Yes, industry influence is excessive

Defining the debate

The pharmaceutical industry has made significant contributions to the field of geriatric psychiatry. Drug treatment has improved the quality of life for many vulnerable patients suffering from burdensome psychogeriatric syndromes. We do not dispute here the contributions of the pharmaceutical industry to patient care. Rather, we describe how the industry, driven by the need to produce profits, has implemented conscious strategies to promote the prescribing and thus the sales of drugs, without regard to patients' best interests. The industry has influenced the conduct and publication of research, and the promotion of drugs to physicians and patients, for purely marketing purposes.

Influence on prescribing: definition of disease

Sick patients are the prime customers for pharmaceutical products, and expanding the number of potential customers is a time-honored marketing strategy. An article in the *Pharmaceutical Executive* (a trade journal for pharmaceutical company management) discusses the "making of a new disease" – how new markets can be created by creating and defining new diseases (Breitstein, 2004). For example, drug companies developed an explicit campaign to promote shyness as an important and treatable disorder, successfully shaping medical and public opinion about social phobia (Moynihan *et al.*, 2002). A senior pharmaceutical industry executive involved in the promotion of social phobia in Australia acknowledged that marketing efforts exaggerated the prevalence of social phobia. He also recognized the inherent conflict of interest when a drug company sponsors publicity about a disease for which it markets a treatment, as his company did with social phobia (Moynihan, 2002). Efforts like these have led some commentators to suggest that the industry's products include diseases as well as drugs (Wolinsky, 2005).

Pharmaceutical connections are prevalent among authors of the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders (DSM), whose structure and content define psychiatric illnesses. A study of panel members of the latest edition revealed that 56% of the panel members had one or more financial associations with pharmaceutical companies (Cosgrove *et al.*, 2006). Of the panelists, 42% received research funding from industry, 13% served as members of the board of a pharmaceutical company, and 2% had known equity interest in a pharmaceutical company. Two DSM working groups – mood disorders and psychotic disorders – were composed entirely of members with financial ties to the pharmaceutical industry. There is no disclosure in the latest editions of the DSM (DSM-IV and DSM-IVTR) of these conflicts of interest (Cosgrove *et al.*, 2006).

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Influence on prescribing: encouragement of off-label prescribing

Another way to increase sales of a drug is to expand the range of diseases for which it is prescribed. In the U.S.A., the Food and Drug Administration (FDA) regulates the approval of prescription drugs and their labeling as "indicated" for certain diseases. Companies are prohibited from marketing a drug to consumers or physicians for "off-label" use – for indications not specifically approved by the FDA. Doctors, however, may prescribe drugs for "off-label" indications. For the top 160 most prescribed drugs in the U.S.A. in 2001, 21% of all prescriptions were for off-label uses, an estimated 150 million prescriptions (Radley *et al.*, 2006). Little to no scientific evidence was found to support 73% of these off-label uses. Gabapentin and risperidone topped the list of medications prescribed with scanty scientific support (Radley *et al.*, 2006). Aggressive and creative marketing by the pharmaceutical industry drives much of this "off-label" prescribing. Conducting small, positive, industry-sponsored trials (SPIT) for off-label uses and then aggressively disseminating the results is a well-described sales tactic. In 2004, the vendors of gabapentin received the largest fine in FDA history ($430 million) for their illegal and fraudulent promotion of off-label uses for the drug (FDA Office of Public Affairs, 2004). Promotional activities included systematically influencing educational activities, suppressing publication of negative research studies, sponsoring "research" which was really marketing rather than scientific investigation, and creation of "peer-to-peer selling" by physician speakers (Steinman *et al.*, 2006).

Internal marketing documents, released into the public record due to a lawsuit, revealed that sales representatives were told to suggest to physicians that olanzapine be used for treating behavioral symptoms of dementia (Berenson, 2006). Olanzapine is only approved for bipolar disorder and schizophrenia in the U.S.A. This marketing campaign contributed to the doubling of annual sales of olanzapine from $1.5 billion to $3 billion over three years (Berenson, 2006). A non-industry funded, double-blind, placebo-controlled, head-to-head trial of the three top selling atypical antipsychotic drugs widely used off-label for the treatment of agitation, aggression or psychosis in Alzheimer's dementia patients concluded that there was no significant difference from placebo in the primary study endpoints, and a greater incidence of adverse effects (sedation, confusion, extra-pyramidal signs, and weight gain) (Schneider *et al.*, 2006). These drugs also carry an FDA-mandated black-box warning because of an increased risk of death in dementia patients who receive them.

Influence on prescribing: trade shows and violations of ethical codes

Pharmaceutical industry presence at trade shows and meetings is so extensive as to be problematic. An analysis of the exhibition hall at the 2002 American Psychiatric Association (APA) Annual Meeting revealed that 79% of the space was occupied by pharmaceutical companies (89,800 square feet) and 54% of all companies with booths were in violation of APA or FDA rules about marketing to physicians (Lurie *et al.*, 2005). In one egregious instance, a single drug company

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flew more than 30 psychiatrists from Mexico to this same meeting, all expenses paid (Barry, 2002). This is a clear violation of the Pharmaceutical Research and Manufacturers of America (PhRMA) Code of Interactions with Health Care Professionals (PhRMA, 2006) and the American Medical Association (AMA) Code of Ethics (American Medical Association, 2006) – codes which were established to prevent activities that are obviously promotional. However, these codes lack enforcement and have many loopholes. For example, the PhRMA code would in fact allow a company to fly 300 physicians to a resort destination and pay all expenses if the purpose of the meeting was "to train them to become members of the company's stable of paid speakers" (Moynihan, 2003). The vice-president of PhRMA described this code as being for the benefit of patients, and the above activity as necessary "to support its communications effort." Relying on industry, academic institutions, or professional codes seems clearly inadequate as a mechanism to limit or rationalize industry promotional activity (Moynihan, 2003).

Influence on prescribing: direct to consumer advertising

Direct-to-consumer advertising (DTCA) is an explicitly promotional technique on which $4.2 billion was spent in the U.S.A. in 2005 (IMS Health, 2006). The effectiveness of DTCA is suggested by a comparative study of patients in the U.S.A. with those in Canada (where direct-to-consumer marketing of prescription drugs is illegal). U.S. patients were more likely to request drugs that were advertised on TV in the U.S.A. and more likely to leave the doctor's office with a new prescription. About half the time, however, prescribing physicians felt that these new prescriptions were "unlikely" or only "possible" choices for patients with similar complaints, suggesting that pressure from patients affected physicians' prescribing independent of best care for patients (Mintzes *et al.*, 2003).

DTCA has also been shown to increase drug treatment of conditions that would not usually be treated with medications, and to increase market share for particular drugs. In a randomized trial, community physicians were visited by three groups of standardized patients (actors) who portrayed adjustment disorder (not typically treated with medication). One group said that they saw the drug paroxetine advertised on television and asked for it by name, the second group asked for medication to treat their symptoms, and the third group made no request for medication to treat their adjustment disorder. Of those asking for paroxetine, 55% received the medication versus only 10% who made no request for a medication. In addition, the frequency of paroxetine prescriptions was 3.6 times greater in the group asking for paroxetine by name versus the group that made general requests for an antidepressant (Kravitz *et al.*, 2005).

Influence on prescribing: a summary

Any idea that physicians are upright and invulnerable to the billions of promotional dollars spent to influence their behavior is lamentably naïve. A study of psychiatrists in training in Canada revealed that the more money and

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promotional items a physician-in-training had received, the more likely he or she was to believe that discussions with representatives did not affect prescribing ($p < 0.05$) (Hodges, 1995). Discussing a promotional campaign for the irritable bowel drug tegaserod, a company official said, "The weeks we go off the air, the growth flattens ... When we restart, you see growth accelerate again." The campaign featured attractive women lifting their shirts to reveal writing on their bellies. The drug has now been withdrawn because of concerns of serious cardiovascular toxicity (Harris, 2007). If these billions spent did not increase sales, then they would violate the companies' fiduciary duty to stockholders.

Influence on research and publication: financial support and conflict of interest

An essential tenet of evidence-based medicine is that treatment decisions should be based on the results of relevant clinical trials. Thus, affecting the outcomes of the primary research literature would affect prescribing decisions, and would affect drug sales. Clear evidence shows that clinical trials receiving pharmaceutical support tend to produce results that promote sales for the vendor and sponsor. A systematic review of clinical trials published in four leading psychiatry journals from 2001 to 2003 (Perlis *et al.*, 2005) found that 70% of the 162 randomized controlled trials were drug-company funded, and 46% had one or more authors who received drug company support. If a study had one or more authors receiving drug company support, it was five times as likely to report positive results as were studies without industry sponsorship. A review of studies comparing one cholinesterase inhibitor with another for Alzheimer's disease concluded that "All studies were funded by pharmaceutical companies, coauthored by their employees, and reported results that favored the sponsor's product" (Hogan *et al.*, 2004). The primary research literature on selective serotonin reuptake inhibitors (SSRIs) is also heavily supported by industry; between 1980 and 2005, 96% of comparative trials received support from a drug company (Hansen *et al.*, 2005). The editor-in-chief of the *New England Journal of Medicine* had a difficult time finding a research psychiatrist to write an editorial about chronic depression who did not have ties to the pharmaceutical industry (Angell, 2000).

Influence on research: touting of statistically significant but clinically meaningless results

Industry-sponsored rhetoric in peer-reviewed papers often differs from the conclusions of independent authors. A flawed industry-supported *post hoc* analysis on the cholinesterase inhibitor donepezil claims that use of the drug "results in" delayed nursing home placement in patients with Alzheimer's disease and concludes with the statement "doctors and caregivers need to be educated that, in the same way as the actual benefits of treating hypertension or hyperlipidemia are seen only after years of treatment, treatment of Alzheimer's disease with donepezil needs to be maintained to see important long-term

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benefits" (Geldmacher *et al.*, 2003). Studies of donepezil show consistent, statistically significant improvement in cognitive function on psychometric tests (about 1.3–1.8 points out of 30 on the MMSE and 2.5–2.9 points out of 70 on the ADAS-Cog). These improvements on testing have not been shown to be of everyday importance to the patient, the caregiver, or society. Improved quality of life scores, impact on behavioral symptoms, decrease in time spent by caregivers in assistance with activities of daily living, or decreased health care utilization, institutionalization, or costs have not been demonstrated (Birks and Harvey, 2006). An independent, systematic review concluded: "Because of flawed methods and small clinical benefits, the scientific basis for recommendations of cholinesterase inhibitors for the treatment of Alzheimer's disease is questionable" (Kaduszkiewicz *et al.*, 2005).

Influence on research: "me-too" drugs

From 1990 to 2004, 1284 new drug applications were approved by the U.S. FDA. Of these drugs, 995 (77%) were classified as "appears to have therapeutic qualities similar to those of one or more already marketed drugs" and only 183 (14%) of the approved drugs were new compounds that were considered to be a "significant improvement compared to marketed products in the treatment, diagnosis, or prevention of disease" (FDA, 2006). Thus, the main "new drugs" brought to market are actually "me-too" drugs (Angell, 2004). These drugs, which differ slightly from already marketed drugs, are generally developed to enable a company to get or maintain market share in an established niche. A variety of SSRIs are available, for example, but none has been convincingly shown to be better or less toxic than any other.

When a drug's patent is set to expire, a company may develop, patent and market a minor variation that is fully proprietary. For example, when the patent for the highly successful SSRI citalopram was set to expire in 2003, its manufacturer released escitalopram (approved late 2002), the active S-enantiomer of citalopram with the same mechanism of action. Escitalopram has not conclusively been shown to be more effective, more rapid-acting or less likely to cause adverse effects than citalopram or any other SSRI (Anonymous Medical Letter, 2002). Escitalopram is now the second most prescribed antidepressant in the U.S.A. with 29.6 million prescriptions written in 2005 (IMS Health, 2006) and U.S. sales are expected to exceed $2 billion in 2007 (Forest Laboratories Inc., 2006).

Influence on publication: negative trials that disappear

Data submitted to the Swedish drug regulatory authority was compared with the published literature on SSRIs (Melander *et al.*, 2003). The investigators were able to identify several negative industry-sponsored trials that had never been published, or had appeared only within publications reporting pooled data. Positive data, in contrast, were often published more than once, both as stand-alone publications and in publications reporting pooled data. Of the 42 studies submitted to the agency, 21 showed the SSRI to be better than placebo and 19

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were published in 22 stand-alone publications. Of the 21 studies that showed non-significant differences, only six were published in stand-alone publications (Melander *et al.*, 2003).

In at least one case, the suppression of negative studies on SSRIs has proved to be deliberate. An internal document released by GlaxoSmithKline written in 1998 discussed how to manage the results of two negative clinical trials of paroxetine in the pediatric population. The document stated that the clinical trials results were "insufficiently robust" to support an application for a regulatory approval for use in pediatric depression and recommended that the company "effectively manage the dissemination of these data in order to minimize any potential negative commercial impact." It went on to state, "It would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine" (Kondro and Sibbald, 2004). Two of the three studies of paroxetine in children were suppressed and have never appeared in the literature (Whittington *et al.*, 2004). The International Committee of Medical Journal Editors now requires registration of all clinical trials, at least in part to make it more difficult to conceal negative trials (De Angelis *et al.*, 2004).

Influence on publication: ghostwriting and involvement of PR firms

The use of "ghostwriting" and PR/marketing firms has become commonplace in the pharmaceutical industry. These firms are euphemistically called medical information or medical education companies. Such arrangements help to conceal conflicts of interest and the paper trail from the drug company to the article. Academic physicians have been known to receive near complete articles needing only their stamp of approval and name added (Fugh-Berman, 2005). An academic physician who refuses knows the company will find another who will be willing (Fugh-Berman, 2005). During the course of a lawsuit, 85 internal documents regarding sertraline were discovered that had been prepared for Pfizer by a medical information company. Article drafts were prepared, with authorship often listed as "to be determined," while an author with good academic credentials was identified and added prior to submission to a high-impact journal. Articles coordinated by the medical information company were published in "bigger name" journals (with higher impact profiles) and were likely to be cited more often than articles not prepared by the company (Healy and Cattell, 2003). Internal memos outline how SmithKline Beecham used a public relations firm to ghostwrite letters to the editor to counterattack claims by a rival drug maker about the side effects of paroxetine discontinuation (McHenry, 2005). The willingness of academics to participate in this strategy is a sad chapter indeed in the history of science.

Conclusion

The pharmaceutical companies' fiduciary duty to make profits for their stockholders – a 15.7% margin in 2005 (Trombetta, 2006) – conflicts directly with physicians' fiduciary duty to do what is best for patients. The drive to sell

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drugs has blurred the distinctions among research, publications and promotional activities. The profit motive permeates the way that diseases are identified, drugs are studied, studies are written, decisions are made about publication, and information from the sponsored trials is disseminated. Illegal promotion of unproven off-label uses of drugs, often using corrupt literature, suppression of negative research results, and ghostwriting in the literature are all examples of how research and marketing have become joined. The triumph of drug company marketing activities can be seen in the multibillion dollar sales of drugs that are ineffective, marginally effective, unexpectedly toxic, more expensive than equivalent alternatives, completely unnecessary, or some combination of these. In all of these cases, the profit motive has clearly divorced itself from any relationship to the ideals of best patient care. The pharmaceutical industry has used its considerable influence to embrace a different agenda from assisting physicians and patients to find the best possible care for these tragic diseases. Patients are undertreated, overtreated, impoverished, and harmed as a result. That influence is excessive.

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Is the influence of the pharmaceutical industry on prescribing, research and publication in the field of psychogeriatrics excessive? – No.

Concerns increasingly have been raised about the influence of pharmaceutical companies on doctors and their practice of medicine. The pharmaceutical industry has grown in profitability and influence over the past twenty years and is now second only to armaments in the U.S. economy (Public Citizen, 2002). Guidance is available from most Royal Colleges on the appropriateness of using finances/gifts and other benefits from pharmaceutical companies. A declaration of conflict of interest is required for most journals, and evidence shows that there are signs of a small but increasing proportion of articles declaring competing interests in some journals (Hussein and Smith, 2001). Concerns are probably greater in psychiatry, as psychiatric research is particularly susceptible to the influence of vested interests because of the subjective nature of diagnosis and

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