *Prescription Drug Trends. A Chartbook Update*. November 2001, using data from IMS Health, Inc. *Integrated Promotional Service*, and Competitive Media Reporting. 1996-2000; 2001 data from IMS Health at www.imshealth.com

for trade show booths at medical conferences and exhibitions. For example, a 2001 report put the annual spending for educational meetings and events for physicians alone at $2.1 billion. [3] In 2009, new guidelines developed by Pharmaceutical Research and Manufacturers of America (PhRMA) will place greater restrictions on how pharmaceutical companies spend marketing dollars and how they report on them. [4]

3. Finally, it should be noted that figures presented in this paper extend across all therapeutic classes. The data presented here have as much relevance for mental health professionals as they do for the general practitioner or cardiac specialist. For example, as Figure 2 below shows, in 2006/2007 anti-depressants and benzodiazapines accounted for nearly 10% of the $3.7 billion (USD) spent for the top ten prescriptions.

Understanding the Marketing Mix – the Trends

In the first five years, following the relaxing of FDA regulations for direct-to-consumer advertising, the expenditures on promotion to both physicians and consumers rose in three out of four areas – with DTCA rising at a rate of roughly 28% annually. (See Figure 3.)

The largest expenditure shown is for sample costs (though it should be noted, these costs reflect retail value).

The second greatest expenditure of the four is in the cost of "detailing" – direct visits of sales representatives to office-based physicians (roughly 86% of the $5.5 billion total) and hospital-based physicians (the remaining 14%). According to the American Medical Association in 2002, pharmaceutical companies employed about 90,000 sales reps – or one for every 4.7 doctors in the United States. [6]

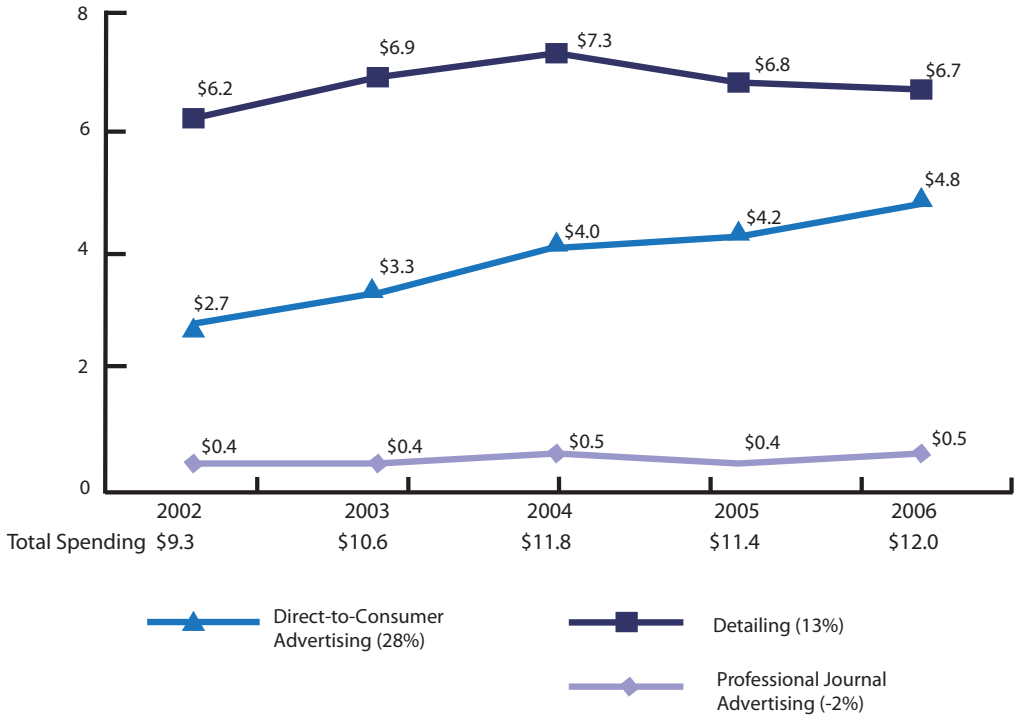
The third shows DTCA rising from $1 billion USD to nearly $3 billion USD in the first five years. Professional journal advertising showed a decrease of 2% in the same five year period.

As Figure 4 shows, these trends continued with detailing to healthcare professionals leveling off and showing a slight decline to $6.3 billion in 2007. While spending on DTCA continues to increase, the rate of growth has fallen dramatically from 28% in the first five years to just 2% from 2006 to 2007.

Examining the Results:

A recent study published in the *British Medical Journal* (Sept. 2008), "the first-ever controlled study of direct-to-consumer advertising (DTCA) of pharmaceuticals", concludes that for two of the three

Figure 4. Total U.S. Promotional Spend by Type, 2006 ($ in Billions)



SOURCE: Data from IMS Health, at www.imshealth.com;

http://www.imshealth.com/imshealth/Global/Content/Document/Top-Line%20Industry%20Data/2006%20Total%20U.S.%20Promotional%20Spend%20by%20Type.pdf

drugs studied, DTC advertising "had no effect whatsoever". In the case of the third product, sales increased 40% after the campaign began, then tapered off with no demonstrable effect after several years.

However, an earlier 2003 study conducted by the Kaiser Family Foundation found:

> "On average, a 10% increase in DTC advertising of drugs within a therapeutic drug class resulted in a 1% increase in sales of the drugs in the case. Applying this result to the 25 largest drug classes in 2000, the study found that every $1 the pharmaceutical industry spent on DTC advertising yielded an additional $4.20 in drug sales."[7]

While these studies may seem contradictory, they do not fully contradict what pharmaceutical marketers have known and how they market their products.

Direct- to-consumer advertising is concentrated among a relatively small number of drugs. As a study by *The New England Journal of Medicine* showed: "the 20 drugs with the highest spending made up 54.4% of total industry spending in 2005." [8] In addition, an estimated 67% of medicines prescribed in the U.S. are generic (i.e., not advertised).[9]

Pharmaceutical companies focus most of their advertising spend on the initial introduction of drugs used to treat chronic conditions. The *New England Journal of Medicine* article cited above noted: "Ten of the top 20 drugs, as ranked by advertising spending, were introduced in 2000 or later. Notably, nearly all (17 of 20) advertising campaigns for the most heavily advertised drugs began within a year after FDA approval of the drug." For pharmaceutical companies the importance of building Awareness during what is called the "launch phase" of a drug's product lifecycle is critical to the long term sales of the product.

A majority of physicians agree that patients exposed to DTC advertising ask more thoughtful questions during their visit and made them more involved in their healthcare. A 2003 study conducted by the Food and Drug Administration (10) found that 92% of physicians could recall a patient who initiated a conversation about a prescription drug they saw advertised; 53% said that it led to a better discussion with the patient. When asked if this created any problems for the interaction with the patient, 82% said No; of the 18% who said Yes – "Time correcting misconceptions" was listed as the #1 problem (41%) with "Drugs not needed/did not have condition" listed as #2.

"The ads can prompt thoughtful discussions between patients and physicians that results in needed treatments being prescribed – often not the treatment mentioned in the ad."(11) This finding from the FDA study, like the three previous observations, present paradoxes and ethical implications.

Four Ethical Implications:

1. **Direct-to-Consumer advertising is concentated among a relatively small number of drugs.** The findings from the *British Medical Journal* in September 2008 have raised questions about direct-to-consumer advertising as well as doubts about the study itself.[12] After ten years of direct-to-consumer advertising in the United States, adherents and opponents appear to be as divided as ever. At the present time, it would appear that pharmaceutical companies have enough sales data pointing to the efficacy of their advertising to continue to spend $5 billion USD on direct-to-consumer advertising. Similarly, the general public appears to support direct-to-consumer advertising. [13] Decoupling discussions of "how much" is being communicated and marketed from "what" is being communicated and marketed will help focus ethical conversations about what physicians know about medications they prescribe and what patients know about the medications they consume.

2. **Pharmaceutical companies focus most of their advertising spend on the initial introduction of drugs used to treat chronic conditions.** In the United States, patents expire after seven years (which is one reason why pharmaceutical companies seek out new indications for their products in hopes of extending the patent for these new indications). A current tension exists between companies looking to build "brand awareness" in the critical time immediately following a launch and the medical reality that a drug recently approved by the FDA is being released to a population much larger than clinical drug trials.

   The case of Vioxx is instructive. Rofecoxib, an inhibitor of cyclooxygenase-2, had been found to have fewer gastrointestinal complications than naproxen, a standard nonsteroidal anti-inflammatory drug. It was approved by the FDA and marketed in May 1999. In November 2000, studies showed that the drug increased the risk of myocardial infarction. As Congressman Henry Waxman later reported: "By the time of rofecoxib's withdrawal from the market in September 2004… more than 100 million prescriptions had been filled in the United States." [14]

   In 2008, following deliberations by the Energy and Commerce Committee in the House of Representatives, the drug companies Merck, Johnson & Johnson, and Pfizer agreed to a six month waiting period on new drug advertising[15]. However, the committee had proposed a *three-year* moratorium after approval. [16] What would be the appropriate amount of time between the approval of a pharmaceutical product by the FDA and promotion of that product? This question needs to be reviewed in light of information accessed by *both* physicians and their patients on-line.

3. **A more informed physician/patient conversation.** A 2003 study published in The *New England Journal of Medicine*[17] found participants from 12 metropolitan areas in the U.S. received only 54.9 percent of recommended care. Only 24 percent of those with diabetes received three or more glycosylated hemoglobin tests over a two-year period. Overall, only 68.0 percent were receiving recommended care for coronary artery disease. In addressing the gap that exists between diagnosis and treatment, authors of this report ask: "What can we do to break through this impasse?" Additional studies have pointed to the possible number of deaths and hospitalizations [18] that might be avoided and the costs that might be saved [19] if there was greater compliance.

   With studies indicating that direct-to-consumer advertising increases the number of questions patients ask – and with the Internet increasing access of patients to therapeutic information – is it time to reassess the physician/patient dialog in light of a more well-informed patient? Results of a 2004 report published in *Medical Care* "suggest that DTCA of antidepressants was associated with an increase in the number of people diagnosed with depression who initiated medication therapy."[20]

   What trade-offs are physicians willing to take between patients who may have an initial exaggerated view of efficacy and the fact that the patient is taking initiative? Is there a possible reduction in the stigma of some illnesses through a broader cultural dialog on certain illnesses – whether that be through advertising on television or bulletin boards on the Internet? Are there ways physicians – perhaps in partnership with pharmaceutical companies – could light a candle and disseminate clearer information, rather than cursing the darkness of ads or websites touting bogus therapies such as dietary supplements?[21]

4. **The paradox of more information.** A 2005 study published in the *Journal of the American Medical Association* found that "DTC-advertisement-driven requests (along with general requests) dramatically boost prescribing." [22] But the authors warn that while the study points to "opportunities for improving care of depression (and perhaps other chronic conditions) by using public media channels to expand patient involvement in care," [23] evidence "supports the hypothesis that DTC advertising may stimulate prescribing more for questionable than clear indications." [24]

   If a rising tide lifts all ships, does an improvement in overall care for those suffering from depression also bring with it the risk of overprescribing? The study found that "the prescription of antidepressants in this context is at the margin of clinical appropriateness." [25]

   That margin may be tested further by "off-label prescriptions." An editorial in *The New England Journal of Medicine* addressed research indicating that "nearly half of all prescriptions in some drug classes may be off-label and more than 70% of off-label uses may have insufficient scientific support." (26) The authors further conclude that:

   "although off-label use of drugs may sometimes represent a reasonable therapeutic choice, the substantial influence that promotion can have on the prescribing practices of physicians, combined with the potential risks to patients and the often greater costs associated with off-label use, in our view justifies the higher level of scrutiny applied to statements made by pharmaceutical manufacturers." [27]

   What would that higher level of scrutiny look like? Is that

the role solely of the FDA? At what point would a physician's judgment and discretion in prescribing to a patient be limited by further limits in off-label use? Are disclaimers enough for busy physicians and their patients? Recently, in November 2008, in a case before the U.S. Supreme Court, Justice Ruth Bader Ginsburg expressed incredulity about the current effectiveness of the FDA in monitoring ongoing warnings for roughly 11,000 prescription drugs. "Is the FDA really monitoring every one of these?"[28]

Oversight and regulation is tested further still when internet marketing is considered as part of the marketing mix. As we shall see, technological advances in user-generated content (sometimes referred to as Web 2.0) provide an opportunity for both physicians and patients to join the conversation.

Adding to the Marketing Mix:

The findings above and their attendant ethical implications are the result of roughly ten years of Direct-to-Consumer advertising in the United States. As indicated earlier, internet usage has grown even faster than DTC advertising, further amplifying ethical issues raised earlier.

As Khee Lee, vertical manager, health at Google puts it: "The dramatic change that's occurred over the last 10 years is that consumers have changed. So the challenge is for consumer marketers to get away from what they've traditionally done and examine their consumers." [29]

Lee and others at Google see both risk-aversion and the relatively new (10-year old) consumer advertising as two reasons pharmaceutical companies have lagged behind other industries in utilizing the web. "[Pharma companies] started off with TV, print, and radio and the needle just never moved because as new brand managers came on board, they didn't change the media mix."[30]

For those with serious reservations about online marketing of pharmaceutical products, this news might not seem as negative as Mr. Lee and his marketing colleagues at Google paint it. But regardless of one's view on direct-to-consumer advertising, one thing is very clear: the internet is changing channels of communication and availability of information far faster than government regulation has – or perhaps can – adapt.

A recent search of brand names for three antidepressants on YouTube garnered thousands of videos ranging from television commercials [31] to parodies of those commercials [32] as well as segments from television news programs [33] to personal videotaped stories. [34]

Among the top 10 results for the searches conducted for each product were videos produced under the brand "illumistream" by FullTurn Media. The company produced two-and-a-half minute videos on: Fluoxetine Hydrochloride (Prozac™) [35], Sertraline Hydrochloride (Zoloft™) [36], and Paroxetine (Paxil™) [37]. It is unclear who funded the creation of the videos, which are titled "Professional Medication Reviews" and presented by a pharmacist from Memorial Sloan-Kettering at the University of Southern California. Each video includes warnings such as a closing title: "The information in this video is intended to supplement not substitute for, the expertise of your physician. Always consult your doctor before using…."

At the time of this writing, statistics for each of these videos showed thousands of views (11,978 for Prozac, 4,733 for Zoloft, 5,077 for Paxil). However, unlike television, radio or print media, the Internet provides feedback mechanisms and dialog for videos like this. In this case, there were but 59 viewer comments for Prozac, 30 for Zoloft, 37 for Paxil. Text comments in the area below the videos range from personal experiences to comments on the video quality itself, as well as comments on comments.

Earlier, we presented data on growth of Internet usage from 2000 to 2008, an increase of 305%. Save for some countries where internet access is limited [38], one-billion-plus visitors to the world wide web have access to all of the materials posted from any country.

Perhaps more astonishing is the growth of on-line video viewing. As technologies and media platforms continue to converge (with web content delivered to cellphones, for example), the current trend is for further exponential growth. Consider that YouTube viewership grew from 58,000 visitors per month in August 2005 to more than 20 million monthly visitors by August 2006.[39] By January 2008, that number had reached 11 billion visitors per month in the U.S. alone.[40] In that same year and a half period, the amount of time spent watching videos online had risen from 73 minutes per month to nearly four hours per month.[41]

Lest the reader think this is a phenomenon among the young, currently, 64% of YouTube watchers are over the age of 35, and nearly a quarter (22%) are over the age of 55 with viewership split almost equally between males (51%) and females (49%).[42]

Consider: those numbers reflect only video viewing – and only video delivered on YouTube!

Add blogs, podcasts, and social networking sites (e.g., Facebook.com and MySpace.com) to the communication mix and one begins to wonder: just how effective is the current government regulation paradigm? The most cursory searches on the internet uncover hundreds, thousands of references to information of all kinds on prescription drugs and therapies. Today, after a drug has been approved by the FDA, current regulations on labeling and advertising seem a bit like posting a traffic cop at the entrance ramp to a highway of information: you may limit a portion of the information making it onto the road, but as the Google marketing executive pointed out earlier: because consumers are driving the demand on the information superhighway, government regulation appears to be less and less relevant.

Time for a New Paradigm?

In the United States, the Food and Drug Administration evolved out of legislation signed into law in 1906. Since that time, print mass media and marketing have been eclipsed by broadcast media of radio, then television. These media in turn are being both augmented and eclipsed by the interactive experience of

the internet – with consumers exercising greater control over the information they access, not only in terms of content, but when and how they access that information.

Executives of pharmaceutical companies who may decry what they see as antiquated or Byzantine guidelines for approval and promotion of their products are themselves faced with challenges to antiquated Darwinian business models focused solely on dominating competitors and gaining new market share.

The most robust, fastest-growing industries are those who have begun to explore business models that rely more heavily on collaboration. A few pharmaceutical companies have begun to embrace this concept of collaboration. In 2007, Novartis released the results of its genomic analysis of Type 2 diabetes on the web. [43] In February 2009, in an effort to address diseases in the poorest countries, GlaxoSmithKline "put any chemicals or processes over which it has intellectual property rights that are relevant to finding drugs for neglected diseases into a 'patent pool', so they can be explored by other researchers." [44]

"Convergence" has been a buzzword in the technology industry for over a decade and we are seeing the results of that convergence with information being delivered across multiple platforms. [45] Collaboration and a convergence of information would help to bridge the clear chasm that exists between the public and private sectors. At present, public health is not well-served by impotent regulators threatening court action against pharmaceutical companies that walk litigious tightropes between the letter and spirit of government laws.

In the opinion of this author, in the coming decade government regulators need to begin thinking more like pharmaceutical companies and pharmaceutical companies must begin thinking more like their much-maligned government regulators. That is, in addition to risk mitigation, government regulators need to spend more time thinking about what information physicians and consumers really need and want (as pharmaceutical marketers do). At the same time pharmaceutical companies need to see themselves as public servants to their customers (as government regulators are charged to do).

Rather than add to the Tower of Babel of websites which threatens to confound the best search engine, what is called for is an amalgamation of information. An opportunity exists for an organization like the World Psychiatric Association – or perhaps a forward thinking company or governmental body – to develop a resource that could:

- Deliver more comprehensive and reliable information to both physicians and patients;
- Provide an improved understanding of the disease states and the variety of treatments available, including non-pharmacological therapies; this improved linkage could:
    - Assist physicians in educating patients, their families and caregivers;
    - Help further educate on complex issues such as comorbidity through a centralized information database;
    - Help reduce the stigma associated with some illnesses.

Ten years of astonishing growth of the internet has made it a resource for patients seeking information on medical conditions and pharmaceutical products. In a survey of searches by drug brand name, conducted by comScore in February 2008 [46], five of the fifteen most searched-for prescription drugs were for treatment of depression – with Chantix™ topping the list at half a million (507,000) searches in that month alone.

Obviously, such a strategy of collaboration between business and government carries with it the possibility for collusion and corruption. Here again, new technologies point a way to opportunities for on-going regulation. Physicians *and* patients represent the other legs of this stool. The most effective resource would include the experience of medical professionals and the general public.

Space does not allow us to outline the pros and cons of these feedback mechanisms and user-generated content. [47] What is clear, however, is that an opportunity exists to take advantage of new media to address existing conflicts between governments and business. The healthcare and pharmaceutical industries have traditionally lagged in the uptake of new operational processes and technologies. (In the United States, the on-going challenge of electronic patient records is just one example.) But just as Google has become a global search engine of choice through a clear, easy-to-use user interface and proprietary search algorithms, a clear opportunity exists for collaboration among government, business, healthcare providers and the general public to apply new technologies for a dynamic, continually-updated resource.

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ARTICLE
SPECIAL THEME ISSUE ARTICLE

The Ethics of the Pharmaceutical Alliance with Psychiatry: A Developing Country Perspective

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ABSTRACT

The socioeconomic and political conditions of developing countries must be considered when evaluating the ethics of Industry involvement with psychiatry in this context. Specifically, the medicalisation of distress and the globalization of biomedical psychiatry undermines local methods of coping as well as community efforts to change society. It creates a market for expensive psychotropics in an environment characterized by poverty, unemployment and a lack of basic material needs, raising issues of distributive justice. Patients, subjects in drug trials and psychiatrists themselves should be regarded as 'vulnerable' in relation to their interactions with Industry. Poor regulation and control of both Industry and professionals in many developing countries invariably leads to ethically questionable behaviour. Partisanship by Industry towards the private sector and a lack of interest in and commitment to public and academic sectors is a destructive influence. Industry's prime objective of profit does not serve mental health needs of developing countries.

Key Words:

Ethics, Pharmaceutical Industry, Psychiatry, Developing countries

Introduction

The relationship between the pharmaceutical industry and the discipline of psychiatry is increasingly a focus of discussion and sometimes heated debate. Seminars and symposia at psychiatric congresses regularly address the issue while psychiatric journals often dedicate entire sections to the topic. *World Psychiatry* for example published a feature article by Giovanni A Fava in its June 2007 edition (Fava, 2007) with a number of invited commentaries. Interestingly, most of these commentaries, authored by individuals with close links to Industry, adopted a defensive and even combative tone towards Fava's critical paper. What is less commonly the focus of discussion in the psychiatric literature however is the relationship between Industry and Psychiatry in so-called 'developing world' contexts. This then is the subject of this paper. Specifically, a case is made for the particular 'vulnerability' of developing country contexts in relation to three issues pertaining to Industry – psychiatry engagement: the medicalisation of mental distress and questions of distributive justice; drug trials and the private sector; and Industry involvement with public and academic sectors.

Many of the issues raised in debates emanating from 'developed countries' are shared with 'developing' contexts, for example issues of drug licensing and regulation, long-term availability of trial drugs to participants and the giving of gifts to clinicians. However there are some issues that are perhaps of greater importance and have greater impact in developing countries (DCs) by virtue of the socio-economic, cultural and political environments therein. For example, the development and marketing of expensive pharmaceutical agents within societies characterized by widespread poverty, income inequality and poor access to health services, raises ethical questions relating to distributive justice (Benatar, 2002.)

Furthermore, the concept of 'vulnerability' – familiar to discussions of ethics and research – needs to be understood in a much broader manner in DC contexts. This is particularly important in relation to the Industry's engagement with Psychiatry in DCs. Of course poor socio-economic conditions, lack of education and political disempowerment cause patients, who are potential research subjects and also recipients of medications, to comprise a particularly vulnerable group (Ogundiran, 2004; Park & Grayson, 2008.) However, the concept of vulnerability in DCs also should be extended to include mental health professionals, professional societies and organizations, governmental legislators and policy-makers and the consumer public as a whole. This is because in contexts where professional salaries are poor, funding for mental health care is limited and the public is generally uninformed about mental health and its treatment, opportunities exist for the Pharmaceutical Industry to wield far greater power and influence

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than is possible in more 'developed' countries. Exploiting these opportunities may, in many cases, not be a deliberate strategy. In fact the Industry is, for the most part, careful to conduct its activities with adequate attention to ethics. But the reality remains – financial rewards, opportunities for travel and the pampering that accompanies it and the ego-boosting possibilities of being invited to be an 'opinion leader' or member of an advisory board, all constitute major forms of inducement to serve the needs of Industry. And while individual professionals are subject to the charms of individual rewards, so the consumer public – who in most DCs are not exposed to a strong public mental health system – are susceptible to rampant and aggressive marketing and the blatant promotion of medical models of distress. In a context where multiple other social, economic and health priorities give rise to significant individual need as well as competing financial demands on government, the damaging effects of unscrupulous marketing tactics by Industry cannot be overstated.

The Medicalisation of Mental Distress and the Question of Distributive Justice

A number of authors have critiqued the manner in which biomedical psychiatry has become globalised hand-in-hand with the expansion of western free-market economics and politics (Thomas et al, 2005; Moncrieff, 2006.) These authors argue that there has been a gradual expansion of the boundaries of what is considered mental disorder over the last 3 to 4 decades so that one now finds biological explanations for such 'disorders' as 'compulsive buying disorder' and 'premenstrual dysphoric disorder.' The result of this medical expansionism is that more and more people now define themselves as psychiatrically ill and in need of medical treatments – especially pharmacological treatments. This of course translates into an expanded market for pharmaceutical companies; and it is not surprising therefore that one finds the Industry actively involved in disease awareness campaigns and other educational activities aimed at increasing consumer demand for medications and altering the prescribing habits of clinicians. Moncrieff (2006) links this process of the medicalisation of distress to the growth of neoliberal policies since the 1970's, whereby extensive deregulation and privatization have led to a massive transfer of wealth from the public sector to the private sector. It is undoubtedly serving the interests of Industry for more and more variations in human behaviour and experience to be brought under the umbrella of biologically based 'mental disorder', amenable to pharmaceutical treatment. Moncrieff (2007) argues that this expanding medicalisation of distress serves to undermine people's confidence in their traditional methods of coping and makes them "more vulnerable and less able to challenge social forces that act against their interests." In this way, the pharmaceutical answer to distress acts as a panacea against resistance to social and political change. The distress caused by rising unemployment, socioeconomic deprivation and growing income inequality that accompanies the neoliberal economic programme is defined in pathological and biomedical terms and is palliated with chemical solutions. And in the process, the pharmaceutical industry benefits from the ever-expanding market that results. The psychiatric profession is a willing partner in this process, lending professional credibility to what might be termed a brilliant marketing strategy. Whether or not one agrees with this sentiment and its obvious political stance, it is a useful analysis when looking at the ethics of the pharmaceutical alliance with psychiatry in the developing country context. One important issue here is the reality that the increasing use of pharmaceutical agents is accompanied by an increasing risk of inappropriate or excessive prescribing and potential adverse effects. This is particularly relevant to the increasing use of psychiatric medications in children, adolescents, the elderly and those with organic brain diseases. In well-resourced countries such as those of North America, Europe and Australasia these concerns are present and are the subject of much debate and careful regulation and control. In many developing countries however, the risks are likely to be much greater as there are generally fewer psychiatrists, poorer community mental health services to monitor patients and, in some cases, inadequate systems of regulation and control. It is inevitable that where there are few human and infrastructural resources for mental health care, there is a greater risk of indiscriminate and inappropriate use of psychotropic medications in vulnerable populations. For example, the prevalence of tardive dyskinesia (a neurological disorder resulting from the chronic injudicious use of antipsychotic medications) is much higher in developing countries than in developed countries (Kasper et al, 2006.)

A further issue of concern relates to the potential that exists, in contexts of poor regulation and control of psychotropic prescription and dispensing, for either covert or overt corruption. For example, Khan (2006) has described how in Pakistan most psychotropics are available over-the-counter and are often dispensed by untrained staff not subject to regulation by any professional body. Furthermore, these 'chemists' have considerable influence on psychotropic sales as many people present primarily to them with their complaints. Thomas and colleagues report that local pharmaceutical companies in India and Pakistan produce cheap 'bootleg' versions of psychotropic agents which are then freely available to consumers on the streets and in private clinics (Thomas et al, 2005.) While the argument might be offered that this is in the interests of the poor in these countries who cannot afford highly expensive original ('ethical') versions, one wonders whether this practice is actually in the best interest of patients (or merely another clever marketing strategy.) One might ask whether the provision of cheap generics in developing countries is a form of altruistic 'charity' or whether in fact it amounts to 'poor drugs for poor people.' This is a complex ethical debate that extends well beyond the scope of this paper.

Nevertheless, it is pertinent to question the ethics of both the rampant marketing of products and the scientific development of new agents by Industry, in partnership with psychiatrists, in contexts where there is little regulation and control. One hopes that efforts to enforce regulations in developed countries have played a part in minimizing the blatant use of perverse incentives by Industry and the acceptance of such incentives by professionals. Where there is still inadequate regulation in other countries, it is only too easy for such unethical practices to flourish. For example, Khan (2006) describes the situation in Pakistan where there is "little or no regulation of medical practice or drug prescribing and dispensing" and where "malpractice litigation against doctors is unheard of." He states: "The traffic is bidirectional – psychiatrists are as demanding of favours as companies are of providing them." Some of the inducements include: all-expenses paid trips

for self and spouse for a drug launch abroad; free drug samples, expensive gifts (such as watches, air conditioners, briefcases, laptop computers, etc); as well as the funding of a doctor's family wedding, holidays and other events of this nature. The issue at stake is the following: an environment where there is little regulation is a vulnerable environment – while doctors are clearly complicit in this unethical trade of favours for scripts, their circumstances need to be considered carefully. In low-resourced settings where remuneration for professional services may be low and rewards few, the persuasive offering of gifts is likely to constitute a significant temptation, difficult to refuse. While undoubtedly unethical, the acceptance of such rewards can be understood and contextualized. Viewed in this fashion, I would argue that the socio-economic conditions and the unchecked forces of a globalised, free-market system that emphasise material gain are primarily to blame for this blatantly unethical alliance.

One also needs to consider whether the biomedical development of new products by Industry in developing countries is justifiable. The scientific development of new agents is hugely expensive and consumes extensive resources – both material and human. Clinicians are routinely involved both in the early laboratory-based stages and the later clinical trial stages of drug development. If salaries are low for clinicians (as they are in many low-and-middle-income countries) the significant financial payouts for participation in clinical trials becomes a serious option to augment income. This means that the existing shortage of psychiatric expertise for clinical work is exacerbated as specialists give large portions of their time to the well-rewarded service of Industry. Furthermore, as is increasingly acknowledged by leaders in the field, we already have effective drugs; and the challenge now becomes how to improve delivery of and access to existing drugs, rather than how to develop new agents (Kane 2007.) Of course questions of access are of great importance within developing countries. Finally, one should ask the question as to how developing countries are supposed to sustain hugely expensive biomedical developments where there are so many other competing financial needs (such as fighting poverty and unemployment, managing HIV-AIDS, etc.) As Thomas and colleagues (2005) state: "Whether in the guise of new drugs or new therapies, technology is costly. How long should we reasonably be expected to go on paying for these developments … How are economically disadvantaged countries supposed to fund these developments, given the competing priorities of providing food and combating illnesses like AIDS?" (Thomas et al, 2005.) These are issues of distributive justice and are linked inextricably to the spread of the neoliberal programme across the globe. In an excellent review of the ethics of research in developing countries, Benatar (2002) states:

> "Erosion of the economies of many poor countries, under the impact of globalisation and debt, has prevented the introduction of effective forms of modern medicine into deprived communities and thus prevented achievement of widespread access to even basic health care for billions of people. In the 1990's, 89% of annual world expenditure on health care was spent on 16% of the world's population who bear 7% of the global burden of disease in DALYs (Iglehart, 1999), and of the estimated US$56 billion spent annually on medical research, less than 10% is spent on health problems of the developing world (Commission on Health Research for Development, 1990.) These are examples of global injustice that should surely be intolerable if there were genuine commitment to universal human rights and human dignity."
>
> (Benatar 2002)

Drug Trials and the Private Sector

South Africa is popular with the Pharmaceutical Industry when it comes to finding investigators for large multi-site drug trials. This, I am informed by both psychiatrists and Industry representatives, is because South African investigators are efficient, reliable and are easily able to produce the numbers of subjects required of them. Furthermore, the large numbers of available patients, together with the fact that many cannot afford newer psychotropics, means that there are always willing subjects available and keen to participate. Generous payments to subjects further increase the attraction for those without great means. Although consent procedures are taken seriously and generally adhered to with rigor by investigators, I would argue that the pool of potential trial subjects represent a vulnerable group. This is because they are very often coming forward to participate, not for altruistic reasons such as contributing to the progress of science, but because of financial difficulties and their desire to receive newer, apparently more tolerable agents. They have been lectured on the great benefits of such novel drugs by their doctors and are often desperate for another option (having either experienced undesirable side-effects from or failed to improve on other medications.) Enrolment in a drug trial is for many the only way to access this new 'wonder drug.' What about free choice then – free choice to choose treatment and research participation without coercion? I would argue that the difficult social and economic conditions that strongly influence the patient's decision to enroll in a clinical drug trial are in fact a form of environmental coercion. For this reason potential research subjects in developing country contexts represent a particularly vulnerable group. In my view it is unlikely that either Industry or clinician participants in drug trials take account of this complex ethical problem related to patient involvement.

A further issue related to patient enrolment in drug trials in developing countries without strong public health systems is the following: Most trials are conducted by psychiatrists working in the private sector. Many patients join the trial for the reasons given above, hopeful and expectant of positive results and improvement in their mental health. However, at the end of the trial period of 4 weeks or 8 weeks or longer, the new medication (on which they may well have improved and now lay their hopes upon) is no longer available. The drug may be available for private purchase at high and often unattainable cost, but for most individuals they cannot afford ongoing care in the private sector and are forced to turn to the public health system for treatment. The problem is, because of the high costs of these newer medications, most are not available in the public sector and these patients are then forced to change to older psychotropic agents, risking relapse or the return of unpleasant and debilitating side effects. This is the reality of being a trial subject in most developing country contexts. What we should be asking is whether it is ethical for Industry and psychiatrists to collaborate in drug trials in an environment where this is often the outcome for many of the subjects involved.

Finally, it is well known that participation in a drug trial as a

psychiatrist raises a number of ethical issues and challenges which are often unapparent at first glance and place the doctor in a questionable position. Firstly, the ethics approval process for drug trials is invariably handled by the pharmaceutical company and not the clinician. If the clinician is within the academic or state sector, trial protocols are required to pass through research ethics committees at institutions such as universities and hospitals. This provides a measure of control and peer review. However, for psychiatrists in the private sector, no such additional review processes are required and the ethical procedures preceding the trial are the responsibility of Industry alone. As Fisher (2008) discovered in a survey of private sector physicians involved in drug trials in the USA, "[they] often feel that third parties are responsible for determining the ethics of the clinical trials they are conducting." Fisher cites one physician who felt "his conduct was ethical because he followed the protocols as given to him by the pharmaceutical company sponsoring the studies." Thus, by involving themselves in drug trials, clinicians are able to rationalize their own ethical position by pushing responsibility for safeguarding ethical standards onto a third party – the Industry who are in fact the owners and beneficiaries of the trial. Of course Industry has a major vested interest in the success of the trial and cannot be said to be objective when it comes to evaluating the professional ethics of the project. Psychiatrists are therefore placing their own ethical standards in the hands of a party that has clear financial objectives in running a trial.

A more obvious challenge for individual professional ethics is the fact that most trials employ a method of contracting doctors whereby remuneration from Industry is directly related to numbers of trial subjects recruited. The more subjects a psychiatrist recruits the more he or she is paid. Furthermore, if a clinician proves he or she is particularly adept at recruiting the required sample efficiently and within the given time frame, it is highly likely that site will be invited to participate in further trials – thus securing future income and benefits from Industry. Successful trial doctors are invariably rewarded with sponsorship to international conferences, honoraria for speaking at Industry sponsored events and a host of other gifts and material expressions of gratitude that are dressed up in acceptable language designed not to offend one's ethical sensibilities. The problem with these inducements to perform well as a trial doctor is that numbers of patients recruited counts everything. And where there is a pressure to recruit the numbers, clinical judgment of what is actually in the individual patient's best interests may become blurred. It becomes only too easy to stretch selection criteria or ignore borderline laboratory results when one is desperate to enroll a patient in a study and keep them in the study to the end. In Fisher's interviews with trial physicians she quotes one doctor who stated:

> "There's all sorts of ways people will justify blurring lines of distinction, which may or may not be clear actually. Throwing away a lab value is way over the line, right? Does it have to be fudged when you're doing a blood pressure study and this person is two points out of range on their fifth visit, and you've already put in a month of time on that person? I don't know. Does that betray the spirit of what you're trying to do? As opposed to 10 points out of line, then they're out."
>
> (Fisher 2008)

Industry Involvement with the Public and Academic Sectors

In South Africa public sector and academic psychiatrists are generally not involved in drug trials. One reason is the difficulty Industry encounters in having trial protocols passed by institutional research and ethics committees. Common concerns raised by such bodies include: What happens to the subjects' ongoing need for the drug after the end of the trial? How can one justify placing seriously ill patients on placebos? The already over-burdened public psychiatric hospitals cannot justify keeping patients in a hospital bed for 8 or 12 weeks for the sake of research and cannot justify the expense and time spent on multiple, repeated laboratory investigations and assessments. Furthermore, the value of drug trials on agents that will probably never become available within the public health services is questionable, especially when other types of research are so urgently needed (for example epidemiological studies and research on health service development.) For the most part, Industry is not interested in service-related research or public health service development. Their marketing strategies are not focused on older cheaper agents used in the public sector. Where companies do occasionally woo public sector and academic psychiatrists they do so because they need their advice and guidance on how best to get their newer more expensive psychotropics onto the state essential drug list. On these occasions, these psychiatrists receive the same attention and rewards routinely provided to their colleagues in the private sector. Such partisanship towards the private sector gives rise to resentment and petulance amongst those working in academia and the public services where funding is limited for conference attendance and other educational and research-related activities. In low-and-middle-income countries it is very often the case that without pharmaceutical sponsorship most psychiatrists do not have the financial resources to attend conferences abroad.

Perhaps of greater concern is the close relationship that often exists between Industry and professional psychiatric societies. In South Africa for example, there is a particularly close relationship with the production of Industry-sponsored clinical guidelines, routine sponsorship of branch meetings and a not very transparent system for allocating Industry sponsorships to society members for conferences, etc. This has led to friction within the professional society with a number of individuals canceling their membership and withdrawing from society activities. While these kinds of problems undoubtedly occur in developed countries, I would argue that they are intensified and are potentially more destructive in contexts of socioeconomic difficulty and need. Resources are fewer, support from state and academic institutions is limited and work-loads are enormous and endless. Introduce the pharmaceutical industry, bearing gifts and favours for some but not others and you have a recipe for conflict and division.

Conclusion

For these reasons I believe that on balance the Industry plays a negative and divisive role within the psychiatric profession as a whole in developing countries such as South Africa. It has its agenda and that is profit. Within poorly resourced and over-

ARTICLE
SPECIAL THEME ISSUE ARTICLE

An Operational Proposal for Addressing Conflict of Interest in the Psychiatric Field

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ABSTRACT

The issue of conflict of interest has brought clinical medicine to an unprecedented crisis of credibility. Corporate actions that have placed profit over public health have become regular news in the media. The public seems to be increasingly sceptical of the integrity of medical practice, including psychiatry. Clinicians are more and more disoriented because of the discrepancy between the campaigns to shape a favourable climate of opinion for new drugs and the disappointing results in practice. Attempts to control conflict of interests by simple disclosure have yielded very limited results.

A radical proposal for addressing the issue of conflict of interest in psychiatry and regaining credibility is advanced. It is based on the definition of "substantial" conflict of interest: being an employee of a private company; being a regular consultant or in the board of directors of a company; being a stockholder of a company related to the field of research; owning a patent directly related to the published work. Occasional consultancies, grants for performing investigations, or receiving honoraria or refunds in specific occasions would not be a source of substantial conflict of interest.

Psychiatric investigators who hold positions in scientific societies, medical journals (editorship), groups for guidelines and clinical matters, should be devoid of substantial conflict of interest. Disclosure is no longer sufficient for the independence of the psychiatric field.

Key Words: conflict of interest, ethics, disclosure, practice guidelines, psychiatry

The issue of conflict of interest has brought the credibility of psychiatry to an unprecedented crisis (Anonymous, 2008). The public seems to be increasingly skeptical of psychiatry, since corporate actions that have placed profit over public health have become regular news in the media (Anonymous, 2008; Fava, 2007). The dangers of psychiatry's complicity with big business have been disclosed to the lay public in the media with a regular pace in the past two years. Conflict of interest undermines the credibility of papers which are submitted, their review process, and even the editorial decisions about acceptance or rejection (Jureidini & McHenry, 2009)

The reaction of the psychiatric establishment (scientific societies, academic centers, educational activities, journals) has been generally slow and inadequate. A typical example is provided by the American Psychiatric Association which has failed to endorse adequate changes in its highly criticized policies. A notable exception has been the World Psychiatric Association which has hosted an operational proposal (Fava, 2007) in a forum in its journal, with several discussants, such ad David Healy (2007), Michael Thase (2007) and Paul and Tohen (2007), and whose current president has regarded conflict of interest as a major challenge (Maj, 2008).

The notion of conflict of interest is widely used but may entail different meanings. Margolis (1979) distinguishes between conflicting interests and conflicts of interest. The former occur in any situation where competing considerations are presumed to be legitimate. Conflicts of interest, on the other hand, are characterized by individual occupying dual roles which should not be performed simultaneously. Because of the potential for abuse, performing both roles at the same time is considered to be inappropriate. Which roles? For instance, being a researcher and holding a financial interest in an area related to the research one is involved in. Table 1 lists the main sources of conflict of interest.

I will describe some of the insights that research on conflict of interest has generated in medicine and psychiatry, and some strategies which may counteract this phenomenon (Fava, 2007; Fava, 2008).

Conflict of Interest In Psychiatry

Important insights have been gained in the past decade as to the importance of financial conflicts of interest in medicine. These findings may apply to the psychiatric field.

TABLE 1: MAIN SOURCES OF CONFLICT OF INTEREST IN PSYCHIATRY

Being a clinician/researcher and:

- an employee of a private company
- a stockholder
- a member of a company board of directors
- a regular consultant of a private company
- an occasional consultant of a private company
- an official speaker of a private company
- an occasional speaker of a private company
- getting refunds from a private company
- recipient of honoraria
- a clinical investigator in a sponsored trial
- recipient of research support from a private company
- owning a patent

Prevalence is very high

The first idea of the prevalence of situations of conflict of interest in scientific research came from a landmark study which appeared in the 1990s. Krimsky, Rothenberg, Stott & Kyle (1998) analyzed 789 articles written by authors from Massachusetts universities publishing in leading scientific journals in 1992. In one out of three cases, at least one author had a vested interest in research. Krimsky et al (1998) took a very conservative stand as to what constitutes a financial conflict of interest: owning a patent directly related to the published work; being a major stockholder or executive in a company with commercial interests tied to the research, or serving on the board of directors of such a company. The percentage of cases of conflict of interest would have greatly increased if consultancies and honoraria had been taken into account. The study clearly showed the extent of corporate presence in scientific publishing.

The same group of researchers addressed the issue of the financial ties with the pharmaceutical industry of the 170 DSM-IV panel members. 95 (56%) had one or more associations with companies (Cosgrove, Krimsky, Vijayaghavan & Schneider, 2006). The percentage reached 100% of the members of the panels on mood disorders and schizophrenia and was above 80% in anxiety and eating disorders.

Disclosure is seldom performed

Disclosure has emerged as a first and essential step for dealing with conflict of interest contamination in science. But, despite journals' policies, it is seldom performed (in less than 1% of medical articles according to a study by Krimsky (2001)).

Such disclosure often takes place in the media, instead of coming from the authors or scientific community. Such scandals have also involved psychiatric researchers. A recent one about an article on vagus nerve stimulation has lead to the resignation of the lead author from the editorship of an important journal (Armstrong, 2006).

Scientific societies may be beholden to the drug industry

Glassman, Hunter, Hayer & Nakamura (1999) investigated whether revenues generated from pharmaceutical advertisements in medical journals create potential conflicts of interest for nonprofit physician organizations that own those journals. They found that financial conflict of interest were substantial, and some prestigious medical organizations, such as those underlying the *JAMA* and the *New England Journal of Medicine*, could be viewed as beholden to the drug industry.

Scientific societies may control medical journals and affect editorial policies and the selection of papers. Further, financial ties may also affect the scientific meetings of those societies. This is something anyone walking in a major society meeting may easily perceive. Not surprisingly, in a study of all exhibit booths of pharmaceutical companies at the 2002 American Psychiatric Association (APA) convention, a total of 16 violations of the APA's own exhibit rules has been found (Lurie, Tram, Wolfe & Goodman, 2005).

Authors of clinical practice guidelines are often linked to the pharmaceutical industry

Choudhry, Stelfox & Detsky (2002) examined authors of clinical practice guidelines endorsed by North American and European societies on common adult diseases. Eighty-seven percent of authors had some form of interaction with the pharmaceutical industry (58% had received financial support to perform research and 38% had served as employees or consultants for a pharmaceutical company). In published versions of the 44 clinical practice guidelines, specific declarations regarding the personal financial interactions of individual authors with the pharmaceutical industry were made in only two cases. Cosgrove, Bursztajn, Krimsky, Anaya & Walker (2009) have examined, by multimodal screening techniques, the degree and type of financial ties to the pharmaceutical industry held by authors of 3 Clinical Practice Guidelines of the American Psychiatric Association. Ninety percent of authors had financial ties to companies that manufacture drugs which are identified in the guidelines as recommended therapies. None of the financial associations were disclosed.

Attending drug sponsored scientific events is associated with an increased prescription of the sponsor's medication

A review (Wazana, 2000) has outlined how attending sponsored continuing medical education (CME) events and accepting funding for travel or lodging for educational symposia were associated with an increased prescription rate of the sponsor's medication. Attending presentations given by pharmaceutical representative speakers was also associated with nonrational prescribing.

Studies sponsored by pharmaceutical companies are more likely to have outcomes favorable to the sponsor

It has been repeatedly reported that studies sponsored by pharmaceutical companies are more likely to have outcomes favorable to the sponsor (Melander, Ahlquist-Rastad & Beermann, 2003). Industry sponsorship also results in restrictions on publication and data sharing and in selective reporting. Perlis, Perlis, Wu, Hwang, Josep & Nierenberg (2005) examined funding sources and authors' financial conflict of interest in clinical trials published in four leading American journals concerned with

psychiatry. Sixty percent were funded from a pharmaceutical industry, and conflict of interest was associated with a greater likelihood of reporting a drug to be superior to placebo. Further, Melander et al (2003) analyzed controlled studies of selective serotonin reuptake inhibitors and found that sponsored studies with favorable results were more often published than negative studies. A very good example of this selective publication is given by the scandal following the finding that a major pharmaceutical company allegedly withheld from the medical community clinical trial findings which indicated that a widely used antidepressant had no beneficial effect in treating adolescents (Kondro, 2004). Jureidini & McHenry (2009) have illustrated how selective reporting, publication bias and poor methodology may lead to unjustified conclusions in prescribing antidepressant drugs in children and adolescents. This casts serious doubts on the representativeness of the drug trials which are included in a meta-analysis. Further, even systematic reviews require careful critical appraisal. Conflict of interest may affect this appraisal. Evidence-based medicine thus may be a deceptive instrument of propaganda.

Ghostwriting has become increasingly common

Ghostwriting is an increasingly common practice which may involve up to 75% of papers concerned with drug trials (Sismondo, 2007). Jureidini & McHenry (2009) have illustrated the implications of this procedure for data presentation and marketing.

An Operational Proposal

A crucial problem lies in the lack of a definition of substantial conflict of interest. Are eating a pizza at a drug-sponsored lunch or being a regular consultant to a firm the same thing? Table 2 outlines some tentative criteria which are based on Krimsky et al's work (1998). The first two situations shown in the Table involve the concept of continuity of a relationship with a private firm. Indeed, occasional consultancies, grants for performing an investigation, or receiving honoraria or refunds in specific occasions would not be a source of substantial conflict of interest. For instance, if a researcher is a regular consultant to a pharmaceutical industry, he/she may be reluctant to endorse positions which may threaten a fixed source of income. A researcher who is involved only with a specific project (e.g., a drug trial) is less likely to be concerned about independent stands. The latter two situations depicted in Table 2 indicate major financial sources of bias.

Another issue is the fact that the problem of conflict of interest has been viewed so far mainly in negative terms: how to limit corporate influence in medical research. There has been little or no emphasis on the fact that the scientific community is draining itself of a reservoir of disinterested experts who can be called upon to advise government policy makers and physicians on the safety and efficacy of treatments, on the hazard of chemicals and on the safety of technology (Krimsky et al., 1998).

Yet, the experts who are free of conflict of interest may find increasing difficulties in obtaining appropriate visibility at meetings and in journals and in getting support for their research. It is not that disinterested experts are extinct: it is that they are marginalized by the gatekeepers of corporate interest within public institutions, scientific societies and medical journals (Fava, 2001) .

Table 2: Criteria for the presence of substantial conflict of interest of a researcher

The researcher meets at least one of the following:

1. Being an employee of a private firm
2. Being a regular consultant or in the board of directors of a firm
3. Being a stockholder of a firm related to the field of research
4. Owning a patent directly related to the published work

As a result, if we believe in the value of independent research and researchers and in the need of preserving and promoting this independence, we must endorse the steps which are outlined in Table 3 (Fava, 2007; Fava, 2008). These steps may appear to be radical and excessive, but are necessary for quickly re-establishing credibility. The idea that the problems which have been exposed in the lay press are only the result of lack of appropriate disclosure by individual researchers runs counter an increasing amount of findings pointing to loss of intellectual freedom by academic researchers and institutions (Fava, 2009). The operational feasibility of setting a threshold for substantial conflict of interest has been demonstrated by Krimsky, Rothemberg, Stott & Kyle (1998).

Table 3: Lines of support of independent researchers who are free of substantial conflict of interest

1. Priority for obtaining grants from public agencies supported by taxpayer money
2. Priority for scientific societies and medical journals editorship positions
3. Adequate visibility in scientific societies meetings programs
4. Inclusion only of researchers with no substantial conflict of interest in clinical practice guidelines groups
5. Conflict-free investigations and reviews should be emphasized in training and continuing medical education and should have priority in medical journals.

If a grant agency committee, or a medical journal, or a scientific meeting committee does not include at least some experts with no substantial conflicts of interest, and particularly those who have none, it does not deserve credibility.

For certain positions (e.g. editor-in-chief of a medical journal), the situation should be evaluated on an individual basis. For instance, tie to a single firm, contrary to what is often assumed, allows an easy monitoring of an editor's job (he or she can be excluded from assessing papers dealing with products of that firm), whereas multiple forms of conflict of interest make this control impossible. At times advertising departments appear to influence editorial decisions in journals which advertise drugs or devices (Dyer, 2004). Such influence may be particularly strong if the editor is vulnerable because of his/her conflict of interest.

Information overload may be the key vehicle of selective information (Fava & Guidi, 2007). A psychiatrist may be overwhelmed by scientific articles, often of redundant nature. He or she may become aware of certain articles because of firms pointing to those, or because they appear in very well-known and

distributed journals. Yet this may be very misleading. Conflict-free articles (particularly review papers) and purely subscription-based journals should become the focus of attention of clinicians who have become educated to the issues of conflict of interest (Fava, 2007).

Only in this context, interventions aimed to getting a better control of conflict of interest may become successful (Table 4). While disclosure has become standard practice in North American meetings and journals, it is still poorly practiced in Europe. It should be emphasized that in psychiatry conflict of interest may arise not only when there are ties with the pharmaceutical industry, but also when the researchers, for instance, are involved in private schools for training in psychotherapy. Disclosure is the minimal requirement for scientific credibility. It should have a specific time frame (e.g., 3 years). When an endless list of financial ties is provided, it should be clear that it becomes virtually meaningless, unless the potential implications of such ties are described in a note.

Table 4: Steps to addressing financial conflict of interest in medical research

1. Disclosure should become the rule in all scientific meetings and journals
2. Each scientific organization should have a conflict of interest advisory committee
3. Individual members of societies and readers of medical journals should express their dissent from presentations and articles biased by conflict of interest
4. Specific policies for integrity in science by professional societies, universities, granting agencies, pharmaceutical companies
5. Independent review bodies (within each field) for examining the issues concerned with conflict of interest
6. Educational plan for recognizing conflict of interest and the role of treatment ingredients

Each scientific organization should have a conflict of interest advisory committee that represents different segments of the organization and that should be a referral point to individual members identifying possible conflicts of interest (Warner & Gluck, 2003). Scientific organizations may also request disengagement from corporations that abuse public trust (e.g., false advertising, regulatory fines etc.) and do not allow publications of scientific results. Individual members of a society, not unlike the alternative consumer, can also decline participation in specific meetings or society events, or refuse to pay the dues of the society, or write to the journal which was involved in a specific case of conflict of interest (and the letter should be published, whereas it is seldom done with the excuse of lack of space or by not having a dangerous letter section). Members attending a meeting of their association should be able to rate the quality and the influence of the pharmaceutical industry with appropriate evaluation forms and to manifest their dissent (electronic mail is a powerful instrument for it).

The development of specific policies for integrity of agencies and pharmaceutical industries are also important (Brennan, Rothman, Blank, Blumenthal, Chimonas, Cohen, Goldman, Kassirer, Kimbill, Naughton & Smelser, 2006).

Finally, professional training programs (e.g. medical school, residency training, etc.) should teach individuals to recognize conflict of interest situations and increase awareness of biased interpretations of research results and treatment ingredients (Dubovsky & Dubovsky, 2007).

Conclusions

The problem of conflict of interest in psychiatry does not appear to be different from other fields of clinical medicine. It can be addressed only by a complex effort on different levels, which cannot be postponed any longer. In fact, either clinical researchers become salespeople (and the main scope of many scientific meetings today is apparently to sell the participant to the sponsor) or they must set out boldly to protect the community from unnecessary risks (Fava, 2001). The increasing influence of pharmaceutical industry on psychiatric research and practice is lending to an intellectual and clinical crisis (Fava, 2006). A proper and brave handling of the issue of conflict of interest may foster an overdue renewal of the field (Fava, 2009).

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stretched public and academic sectors, it is largely disinterested and uninvolved in the work of professional training and education and the provision of mental health services to the majority of the population. In its interaction with the private sector it provides inducements that test the ethical resilience of the most honest and scrupulous practitioner. In many 'developing countries', the pharmaceutical industry reaps in billions of dollars every year in sales of drugs from a population characterized by considerable levels of poverty, unemployment and a widespread absence of basic needs. Generally speaking the involvement of Industry with the psychiatric profession in realizing its prime objective of profit represents an unhealthy and regrettable alliance.

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ARTICLE
Special Theme issue article

Privatization of Knowledge and the Creation of Biomedical Conflicts of Interest

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Abstract

Scientific and ethical misconduct have increased at an alarming rate as a result of the privatization of knowledge. What began as an effort to stimulate entrepreneurship and increase discovery in biomedical research by strengthening the ties between industry and academics has led to an erosion of confidence in the reporting of research results. Inherent tensions between profit-directed inquiry and knowledge-directed inquiry are instantiated in psychopharmacology, especially in the co-option of academic activity to corporate objectives. The effects of these tensions are visible in research agendas, publication practices, postgraduate education, academic-industry partnerships and product promotion.

Key Words: conflicts of interest, ethics, intellectual property law, key opinion leaders, knowledge-directed inquiry, pharmaceutrical industry, privatization, profit-directed inquiry

Introduction

There are many pressures that potentially undermine the disinterested status of an academic scientist. None are free of bias. We carry pre-conceptions and expectations into research yet rely on research methodology to counter these effects. Most at risk are those who fail to acknowledge bias. In disciplines where research involves measurement, we rely on developing objective measures so that outcomes are less susceptible to researchers' judgments. Medical scientists are doubly vulnerable and may need a greater level of protection from bias than many other academics. They are also likely to be influenced by their idiosyncratic experience with their own patients.

Psychiatry may be the branch of medicine that is most vulnerable to influence. Diagnoses are difficult to define let alone to measure. Given the ascendancy of what Ziliak and McCloskey call the "cult of statistical significance," researchers turn to what is measurable rather than to what is meaningful, so that findings that are likely to be clinical and meaningful are rejected because they fail to reach statistical significance whereas others that appear clinically trivial are accepted (Ziliak and McCloskey, 2007). The disenchantment with the psychoanalytic paradigm of psychiatry led to a massive investment in psychopharmacology and other physical interventions. A concession now to the limited benefit that psychopharmacology offers would come at great cost to the profession. A vested interest in protecting the new paradigm of neurological models of psychiatric disorders reaches beyond the quest for a secure scientific foundation.

To the vulnerability created by personal bias and questionable methodology we must add the dangers of pervasive financial conflicts of interest, of which we investigate the root cause in this paper. With the privatization of knowledge comes a heavy burden of untangling the motives of profit from the motives of scientific objectivity. Conflict of interest has created an epistemological morass and a serious problem of credibility for the profession of medicine. The bias created from researchers' interests and ambitions pales in comparison to bias due to the now pervasive influence of industry.

Profit-Directed Inquiry vs. Knowledge-Directed Inquiry

It is in industry's interests to be competitive, protect discoveries and strategies as trade secrets, demand product loyalty, and suppress criticism, all to the end of gaining market share and maximizing profit. As such, inquiry is profit directed. By contrast, academe is a cooperative enterprise, characterized by free, open critical inquiry and disinterest in the results of research in the pursuit of truth and discovery of error. Richard Horton citing the American historian Steven Shapin, contends that the two cultures of the scientific and trading classes, or what we identity as the knowledge vs. profit inquiry, were kept separate, to protect the integrity and virtues of the former from the vices of the latter. Scientists were, and are still meant to be, trusted to produce a reliable body of knowledge, while no such requirement is supposed from those who seek private advantage (Horton, 2004, 7).

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A marriage of these two very different cultures or motives has produced a situation in which the profit motive threatens the ideal of intellectual inquiry. Addressing the most important needs of humanity becomes subservient to the pursuit of significant revenue. But more importantly for our present concern, profit inquiry instantiated in the corporate model of the academy has resulted in an alarming increase in scientific and ethical misconduct, especially in biomedical research. This is not to say that the industry-academe dichotomy has been sharply drawn and immune from contamination until recently, but in our view what might have been well-intentioned legislation to spur entrepreneurship in the commercial development of research has accelerated the conflicts of interest and the resulting misconduct with virtually no regulatory oversight. In fact, the political motives that created the acceleration of conflicts of interest are the very same ones that have considerably weakened regulation—all as a result of pro-industry legislation. The marketplace, we are assured by apologists, will correct product defects and expose corruption. Yet the harm to public health that has resulted from distortion in clinical research and the use of that research in drug promotion has made it clear that the marketplace is too slow or inept when it comes to medicine (Topol, 2004).

The Privatization of Knowledge and Conflict of Interest

Conflict of interest is defined as a problem of competing motives. A conflict of interest exists when one in a position of trust has competing professional or personal interests which make it difficult to fulfill his or her duties impartially. We take as a case study the United States pharmaceutical industry (by far the world's biggest), and its relationship with Key Opinion Leaders (KOLs), particularly psychiatrists who are amongst those most generously supported by pharma (Sorrell, 2008). In medicine, the phenomenon of the KOL is a result of the industry-academic partnership that has become virtually synonymous with financial conflict of interest. KOL's are individuals who act as consultants, researchers and teachers for drug companies. The relationship is mutually beneficial to the KOLs and the companies but not necessarily to patients. For the company, it provides an apparently independent expert to publish and speak on behalf of its products. For the academic, it offers kudos, research income, publications (including invitations to co-author influential papers that are largely ghost-written) and a profile at major congresses. It also offers great financial benefit. As the inquiries of US Senator Charles Grassley have revealed, senior KOLs have failed to disclose the extent of their financial entanglements with industry (Grassley, 2008). We can only guess at the degree of influence this undeclared income has had on their practice, but even absent any financial irregularities, KOLs are subject to influence through the benefit to their academic careers.

Pharmaceutical companies take considerable effort in recruiting KOLs they identify as malleable to their purpose by carefully monitoring a potential KOLs' prescribing and research. A young academic might be supported in research or asked to teach. If the company likes what it hears, its investment in the KOL will increase. The KOLs need never feel that they are being influenced by the company's generosity. The company will shape and influence existing conducive attitudes rather than attempt to change the opinions of someone who is not sympathetic to its product. Few physicians and psychiatrists can resist the lure of fame and fortune offered by industry, but the primary motive of ethical duties to patients is compromised by profitable drug and medical device promotion; marketing directives threaten the accuracy of research results and university professors become what David Healy calls "ornamental additions to business" (Healy, 2004, xv).

The rise of the KOL and academic entrepreneur coincides with what is arguably one of the most influential pieces of legislation to impact the field of intellectual property law—the Bayh-Dole Act of 1980. Such legislation was explicitly designed for the privatization of knowledge during Reagan Revolution in the United States, and resulted from a shift in the philosophy of government from creating public wealth and safety nets for the less fortunate to maximizing private, for-profit sections (Krimsky, 2004, 108).

The Bayh-Dole Act created a uniform patent policy that allowed universities to retain ownership to inventions made under federally-funded research. Previously the federal government assumed ownership of the research it funded but it did not have the resources to expedite transfer of technology for commercial development. Moreover, when the government granted non-exclusive licenses to businesses, competitors could acquire the same licenses and thus there was little incentive to enter into such arrangements. The motivation behind Bayh-Dole was to speed up the commercialization process of federally-funded research, create new industries and open new markets from the university-patented inventions. Robert Kelch reports that: "since 1980, at least 2900 companies have been formed that were built around an innovation licensed by researchers at an academic institution" (Kelch, 2002, 285).

The growth of university patents and the commercialization of research that followed Bayh-Dole at first seemed to have nothing but positive effects, such as the innovations in the development of biotechnology and rapid development of pharmaceuticals, but it soon became clear that the legislation had opened a Pandora's Box. Universities that were losing government funding found the new source of revenue in the technology transfer to industry, but at the price of a proliferation of conflicts of interest. It increased consulting arrangements with greater emphasis on intellectual property (Krimsky, 2006, 22) and created a culture of secrecy that "may actually have slowed the sharing of scientific information and the exploration of new scientific leads" (Angell, 2004, 203). The most disturbing aspect of these arrangements, however, is the manipulation of research results in favor of the sponsor company's products.

The secrecy involved in privatization created another obstacle to scientific progress since a significant portion of industry misconduct in clinical research is protected under the intellectual property law called "the Uniform Trade Secrets Act." This legislation prevents release of important information on the basis of the alleged necessity of protecting commercial interests that would be of value to competitors.

Pharmaceutical companies under challenge by legal proceedings to release information to the public routinely claim protection under the aegis of trade secrets. While some documents are unsealed and released to the public because they are already in the hands of

a third party such as a peer-reviewed journal or a Public Relations agency, the majority of critical documents remain unknown to the medical community and the public. These include documents that reveal exploitation of academics or physicians for marketing and promotion purposes, budgets that include payments to KOLs and medical communication companies that have produced ghostwritten publications, advisory board and speakers' symposia members, marketing agendas that describe manipulation of the peer-reviewed medical journals, programs designed to increase patient compliance, secret liaisons with patient support groups, disease mongering, and the results of negative clinical trials. Only occasionally does anything of this sort see the light of day and only because of attorneys' errors in submitting documents to the court or because an industry insider has smuggled documents and revealed them to the media. There are, of course, legitimate uses of the Trade Secrets Act such as protecting discoveries of new molecular entities from industrial espionage, but the abuse of the Act in order to protect companies from discovery of misconduct and fraud only adds to the general problem that privatization has created for the attempt at reliable science.

The Consequences of Privatization in Medical Research

Sheldon Krimsky has documented well the misconduct that has resulted from the academic-industry alliance that makes knowledge the property of for-profit companies (Krimsky, 2003). We wish to expand Krimsky's thesis with further evidence of the destructive consequences of ownership of data and industry research agendas.

As mentioned above, the most serious consequence of the privatization of knowledge concerns the reporting of results from industry-sponsored clinical trials. When academic investigators enter into a contact with a pharmaceutical company, they will sign a confidentiality agreement that makes it clear from the outset that the data produced in the trial is the property of the sponsor company and that any publication of results must be approved by company. In fact, before any publication appears the company signs off on release of the results to the named lead author thereby transferring ownership of the paper. Physician-investigators who have signed such contacts and then discovered in the course of the trial that the drug they were testing presented a serious danger to public health have found themselves in an ethical dilemma: either remain silent and violate the primary obligation to patients' health, or reveal the danger, face legal action and the destruction of their careers. The cases of Nancy Olivieri, Betty Dong, Aubrey Blumsohn and John Buse are particularly noteworthy in this connection because in their choice to reveal the danger, the sponsor companies sought retaliation. (Schafer, 2004, Krimsky, 2004, Baty, 2005, Committee on Finance, 2007)

In 2006 we were asked by the Baum-Hedlund law firm to do an independent analysis of study 329, sponsored by GlaxoSmithKline, on paroxetine (Paxil, Seroxat) use in adolescents. While it might seem hasty to extrapolate from this one trial, similar trials conducted on rofecoxib (Vioxx) and gabapentin (Neurontin) have shown a pattern whereby the sponsor companies working with medical communication companies have spun positive results from negative trials (Ross et al, 2008, Steinman et al, 2006). Others such as drotrecogin alfa (Xigris) and aprotinin (Trasylol) reveal further instances of manipulation of data and marketing hype (Singh and Singh, 2007a, 2007b). Indeed as Krimsky reports, this is just the proverbial tip of the iceberg since the majority of cases remain undisclosed (Krimsky, 2004, 9). Industry-sponsored trials conducted by academic investigators are prime examples of the harm done to the reputation of clinical research in the wake of Bayh-Dole. The paper that reported study 329, for example, claimed that: "paroxetine is generally well tolerated and effective for major depression in adolescents" (Keller et al, 2001). Yet documents obtained during litigation reveal that study 329 was negative for efficacy on all eight protocol specified outcomes and positive for harm. The incorrect claim for efficacy was supported by removing four of the eight negative outcome measures specified in the protocol and replacing them in the published paper with positive ones (two of which were introduced after breaking the blind), and by conflating measures to give the false impression that one of the primary outcomes was positive (Jureidini et al, 2008). Harms were either not reported or glossed over.

When the Keller et al paper was published, paroxetine was vigorously promoted to SKB/GSK sales representatives as demonstrating "REMARKABLE Efficacy and Safety in the treatment of adolescent depression" (Hawkins, 2001), and the same message was delivered to the psychiatric community by KOLs, who frequently did not disclose the results for the primary outcomes and serious adverse events (see, for example, Keller 1998, Berard et al, 1998, Wagner et al, 1998, Gagiono, 1999, Wagner, 2003). Reprints of the Keller et al paper were distributed by GSK with Med Query Letters to physicians.

A whole industry has developed as a result of privatization called "medical communications." At last count, there were close to 200 such companies in the United States alone (Golden et al, 2002). These firms have been identified as a major source of facilitating misrepresentation in journal publications and in conference posters which they prepare for industry. For a modest fee, the drug company can retain control of the message via the medical communication company it hires, reward KOLs with publication and thereby ensure that there is little risk that the named authors will take control of the message communicated through the paper. Study 329 was first drafted and then revised by a medical communications company, and there were very few meaningful changes (and therefore little scope for contribution by the named authors) from that first draft to the published paper (McHenry and Jureidini, 2008).

Commercialization of science results in distorted priorities in research. Rush to blockbuster status for relatively trivial medical problems or disease-mongered creations for consumers in first-world countries dominate the research agenda rather than the development of medicines for more serious problems throughout the world. Of 1393 new chemical entities marketed between 1975 and 1999, only 16 were for tropical diseases and tuberculosis (Trouiller et al, 2002). Marcia Angell exposes the main business of the pharmaceutical industry as the development of "me-too" drugs, namely, minor changes in the molecule of a blockbuster drug that is just different enough to qualify for a new patient (Angell, 2004, 76). So, drugs that treat heartburn, obesity, hair loss, toenail fungus, sexual performance, depression, allergies,

high cholesterol, and the like will have a high priority in the company while other important drugs that are less profitable will not be developed or will be discontinued. Examples of this latter group include certain anesthetics, antivenins, antidotes for drug overdoses, anticlotting drugs, antibiotics, and vaccines against flu and pneumonia, many of which are lifesaving treatments, but which have lesser appeal to industry because they are short-term rather than life-long treatments, or they treat diseases of the poor. An investigation into the development of HIV/AIDS drugs reveals that the real source of success was not profit-inquiry via KOL development, but rather liaisons between government, universities and other non-profit research before the compounds were shifted to private drug companies for further development, manufacture and distribution (Angell, 2004, 25-27, 67-68).

The industry-academe alliance has stifled academic freedom and critical inquiry. As Fava has made the point: "Investigators who swim against the tide of corporate-driven research strategies may indeed have difficulty in publishing their findings and observations" (Fava, 2004, 2). Commercial interests have come to dominate the content of academic medical journals. Advertising and reprint revenue alone raise serious questions about the degree to which such journals can claim to be neutral arbiters in the attempt to produce a reliable body of knowledge (Lexchin and Light, 2006). What has become known as "commercially valuable content," allegedly good news about medical breakthroughs in pharmaceuticals and medical devices much to the advantage of the industry, has higher priority over bad news resulting from critical studies about manipulated results or ineffective and unsafe medicine. No advertising contracts or profitable reprint orders follow the publication of a study that demonstrates the failure of clinical trial. Few journal editors seem to realize the degree to which they have been infiltrated by pharmaceutical marketing and the strategy of the latter to use the journals as vehicles of promotion. Richard Horton, in this connection argues that: "Medical journals have become an important but underrecognized obstacle to scientific truth" since they "have devolved into information laundering operations for the pharmaceutical industry" (Horton, 2004, 9 also see, Smith, 2007).

Finally, instead of following the results of peer review, there is much evidence that the final decision to publish is made by legal counsel to the journals. Papers that expose the extent of scientific misconduct and manipulation of trial results in industry-sponsored studies are routinely rejected due to fear of legal action brought by the companies (Healy, 2008). Our papers on study 329 (Jureidini et al, 2008; McHenry and Jureidini, 2008) began life as an invited contribution by the editor of the *British Medical Journal*. Amongst the reasons for her rejection was a "combination of editorial and legal concerns that we feel are unlikely to be resolved even with a great deal of further work on your part and on the part of the journal." This raises an important question about academic freedom when our journals routinely publish ghostwritten articles from industry-sponsored clinical research, but then reject critical studies of those same publications on the basis that legal counsel to the journals has advised of potential libel actions brought by the pharmaceutical and medical device industries (McHenry, 2008). Industry influence on the medical journals has thus led to a form of censorship forced on editors. Under the business model, criticism of products or processes is regarded as little more than competitors' vying for market share and a hostile threat to the company's well being, while in academe it serves a vital function in the pursuit of truth. Pharmaceutical marketing objectives identify academic physicians as hostile adversaries of their drugs and seek strategies to 'neutralize' their criticism. One manner of accomplishing this objective is by alleging that doctors with concerns about efficacy and safety are secretly promoting competitors' drugs (Coyne, 2005). Another is the co-option of KOLs to sign on to ghostwritten letters to the editors that defend the drugs against criticism. This tactic creates the appearance of academic discourse, but in reality is nothing more than exploitation of the medical journals by pharmaceutical marketing (McHenry, 2005).

All of the above has led to an erosion of confidence both in the wider medical community for the integrity of medical research and reporting of such research and in the public perception of the profession.

Conclusion

The profit vs. knowledge-directed inquiry distinction can be a false dichotomy if indeed profit and knowledge motivations merge to produce excellent scientific results and much needed innovations. The evidence of the past twenty-eight years since Bayh-Dole in the United States, however, suggests otherwise. While the short-term stimulus to biomedical research has been much celebrated, the unintended, long-term consequences for medicine have been severe. Scientific progress is thwarted by the ownership of knowledge, especially in clinical medicine where the adverse impact has reached an unprecedented crisis point (Fava, 2006). When the profit motive dominates research agendas, there is relatively little confidence in the results. The level of cynicism in the medical community was summed up in a response to Angell's editorial in *The New England Journal of Medicine*, "Is Academic Medicine for Sale?" with the quip, "No. The current owner is very happy with it" (Ruane, 2000). Competition in industry prevents cooperative research and open, critical evaluation essential to the long-term advance of knowledge. This is not to say that privatization of knowledge is the only source of conflict of interest in medicine, but there is little doubt that it has accelerated such conflicts since the 1980s. When knowledge, and especially that of critical concern to public health, becomes the private property of industry and academics are co-opted for the purpose of advancing this interest, the society that enables such activity has lost all claims to participate in the advance of science.

It may be impossible for medicine to sever its relations to its pharmaceutical and medical device industries. There is nonetheless little doubt that restoring confidence in the profession requires active protection of its autonomy and integrity. Since it seems highly unlikely that there will be any reversal of legislation that led to the problem or competent government regulation, it is the moral imperative of individual practitioners to eliminate conflict of interest. This demands first of all a unified effort of psychiatrists and other physicians to resist the relationships with industry that have distorted results of clinical research and led to habits of overprescription. Second, the profession must regulate itself by moral censure of practices that are profit-oriented and ostracize rather that lionize KOLs. Third, no investigator who has signed a confidentiality agreement with a sponsor company can claim

scientific status for the results of the trial. As Wagner and Steinzor make the point: "Science demands that, to the maximum extent possible, scientists have no stake in the outcome of the research" (Wagner and Steinzor, 2006, 6). Rigorous science can only exist when there is a genuine, risky test that could prove the hypothesis or theory false (Popper, 1959). This demands skepticism towards the outcome of experiments whether those outcomes are welcome or not (Ziman, 2000). As we have seen above, industry-sponsored research seldom if ever meets these criteria.

As for Robert Kelch's dilemma of "how to strike a balance between the need for investigators to act in the best interest of patients and their desire to serve the interests of the product they are developing" we agree that there is no choice to make (Kelch, 2002, 285). Physicians have a primary ethical duty to patients, not to products of industry. The doctor-patient covenant is violated once the physician enters into an agreement that gives industry ownership of the data.

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ARTICLE
SPECIAL THEME ISSUE ARTICLE

Show Me the Evidence: The Ethical Aspects of Pharmaceutical Marketing, Evidence-Based Medicine, and Rational Prescribing

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ABSTRACT

Pharmaceutical industry research and marketing methods and relationships with prescribing providers pose numerous ethical challenges. The authors review the impact pharmaceutical treatments and their costs play in the overall health care system. Several problematic prescribing practices are described along with a discussion of how the pharmaceutical industry has contributed to these practices. The Food and Drug Administration and the legislation that guides it bear much responsibility for how the pharmaceutical industry performs, but is significantly impaired in its ability to sufficiently monitor and regulate some pharmaceutical industry practices.

Although the pharmaceutical industry has made major contributions to the improvement of health through the introduction of newer and better therapeutic agents and through its support of physician education and patient access to some medications, it is nonetheless driven in part by its profit motivation, which may undermine some of its more noble goals. In particular the marketing methods utilized by the industry, including the use of pharmaceutical sales representatives, direct-to-consumer advertising, biased or misleading professional journal advertisements, and biased professional educational events, make it very difficult for prescribing providers to make rational and effective treatment decisions.

The authors review how conflicts of interest can be avoided and how evidence-based decision-making may be accomplished. Many useful and less biased resources on drugs and evidence-based prescribing are provided.

Key Words:

drug industry, marketing, ethics, evidence-based medicine

Introduction:

Several recent newspaper exposés have revealed previously unreported financial relationships between prominent physician researchers and various pharmaceutical companies. Such stories raise serious questions about the objectivity of such research and whether improved effectiveness and safety of pharmaceutical agents is as important as commercial profit to the pharmaceutical industry or the direct financial benefits researchers may derive from their scientific activities.[1, 2]

This paper is an attempt to sort out some of the knottier issues involving the relationship between health care providers and the pharmaceutical industry. We intend to identify and increase awareness of bias in pharmaceutical industry marketing practices. We describe methods for reducing that bias or, at least, to reduce the impact or influence of such bias. This involves encouraging practitioners to increase their understanding and use of evidence-based resources and helping them adopt strategies for managing their relationships with pharmaceutical representatives and interpreting the information the companies provide.

Health Care in the US is Expensive:

Although it is not the main thrust of this paper, it is nonetheless essential to acknowledge that the US spends enormous amounts of

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money on health care and gets mixed results of questionable value for that investment. Health care costs have risen consistently at a much faster rate than the overall economy with a negative impact on affordability, access, and quality of care.[3] The US spends more than any other country on health care, but lags behind dozens of European and Asian countries in key population health indicators, such as life expectancy and childhood mortality.[4, 5] Annual family health insurance premium expenses in the US are projected to exceed average family household income within 15-20 years.[6]

Pharmaceutical Costs Drive Health Costs:

Pharmaceutical costs have historically been among the fastest growing components of the US health care system, and are a major contributor to insurance premium increases.[7] These pharmaceutical cost increases are due to multiple factors, but primarily to increased prescribing (more prescriptions per patient and more patients receiving medications) and increased cost per prescription (greater average prescription price).

Increased prescription drug utilization is driven by both demand and supply side forces. Pharmaceutical coverage in insurance benefit packages has increased, most notably with the passage and implementation of Medicare Part D, even though many of these policies have increased out-of-pocket share costs. With an aging population having higher rates of chronic illness and co-morbidity, more people live longer with more chronic health problems necessitating drug therapy. In addition, prescribing providers are more likely to turn to medications as the choice for treatment for more illnesses in all age groups. Some of these trends are appropriate and reflect the progress that scientific research has made in improving the quality of care.

However, the pharmaceutical industry has actively induced demand, sometimes in excess of what is necessary or appropriate, for their products through marketing to clinicians and directly to the public. At the same time, drug price increases have been significantly greater than the inflation rate and appear to have a greater impact on the overall increase in pharmaceutical spending.[8] Providers tend to prescribe newer (and more expensive) drugs in more circumstances. Many of these drugs compete with drugs that are as effective as their newer cousins. Marketing pressure may be part of the influence for earlier adoption of these drugs, as well as pressure for the Food and Drug Administration (FDA) to approve drugs earlier in the research and development process.

These trends imply further erosion of health care affordability, resulting in increased premiums, deductibles, and co-pays; deeper state and federal health budget deficits; and increasing numbers of uninsured and underinsured individuals and families. As public and private payers seek ways to lower costs and to obtain better value, pressure is building for major reforms in the US health care system. In addition to the overwhelming societal and political responsibility to create a more rational system that provides universal coverage, there are opportunities for providers to learn more about how they can contribute to improving quality and value in relation to prescribing practices and modifying their relationships with the pharmaceutical industry.

Problematic Prescribing Practices:

Three specific practice-related activities that require more attention are:

- Polypharmacy
- Off-label prescribing
- Over-medicalization and premature initiation of drug treatments.

Some practitioners have developed practice patterns that reflect these activities to a greater extent than others. Unfortunately, in addition to the genuine desire to bring more immediate relief to suffering patients, the activities of the pharmaceutical industry have contributed greatly to such behaviors.

Polypharmacy and off-label prescribing are much studied and reported concerns, so they will only be mentioned in passing. Polypharmacy is the use of two or more drugs from the same therapeutic class or multiple drugs from several classes to treat a particular condition when there is limited or no evidence that such multiple drug regimens are effective. Polypharmacy can actually undermine the benefits of certain treatments, can lead to unnecessary side effects or drug-drug interactions, and certainly is associated with increased pharmaceutical costs.[9]

Off-label prescribing is the practice of providing medications for conditions for which they were not approved by the FDA. In some cases, off-label uses are well-established and have some scientific evidence to support them, but in many cases they are the result of speculation, anecdotal experience, or misinformation.[10] Off-label prescribing, sometimes encouraged in indirect ways by drug company representatives and, because such marketing practices are illegal, has resulted in major litigation. One such case involved the mismarketing of Neurontin (gabapentin) as a treatment for bipolar disorder, and off-label pain conditions which led to the funding of this paper and associated educational activities through grants made possible by some of the proceeds from the settlement of the case.[11-12] More recently, Eli Lilly agreed to pay over $1.4 billion in penalties and payments to government agencies for off-label promotion of its antipsychotic drug, Zyprexa and Pfizer agreed to pay $2.3 billion for similar off-label promotions for a number of its products. [13-14]

Over-medicalization can sometimes be due to disease mongering, which is the promotion of sickness that widens the boundaries of illness and expands 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, inform or educate about the prevention of illness or the maintenance of health. Some examples of disease mongering include aspects of ordinary life, such as menopause, being medicalized; mild problems portrayed as serious illnesses, as has occurred in the drug-company-sponsored promotion of irritable bowel syndrome; and risk factors, such as high cholesterol and low bone mineral density being framed as diseases that must be treated with medications. Creating demand for pharmaceuticals has been suggested as the genesis for several new conditions such as premenstrual dysphoric disorder, or expansion of definitions of existing disorders such as pre-hypertension and pre-diabetes.[15]

Needless to say, direct-to-consumer advertising fans the flames of over-medicalization by inducing those who are exposed to such advertising to accept the implied or subtle suggestions that they may have conditions that are serious and necessarily treated with medications. This may contribute to the US having the world's highest per capita pharmaceutical spending. [16]

The Food and Drug Administration's Roles, Responsibilities, and Stresses:

Many would ask what the FDA's role is to prevent such unnecessary treatments or marketing irregularities. The FDA's primary pharmaceutical mission is to review and approve drugs by determining if proposed medications are effective and safe. The usual standard for effectiveness is whether the agent is statistically superior to placebo, which can be based on the results from as few as two randomized controlled clinical trials. There is not requirement that the difference be of clinical significance.

The safety determination is based on a relatively limited number of studies and may be restricted to data provided solely by the pharmaceutical manufacturer's funded researchers.[6] The FDA's safety review does not require sufficiently large trials that would have the statistical power to identify potentially rare but serious side effects. A typical newly approved drug may be tested in several thousand individuals during preapproval clinical research. This may be insufficient to detect adverse effects that occur with an incidence rate of less than 1%.[17] The FDA is also expected to review pharmaceutical advertising for accuracy, but is generally unable to meet this goal sufficiently because of resource limitations.

Unlike drug regulation in most European countries, the FDA's review of drugs does not take into consideration the absolute or relative cost of drugs or the relative effectiveness of the proposed drug to other drugs already approved for the proposed indication. Likewise, the FDA is unlikely to approve a drug for all the indications for which it may end up being used. However, pharmaceutical manufacturers have proposed additional indications for a particular drug for FDA approval, usually at a time towards the end of the drug's patent life. In some circumstances, this allows the drug to continue to be sold exclusively by the proprietary manufacturer at a higher price than if it were to go off patent and be available as a generic drug, but also expands the drug's potential market share by being approved for more indications and, therefore, more patients.

Much has been written elsewhere about the apparent excessive influence of the pharmaceutical industry over FDA operations in terms of pressure to obtain drug approval before sufficient evidence has been gathered; the tendency for data to be manipulated or obscured in ways that increase the probability that drugs will be approved in spite of potentially contradictory findings; the legal methods pharmaceutical companies have used to prevent drugs from becoming eligible for generic status; and the appearance of undue influence derived from federal rules that require pharmaceutical industry financial contributions to the FDA approval process.[18]

The Pharmaceutical Industry's Contributions to Health and Health Care:

It is important to point out the positive contributions of the pharmaceutical industry. The manufacturers provide substantial support, through grants to researchers as well as their own direct research activities, towards the development of new agents for the treatment of illnesses. Pharmaceutical companies provide funding and educational support for a wide range of academic, health care, and professional organizations. The provision of free medications through industry sponsored patient assistance programs provide many uninsured persons access to medicines that may be otherwise unaffordable. Although most of these practices are promoted as beneficial, e.g., good public policy and evidence of the industry's generosity and good will, none of them is without controversy. Numerous studies and media reports highlight the quid pro quo nature of the "generosity" as reflected in increased sales of the drugs which have been provided gratis, the increased appearance of drug company product placement and literature at industry funded events, and the previously mentioned appearance of bias associated with some industry funded research.[19]

In any case, it is abundantly clear that one of the primary goals and functions of pharmaceutical manufacturers, as corporate entities, is to make profits for their owners and shareholders. The individual companies and their industry umbrella organization spend enormous amount of money and time in efforts to influence all persons in key decision-making positions, including legislators, providers, patients, and the general public, to help them maintain or increase those profits. This truth is borne out by the fact that the pharmaceutical industry is among the most profitable of all business types (1999 average profit for 6 major companies was 16% of revenues.).[20] It is difficult to escape the conclusion that the industry's business interests seem to conflict with or confound its efforts to improve health and health care.

Pharmaceutical Industry Marketing Methods:

To fully understand the impact of pharmaceutical industry efforts to influence prescribing providers and patients, it is essential to review how much is spent on such efforts and the specific marketing strategies utilized. It should be no surprise to any resident of the US, especially those who watch commercial television, read newspapers or magazines, or surf the internet, that drug companies spend enormous sums to promote their products.

In 2005, US pharmaceutical marketing expenditures were $29 billion, differentially allocated to: visits to physician offices (22% of the marketing expense), which usually involves the provision of patient samples (62%), direct-to-consumer ads (14%), and professional journal ads (2%).[20] The importance of marketing in relation to research activities can be seen by the gap between the number of persons working in these two areas. In 1995 there were 12% more marketing positions in marketing than in research, but by 2000 that gap widened to 81%, with an absolute increase of 59% of marketing positions while the number of research positions remained relatively static.[21] The primary marketing strategies detail visits by sales representatives, direct-to-consumer advertising, and professional journal advertising, each of which merits separate analysis to understand the rationale and effectiveness for these approaches.

Pharmaceutical Representatives:

The use of sales representatives is the drug industry's main marketing activity and is used to influence providers to prescribe targeted drugs through the provision of selected journal articles and selectively presented data, often supplemented by the provision of gifts for physicians and staff and samples for patients. The number of representatives in the US in 2005 was over 100,000, 1 for every 6 practicing physicians. This sales force provides approximately 6 million office visits yearly, at a cost of over $12,000 per physician. Family practice and internists have been documented to meet with pharmaceutical representatives more frequently than other specialties suggesting a strategy aimed at increasing adoption to a broader range of patients.[22]

Studies consistently show that physicians do not believe that such promotion affects their prescribing habits, but other studies conclusively show that such marketing efforts lead to significantly increased rates of prescription of targeted drugs.[23-26] Reviews on the topic generally show that interaction with the pharmaceutical industry is associated with increased likelihood of formulary requests for targeted drugs; increased awareness, preference and rapid prescribing of new drugs; higher prescribing costs; less use of lower cost, but equally effective, generics; and less rational prescribing.[27]

Direct-to-Consumer Advertising:

Direct-to-consumer (DTC) advertising involves various forms of print, television, radio, and internet promotion of pharmaceutical products, as well as the indirect impact of product and company name placement in entertainment, sports, and recreation venues. In 1997 the FDA relaxed regulations on DTC advertising, eliminating the requirement for detailed lists of potential serious side effects, allowing the substitution of passing reference to informational toll-free phone numbers or websites. As of 2005, the US and New Zealand were the only industrialized countries to allow DTC ads.

DTC expenditures are enormous, totaling over $4.5 billion in 2005, an increase of almost 300% since 1997.[28] For example, Hoescht spent over half a million dollars on one 60-second ad for Allegra.[29] In one year Merck spent $161 million advertising a single drug, Vioxx, (which ultimately was taken off the market for safety reasons), an amount exceeding the entire annual advertising budget for companies like Dell, Pepsi, Budweiser, or Nike.[30]

But, DTC ads result in enormous revenue returns. In 1998-99 the 25 most advertised drugs experienced 43% sales growth, whereas all other drugs only averaged sales growth of 13.3%.[29] In the same period of time, Claritin, Allegra, and Zyrtec, which were heavily advertised, increased their sales by 32%, 50%, and 56% respectively.[29]

The DTC strategy effectively facilitates the practice of over-medicalization, described above. Being bombarded with ads for vaguely described conditions, such as erectile dysfunction, sleep disorders, or conditions that affect one's appearance, understandably leads many people to dread the risk of such conditions but also to overestimate the likelihood that their symptoms may mean that they need such drugs. In 2002 over 53 million persons in the US discussed DTC-advertised drugs with their physicians. Given the greater pressure physicians in the US are under to see more patients for shorter visits, it is not surprising that many of these patients have received the drugs that they discussed with their physicians.[31]

Journal Advertising and Biased Information:

Many professional medical journals depend on advertising support from the pharmaceutical industry in order to provide their publications to physicians free or at subscription rates that are well below their publication costs.[32] However, advertising which often dominates medical journals, has been found to not meet FDA adverstising standards, to be of little educational value, and generally misleading.[33] Much has been written about the unnecessarily close relationship between the pharmaceutical industry and such journals, but also individual physicians and clinics, academic health centers, and other professional organizations.[32, 34-37]

In a 2003 review of all ads in 10 major medical journals, approximately 500 unduplicated ads contained 74 unique graphs, of which 36% contained "numeric distortions" and 66% had "chart junk", leading to confusing and misleading conclusions supporting the advertiser's product without establishing significance of difference from competing medications.[37] In many cases the ads focused on short or intermediate outcomes rather than more meaningful longer-term outcomes that would be more correlated with true therapeutic effectiveness.

Prescribing Practice Profiling Databases:

The pharmaceutical industry has access to a vast prescribing database, that when paired with the American Medical Association (AMA) Physician Master file, allows them to track the prescribing patterns of most prescribing providers.[38-39] The AMA receives a considerable amount of its revenue from the sale of its physician data. The data is frequently used by individual companies to target specific providers for promotional messages or sales representative visits. Very few providers know of this database nor that they have the right to "opt out" of their own practice data from being used for such purposes.[40] The companies must honor the expressed wish to opt out of the program, but the individual provider must renew the opt out provision (www.ama-assn.org/go/prescribingdata) every three years.

What Can Clinicians Do?

The response to the question of what clinicians can do to reduce the influence of the pharmaceutical industry's tendency to promote distorted or biased information is a either denial or hopelessness, in the form of "my practice is not affected" or "what can I, a mere individual do in the face of this overwhelming pressure?"

Of the many strategies proposed in various papers and conference presentations, we have distilled a few:

- Reduce or eliminate contact with industry representatives ("Just say no").
- Identify/use unbiased and independent sources of prescribing information.
- Opt out of use of one's data in the AMA master profile.

Of particular concern is the seductive and influential impact of commercially sponsored continuing medical education (CME) . The ancillary non-educational perks associated with such activities, including free or subsidized tuition, travel support, meals, books, equipment, and other gifts bearing product or company identification are fairly well documented and are now becoming less common, partly because such practices are under serious scrutiny by watchdog groups and Congressional committees. However, the content of such educational offerings bears closer scrutiny as well.

It is important to recognize the extent of industry involvement in continuing medical education. In 2006, half of the $2 billion dollars spent on CME came from industry sponsorship.[41] Medical Education and Communication Companies (MECCs) are private companies that organize meetings, find speakers for grand rounds and symposia, and develop written materials. Approximately 76% of MECC income is derived from industry sources. In addition, many medical school faculty and departments depend on industry to provide support in the form of CME income. This faculty support is above and beyond that for researchers as mentioned in the articles referred to in the opening of this paper.

The question of whether drug company sponsored educational events have a disproportionate influence on prescribing behaviors is well established. In one study, attending drug company–sponsored CME presentations led to a 5-19% increase in rate of prescription of the sponsor's drug versus the competitor's drug. Similarly, Funding for travel or lodging to attend educational symposia increased formulary requests for the sponsor's drug, increased the rate of prescribing of sponsor's drug, and impacted hospital prescribing practices as much as 2 years later.[27]

It has also been clearly demonstrated that the source of funding can affect the content of CME events. Content analysis of two different CME courses sponsored by two different drug companies, in which each discussed 3 calcium channel blockers, showed that the drug company–sponsored CME preferentially highlighted the sponsor's drug(s) compared with other CME programs and that there was a 2.5-3 times greater likelihood of positive effects of sponsor's drug and negative or equivocal effects of competitor's being mentioned.[42]

What can clinicians do to eliminate or reduce their own actual or perceived conflicts of interest? Many are advocating to simply eliminate or dramatically limit any relationships with drug company detail or sales representatives.[18] Even though it may mean ending or significantly altering relationships that have been long-standing ("some of my best friends are…."), the risk of unconscious bias and the appearance to staff and patients that one is more interested in pharmaceutical perks than providing quality clinical care would seem to far outweigh any inconvenience or hurt feelings. To implement such policies for oneself or the organization within which one works may require addressing individual or collective tendencies to rationalize ("It's really an educational dinner", "who is hurt by my accepting this free clock?" or "my patients need samples") or to deny the potential negative impacts of these conflicts ("It doesn't affect my prescribing decisions" or "I take it with a grain of salt").[43]

Evidence-Based and Relatively Unbiased Sources of Information:

In addition to shedding the burden of various real or perceived conflicts of interest, it is incumbent upon clinicians to develop more consistent and evidence-based methods of treatment, including prescribing practices. This is not so easy in an age when all kinds of information is available, much more than anyone can possibly absorb and much of it questionable or ambiguous in terms of its validity and relevance to one's clinical practice. David Sackett, a pioneer of evidence-based medicine (EBM) defines evidence-based medicine as "the conscientious, explicit and judicious use of best current evidence in making decisions about the care of individual patients." By "conscientious", he means good faith efforts to use the best treatment for patients, in ways that are "explicit" or in which one's treatment plan and recommendations are logical and transparent, and with judiciousness, i.e., allowing clinical judgment to remain important to interpret and apply results within individual, cultural and other relevant contexts.[44] It is important to keep in mind that EBM is not:

- The same old thing we've always done
- Something that can only be done from ivory towers
- A "cookbook" method of practice
- A method for administrators to save costs
- Restricted to randomized trials

There is too much variation in clinical behavior among clinicians. There are many examples of clinical teams that have improved outcomes by explicitly using EBM principles, sometimes facilitated by the use of internet resources or other decision supports. EBM may actually be a bottom-up approach that integrates the best external evidence with individual clinical expertise and patient values/choice. EBM makes use of the BEST evidence available, whatever that is. EBM should identify and apply the most efficacious interventions to improve quality and quantity of life for patients, irrespective of its direct costs. Presumably, providing better quality of care over time to a greater portion of the population will lead to decreased burden of disease and reduced overall utilization of health care services.

It has also been said that "evidence based medicine requires the integration of the best research evidence with our clinical expertise and our patient's unique values and circumstances." But how do we do this with so little time and so much information to absorb in order to make an intelligent and rational prescribing decision?

One simple mantra to follow is a restatement of the Hippocratic Oath: [45]

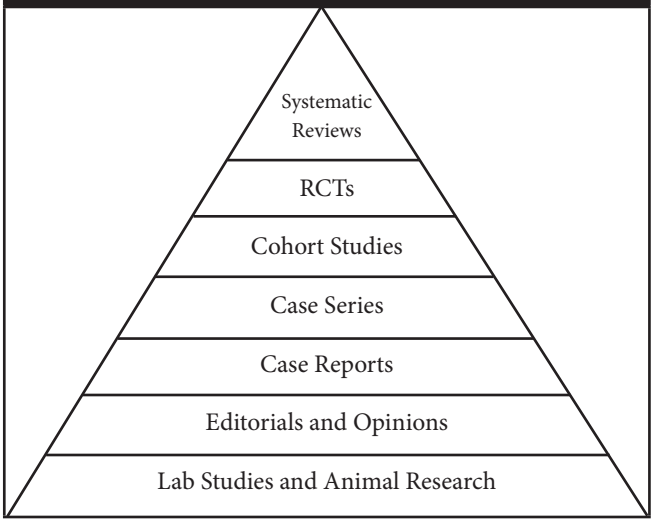
- When there is evidence of benefit and value, do it.

- When there is evidence of no benefit, harm or poor value, don't do it.
- When there is insufficient evidence to know for sure, be conservative.
- When considering the treatment of individual patients, we should also consider the potential help/harm to the patient's family and overall community in this equation.[46]

Such an evidence-based approach involves sorting through the marketing, opinions, and theory to get an accurate assessment of the proven and comparative benefits and risks of various treatments. It supports policies that reduce variations in practice, especially expensive or inappropriate prescribing. It provides incentives to conduct research on more meaningful questions, especially comparative studies.

It is essential to understand the various levels of evidentiary confidence as exemplified by the following illustration. The higher the available data for a particular condition or treatment is on this theoretical hierarchy, the more reliable it generally would be considered to be.

FIGURE 1: LEVELS OF EVIDENTIARY CONFIDENCE



In order to be most successful in understanding and using research findings, it is recommended that the clinician should seek information from sources that are derived from the higher levels of this conceptual pyramid. In reviewing specific studies, one needs to become familiar and conversant with terms associated with research findings, such as generalizability/applicability/relevance, number needed to treat, confounding variables, and target outcomes. It is also important to recognize signs of publication bias when they appear or when the lack of mention of certain key factors is apparent.

However, it is generally difficult, if not impossible for most practicing clinicians to absorb the key research studies in medicine, even those restricted to the clinician's narrower area of clinical focus. Therefore, it is essential that, whenever possible, clinicians seek out and use systematic or comparative reviews rather than single studies. Too often drug company representatives will gladly hand out reprints of single studies that tend to favor their particular product. Objectively conducted systematic and comparative reviews are becoming a much more important area of research.

Systematic reviews are now becoming quite consistent in their methodological approaches and, because of the power of pooling data from numerous studies, can be used to develop more cogent and meaningful recommendations about the effectiveness and applicability of certain treatments, including more reliable treatment guidelines.

Sources of Relatively Unbiased Information:

How can a clinician get connected with reliable, succinct, and user-friendly resources to assist them in their decision-making? There are numerous publications and internet web sites that have emerged to address the wide array of clinical concerns mentioned in this paper. We list a selection of current and relevant resources by type.

Relatively Unbiased Sources on Drugs and Drug Studies:

- Agency for Health Care Research and Quality's Effective Healthcare Program: http://effectivehealthcare.ahrq.gov, conducts comparative effectiveness reviews of many high priority conditions through the network of evidence-based practice centers and other research institutions throughout the US and Canada.
- National Institute for Clinical Excellence: www.nice.org.uk, an independent British organization responsible for providing guidance on the promotion of good health and the prevention and treatment of ill health.
- Cochrane Collaboration: www.cochrane.org, an international collaborative initiative, also based in the UK, whose intention is to improve healthcare decision-making globally, through systematic reviews of the effects of healthcare interventions.
- Drugs @ FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/, the FDA's public access site to search for official information about approved brand name and generic drugs and therapeutic biological products, including available generics, therapeutic equivalent drugs, consumer information, and drug approval history related documents.
- Canadian Common Drug Review: www.cadth.ca/index.php/en/cdr, provides objective, rigorous reviews of clinical and cost effectiveness of drugs, and provides formulary listing recommendations relevant to publicly funded drug plans in Canada.
- Drug Effectiveness Review Program: www.ohsu.edu/drugeffectiveness, aka DERP, funded by and overseen by

public payers from over 15 states and Canada, does systematic and comparative effectiveness reviews on over 25 classes of drugs. Reviews are updated on a regular basis.

- Pub Med: http://www.ncbi.nlm.nih.gov/pubmed/, creates summaries of many of the DERP reports and will have links to them in relation to individual drugs about which users may be inquiring.

- Consumer Union: http://www.consumerreports.org/health/prescription-drugs/index.htm, provides well organized information on most pharmaceutical agents, derived from effectiveness reviews, and translated into less technical language that is more accessible to consumers.

- Clinical Trials Database: http://clinicaltrials.gov/, obtains all registered clinical trials that hope to be published; began including outcomes in 2009.

- Carlat Report: http://www.thecarlatreport.com/, a monthly newsletter (in both print and online form) that provides clinically relevant, unbiased information on psychiatric practice.

- Therapeutics Initiative: http://ti.ubc.ca/, from the University of British Columbia, provides evidence-based reviews of drug prescribing for physicians and pharmacists

- Oregon Health Policy & Research: www.OregonRx.gov, contracts with the Oregon Evidence-based Practice Center to conduct evidence-based reviews of all literature available on specific drug classes; creates one-page summaries for consumers which synthesize the reports focusing on which drugs are most safe and effective.

- Oregon Drug Use Review Board Newsletter:

- http://pharmacy.oregonstate.edu/drug_policy/index.php?nav=newsletter. This is a periodic newsletter published by the Oregon State University College of Pharmacy on behalf of the state's Drug Utilization Review Board. Provides drug utilization reviews, drug and therapeutic guideline reviews, and cost-effective prescribing recommendations.

- Oregon DHS Pocket Drug Guide: http://pharmacy.oregonstate.edu/drug_policy/prescriber_tools/POCKETFinal.pdf, a convenient printable pocket guide of cost comparison data of the more commonly prescribed drugs.

- OregonRx: www.OregonRx.gov, provides information concerning prescription drugs to consumers and health professionals with a goal to provide current, reliable, evidence-based medicine information so as to empower consumers, prescribers, and medical professionals to utilize the information for their needs and practices.

Sources of Information on Industry Practices, Drug Comparisons, Formularies:

- No Free Lunch: www.nofreelunch.org/, a comprehensive collection of primary material and links to other sites, produced in conjunction with the American Medical Student Association, to encourage health care providers to practice medicine on the basis of scientific evidence rather than on the basis of pharmaceutical promotion.

- Pharmed Out: http://www.pharmedout.org/, an independent project (funded by the same grant program that supported the creation of this paper) that empowers physicians to identify and counter inappropriate pharmaceutical promotion practices. PharmedOut promotes evidence-based medicine by providing news, resources, and links to PhRMA-free CME courses.

- Oregon's Attorney Generals Prescriber and Consumer Education Grant website; http://pharmacy.oregonstate.edu/drug_policy/index.php?nav=aggrant, provides a curriculum to educate healthcare professionals (CME accredited) to critically view pharmaceutical marketing strategies and to access unbiased evidence-based drug comparisons to encourage quality and cost–effective prescribing, including the PowerPoint presentation from which this paper is derived.

Conclusion:

In this paper we have attempted to cover a great deal of territory regarding:

- the connections between health care costs and outcomes, with specific reference to the development of and process of treatment with pharmaceutical agents, highlighting some problematic prescribing practices;

- the roles and relationships between the government oversight entity, the FDA, and the pharmaceutical companies that develop and market therapeutic medications;

- the specific marketing methods utilized by the pharmaceutical industry and how those methods appear to be more devoted to maximizing profit than health;

- ethical and practical guidance for clinicians to develop or maintain more distinct and less conflicted relationships with pharmaceutical companies, their representatives, and their proprietary products and profit-motivated interests;

- the relevance of effectiveness research findings and the methods for translating such research into evidence-based recommendations or guidelines; and

- several examples of relatively unbiased sources of information related to medications, formularies, evidence-based systematic and comparative effectiveness reviews.

This is an exhaustive topic about which several excellent books have been written.[47-49] There are undoubtedly areas we didn't discuss that could have been stressed and areas that we did discuss that could have been more comprehensively developed. However, our overarching goal was to present, in a relatively short paper, a broader gestalt view of the issues as they relate to clinicians and

their roles and attitudes vis a vis the pharmaceutical industry and rational clinical practice. If we achieve that level of understanding, provoke sufficient consciousness about the interrelatedness of the topics we covered, and stimulate sober assessments of individual and organizational ethical behavior, we will have succeeded.

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