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Pharmaceutical industry and the market: The case of Prozac and other antidepressants

Anindya Das *

Centre for Social Medicine and Community Health, Jawaharlal Nehru University, New Delhi, PIN 110067, India

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ABSTRACT

Objective: This article attempts to critically evaluate the role of the pharmaceutical industry in health care from the theoretical standpoint of 'medical–industrial complex'.
Methods: The historical context of the expansion of the pharmaceutical industry is summarized followed by a critical evaluation of the methods of studying effectiveness of pharmaceutical agents and the aspects involved in reporting, publication and marketing. Further issues are elaborated with a case study of the antidepressants.
Results: The establishment of pharmaceutical industry is premised on various ethical principles and moral norms yet such guiding values are forsaken resulting in a contradictory stance where human life and suffering are devalued rather than saved and ameliorated in a bid to maximize profits.
Conclusion: The conventional response of more stringent regulation and the broader reason of economic model of unequal power need to be reevaluated.

1. Pharmaceutical industry: its role in health care

Health care or more specifically clinical medicine is said to have 'advanced' many fold in modern times. It is said that not only the etiology and pathogenesis of various disorders are more exemplified; it is also that more and more groups of pharmaceutical agents are being researched, developed, tried, manufactured and marketed for use on the patient. This has brought about increasingly the biological and scientific aspect of the practice of clinical medicine into the arena. In this process of 'advancement' pharmaceutical companies have become an inevitable part of health care. Health care on the other hand is defined by professionals who diagnose disorder in 'patients' and 'prescribe' these medicines. Pharmaceuticals are defined by scientist and businesspeople forming the part of production and marketing of pharmaceutical products. These constitute to what has been referred to as 'biomedicalization', where both the organization and practices of contemporary biomedicine is implemented largely through the integration of techno-scientific innovations (Clarke et al., 2003). Thus critical theorists have evaluated the growth of the new medico-scientific, technological, pharmaceutical interventions as feeding into the 'medical industrial complex' (Ehrenreich and Ehrenreich, 1971) promoting the capitalist interests of the corporations that constitute this complex.

The antidepressant market led by the pharmaceutical industry is analysed situating it in this context.

2. Evolution of the pharmaceutical industry

Throughout much of history, it was traditional knowledge that guided the preparation and the use of remedies derived from plants and other sources, both in Europe and in other parts of the world. Common people could gather their materials and make their remedies at home, although "healers", physicians and members of religious orders often had a particular (and sometimes secret) knowledge of plants and treatments.

With the advent of industrialization and urbanization common traditional knowledge started to decay and the apothecaries became increasingly recognizable as a profession specializing in the making and dispensing of drugs according to established recognized standards. In 1617 in England the Worshipful Society of Apothecaries of London was established which in due course by the eighteenth century acquired a monopoly in supplying medicines to the Army, the Navy, the Crown Colonies and the East India Company (Dukes, 2006: pp. 5–6). Progressively detailed documentation and publication of discoveries of smallpox vaccine, digitalis, morphine, quinine etc. which no doubt were found to be effective, allowed large scale extraction, standardization and production of these agents. With industrialization firmly setting its foot and the discovery of synthetic compounds with medicinal qualities in the nineteenth century, there were rapid emergence and growth of research-based pharmaceutical industry in the late

* Tel.: +9335695823.
E-mail address: andydas@rediffmail.com.

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nineteenth and twentieth centuries. Very like all other industries, the technological-spin off in the early and mid twentieth century, ensuing economic boom and accent of consumer economy attracted investment and expansion in the pharmaceutical industry. This high point was accomplished along with the professionalization and specialization of medicine, establishment of elaboration of new social forms of medical practice (e.g., hospitals, clinics and private practices) and major investments, (both private and public) in the production of medical knowledge and clinical interventions (Clarke et al., 2003). Thus pharmaceutical industry has become, and remains even during periods of recession and in spite of the controls imposed upon it, one of the most profitable sectors of commerce. With an average profit as per the year 2000 of 16.2%, it is lies ahead of financial companies (11.6%) and beverages (10%) (Henry and Lexchin, 2002). Thus as in other industrial sector the profit making motives in a market driven economy carves out the various consequence we see in the present times.

3. Pharmaceutical industries and the market

With time the pharmaceutical industries have evolved over their role as manufacturer of medicines to innovator, provider of information, employer and a significant player in the world economy. The innovations in drug discovery that take place is the responsibility of the R&D division of the companies, but most often are found to take place in tax-funded academic and institutional centers. In the process companies acquire the rights to develop it further (through toxicological and clinical studies) for final marketing. Protected by patent rights (for both the product and the process) they have the authority and the monopoly to fix the prices and the geographic extent of the market. These activities are bound by drug laws and regulations, which deal primarily with the quality, safety and efficacy of products. But with the era of globalization and the spreading web of capitalism as in other corporations, increasingly pharmaceutical companies are going in for mergers across the globe. This allows greater monopoly/oligopoly of the market, cutting cost and multiplication of profits (Henry and Lexchin, 2002). As a result the balance of power concerning trade laws and regulation have shifted policies and decisions in their favorable direction. The most prominent example in this aspect is the formulation of the Trade Related Intellectual Property Rights (TRIPS) which has transferred the process and the product patents to large (transnational) pharmaceuticals allowing an ascendance in monopoly. Counterarguments favoring TRIPS on the other hand point at the logic of giving impetus to innovation.

4. Drug trials, their publication and reporting

Whenever a new molecule is discovered it needs to be evaluated in phases for toxicological analysis (done with animal experiments) after which human experiments ensues. Proof of efficacy currently is judged through the 'gold standard' measure i.e. Randomized Controlled Trials (RCT) (or more precisely randomized double-blind placebo controlled trials with or without cross over design). But the complete reliance on RCTs with the idea that positive results mean the particular treatment is effective has been called into question. This is because the trials set out to (dis)prove null hypotheses which imply that if the effect of placebo differ from that of an active agent it is not that it is undoubtedly effective and that further research is implied. In addition, before studies to verify the long term (adverse) effects of new agents (to treat chronic and recurrent forms of psychiatric disorder) are concluded, they are launched in the market for human use (e.g. newer antipsychotics).

Moreover it has been pointed out that completely controlled nature of such experiments do not exist in real life situations and trials conducted in small subsets of volunteers do not prove a homogeneous effect on other subsets of population and that naturalistic studies with samples of diverse characteristics are necessary to supplement evidence for their effectiveness.

Moreover the blindedness status has been questioned due to spontaneous unblinding of patient's status to an experienced clinician from obvious observable side effects (especially in the case of antidepressant trials) (Leyburn, 1967).

To add to this, approval of a new product which is already an addition to an existing alternative is a contested point. It is rightly considered by some that acceptability of a new drug should only depend on if its effectiveness is equivalent or superior to an existing product of the same type, or that it has some other unique virtue (for example, in terms of safety). While on the other hand firms argue that any product that is more effective than placebo must be considered acceptable under the law. In the process, both extremes have been largely abandoned; as a rule a drug is now considered "effective" in terms of the law if it is clinically and genuinely useful – to an extent that the reasonable man will appreciate. This in the consideration of the author is rather ambiguous and its interpretation can be subjective. Hence in the antidepressant market we can see a large number of "me too" drugs categorized under the name Selective Serotonergic Reuptake Inhibitors (SSRIs).

Besides these drawbacks of the drug trials, the phenomenon of reporting biases of these trials has been an issue of concern. Drug trials funded by pharmaceutical industries have been repeatedly shown to systematically generate favorable results (Lexchin et al., 2003; Bekelman et al., 2003). Sismondo (2008) discusses in detail on this issue and the various patterns and causes of this association. The extent of concern on this matter is reflected by the recent moves to ensure that all clinical trials are registered at the outset (DeAngelis et al., 2005), so that they cannot subsequently disappear from the record. Publication biases which tend to favor drug trials with positive outcome are also a major source of misinformation for the clinician (Carter et al., 2006).

Another important issue is that of ghostwritten and ghost managed articles. These are the literature on clinical trials and other articles related to pharmacotherapeutics which are managed (in terms of trial design, analysis, writing and publication) by Contract Research Organizations (CRO) bearing the name of academic authors (projecting independence and credibility), thus shaping research and medical literature with the intent of fulfilling the marketing objectives of their clients (i.e. pharmaceutical companies) (Sismondo, 2007). An analysis by Healy and Cattell (2003) on a single drug, Sertraline, based on 85 manuscripts coordinated by a CRO to which the first author had access to (due to a lawsuit that the first author was involved with) shows that these manuscripts became an important part of up to 40% of articles during the interval of 1998–2000, a key period for the marketing of this drug. These were published in journals of higher impact factors, had higher Medline listing per author of these articles, and reported higher degree of favorable results compare to articles not written by medical writing agency.

In the post-marketing phase following the formal launch of a drug, an adverse effect reporting mechanism allows the recording of the long term consequences of the use of such agents. Because a large and variable group of people are administered the drug it can be an effective way to evaluate untoward incidents. Pharmaceutical firms have been found to delay reporting of such episodes (Lexchin, 2005).

5. Newer antidepressant, pharmaceutical industries and the market

Prior to 1988 when the Prozac (Fluoxetine) was formally launched conventionally, severe forms of depression was treated

with electro convulsive therapy, monoamine oxidase inhibitors or tricyclic antidepressants. Initially these pharmaceutical agents were not popular with drug companies due to the small market in the 1960s and even lesser was known about the epidemiological pattern of the disorder that these therapies treated. At that time nervous disorder largely constituted by symptoms of anxiety (including milder forms of depression) was treated with the benzodiazepine group of tranquilizer drugs. Due to concern in the lay public as a result of its dependence potential, it went into disrepute along with the launch of Buspirone in the late 1980s marketed as non-dependence producing tranquilizer. This was the first drug with predominantly serotonergic action. Though buspirone's success in the market was limited, it had been shown to be efficacious in both anxiety and depression. Following in its heels was Fluoxetine with similar serotonergic effects. Now this drug's initial success in the market was not as an antianxiety drug but as an antidepressant. Is this success more to do with the marketing strategy of placing it as an antidepressant (rather than its potential to bring about significant benefit)? If not then why did buspirone not do well in the market with similar treatment effect sizes to that of other SSRIs (for both depression and anxiety)?

With the launch of Prozac it rapidly gained popularity in America. In fact by 1994 Eli Lilly & Co. boasted of worldwide sales of Prozac nearing $1.2 billion a year (Newsweek, 1994). Similarly the New Republic reported that in its first five years, Prozac provoked a 50% increase in antidepressant use (Rothman, 1994). In fact in the United Kingdom and United States the sale of tranquilizers by mid 1990s dropped and was overtaken by the sale of antidepressants (Rose, 2003). In current times globally, of the pharmaceutical therapeutic classes on sale, antidepressants now rank fourth among the leading groups (Petryna and Kleinman, 2006).

The marketing success was retorted back by scholars and authors with narration of personal experiences in the bestsellers *Prozac Nation: Young and Depressed in America and Talking back to Prozac* where the authors allege the drug industry, the professionals and ultimately capitalism are to blame for tranquilizing America for their profits.

Amidst these controversies the large popularity of Prozac is exemplified by the example of the lay media projecting it as a pill against everyday hang-ups of life. This popularity was followed by the market being flooded with a whole range of similar drugs now commonly referred to as SSRIs. All of them have been shown to be equiefficacious (but differing only on their side effect profile). Yet all had traversed a successful market life superadded with their approval to treat a flurry of anxiety disorders. Now they are not named tranquilizers but anxiolytics, allowing to avoid the disadvantages associated with the former terminology. But, is it at all true that these drugs are far superior to the benzodiazepines in terms of dependence (habit forming) potential and that they themselves do not have there own additional disadvantages?

6. Marketing strategies for expanding drug sale

To make an impact on the market and to allow growth of sales, pharmaceutical companies employ a number of strategies of which some even are questionable on ethical grounds. Of the many that have been the issue of concern in recent times is that of the case of disease mongering. Though questions on the validity of the diagnosis of depression is not much debated in bio-medical literature (which in anthropological context may reflect differing cultural conventions and attribution of meaning), a lowering of the threshold for prescription for symptomatic treatment can surely amount to disease mongering. A lowering of this threshold can mean that a group of people undergoing certain forms of normal experiences are prescribed antidepressants which have the potential to interfere with natural coping mechanisms and culturally appropriate ways of dealing with them. Of the many ways in which such goals are attained are direct-to-consumer advertising wherever legal, or unbranded disease-oriented advertising with messages that distort either the seriousness of the disorder or its origin (often stating it to be primarily biological rather than psychosocial) or its probable treatment (as mainly pharmacological). A study by Read (2008) analyzing the quality of web based information of schizophrenia did find these differences especially in the case of websites that were schizophrenia funded, compared to those not funded by drug companies. What changes do these techniques bring about in the consciousness of the people remains to be investigated?

The probability that a patient buys an agent depends on whether he/she has been prescribed a certain agent in favor over another. Thus the representative of the pharmaceutical industry befriends, cajoles and provides 'free lunch' (Hill, 2006) and 'small' gifts (Katz et al., 2003) to a doctor influencing in various ways (obvious and subtle) to bias his/her preferences (McFadden et al., 2007). Further influences are created by companies through sponsored trips, conducting of symposia and conferences at exotic locales with prominent personalities in the field delivering lectures thus creating a form of brand loyalty. Fugh-Berman and Ahari (2007) describes in detail how pharmaceutical industries and their representatives employ various strategies to achieves these ends. This is not to say that a rational practitioner does not have the free will to decide based on scientific evidence, but that he also is presented with selected data to incline his/her view. In fact it has been alleged that earnings of pharmaceutical industries are being disproportionately used for advertising and promotion compared to investment on research (Collier and Iheanacho, 2002).

7. Controversies of newer antidepressants and pharmaceutical companies

The popularity of Prozac and similar antidepressants continued amidst controversies that have surfaced from time to time. As a result Eli Lilly, the manufactures of Prozac, have retorted back "extensive scientific and medical experience has demonstrated it is an effective antidepressant" and that "...more than 50 million people with depression have been treated with Prozac since its launch" (New Scientist, 2008). While current evaluation has a different story to tell.

A recent publication states that only 8% of antidepressant trials with negative findings were reported as negative, while positive trials were reported as such 97% of the time (Turner et al., 2008). Similar findings have been noted by other researchers as well with the association especially being stronger when the trials are funded by pharmaceutical industries (Melander et al., 2003). When a meta-analysis of published and unpublished data from studies of six most widely prescribed of the new generation antidepressants registered under the FDA were evaluated, it was noted that antidepressants fail to show benefits over placebo and fell below the accepted criteria for clinical significance. This has been found to be true for both groups of moderately and severely depressed patients, excepting for a very small group of patients at the upper end of the severely depressed category (which is more to do with the decrease in response to placebo rather than a increase in response to the medications) (Kirsch et al., 2008). To add to this, the FDA failed to release data to these researchers on nine more trials which happened to yield negative results (Lenzer, 2008). The reliability of these findings must be judged keeping into view the high rate of placebo response in antidepressant trials.

A more persistent form of debate that has lingered on since the launch of the first SSRI i.e. Prozac, is the suicidality argument in child and adolescent depressed patients. Since 1990 evidence has

Table 1
1999 pharmaceutical company data for the 10 largest U.S. pharmaceutical companies.

	Revenue (billions)	Cost of goods (% of revenue)	Market + admin. (% of revenue)	R&D (% of revenue)	Profits (% of revenue)
Average	17,557	28	32	13	16
Maximum	32,714	54	46	20	27
Minimum	10,003	18	16	6	−9

All data from Securities and Exchange Commission in the USA filings and 1999 company annual reports adapted from Laing (2001).

started appearing for the increased propensity of suicidal ideation and behavior in young patients (King et al., 1991). Later it was only in mid 2003 that the FDA performed an analysis of data from individual pharmaceutical companies for various antidepressant drug trials in pediatric patients, and found a consistent relationship. This along with FDAs joint discussion with various Advisory Committees culminated in just a 'black box' warning accepting this risk relationship, even though it was enough to point toward contraindication (Hammad et al., 2006). Inaction on the part of regulatory authorities still persists, as further evidence continues accumulating with a recent meta-analysis by Hammad et al. (2006). Using FDA data the study shows roughly doubling of suicidality in pediatric and adolescent patients with the use of SSRIs. To add to this a controversy that is yet not clear is the suicide potential in adults with the SSRI Paroxetine. Initial evaluation in 2005 was inconclusive due to lack of complete data (Gunnell et al., 2005). A later analysis on published and unpublished data from Norway show a clear relationship (Aursnes et al., 2005) with the strengthening of this relationship with additional studies included in later analysis (Aursnes et al., 2006). A similar analysis by Healy (2006) using data drawn from FDA license application found the odds ratio of a suicidal act on a new antidepressant compared to placebo to be 2.4 (95% CI 1.6–3.7) and that of completed suicide to be 4.62 (95% CI 1.126–18.953), ($p = 0.031$).

Another persistent debate is related to the dependence producing potential of SSRIs. A London-based consumer watchdog organization, Social Audit has been documenting withdrawal reactions to SSRIs (Bonn, 1998) and has been lobbying for its removal from the market while pharmaceutical companies and other scientists have persistently denied their claims (Medawar, 1997).

Thus certain observations that can be summarized from the above discussion are that pharmaceutical industry in a profit propelled world aims for products that have the largest market. Creating of markets by generating an apparent need is best exemplified in the case of antidepressants as more and more of the population have been prescribed Prozac (SSRIs) (Baker, 2002).

Depression in the 1990s had become a fashionable diagnosis, especially in places which had Prozac and other SSRIs in the market as a 'logical' treatment for this complaint. Whereas Japan [having a similar high-volume pharmaceutical market and being a descendent of the German neuropsychiatry tradition, thus of biological bent as in the West (Kitanaka, 2000)] had none of the SSRIs available till 1999, and retained its prior pattern of tranquilizer sales compared to the antidepressants (a comparable pattern of the pre-Prozac era in the West) (Healy, 2006). This to an extent proves the market driven consumption of pharmaceutical agents and its potential to modify cultural patterns of life experiences rather than a change in recognition or epidemiological pattern of the disorder which the agent is used for.

In recent times newer drugs of the same group have flooded the market without any obvious advantage over the prior available agent. The reasons for high prices have been legitimized based on high innovation cost by the pharmaceutical companies. WHO has calculated that most patented medicines are sold at 20–100 times their "marginal" costs (Dukes, 2006: p. 221). It has also been shown that promotion expenditure which is socially wasteful above a certain minimum adds to the cost of the drugs enhancing the market power of the firms and certainly not to good therapy (Lall, 1979). In fact, in the last few decades a large proportion of expenditure is devoted to drug promotion while research expenditure of the companies is far less in comparison (see Table 1). In addition because R&D expenses can qualify for tax deductions, there is a strong tendency of companies to classify various expenses as "R&D" which does not entirely merit the name (Dukes, 2006: p. 241).

To avoid incurring losses and keep the market going an organized effort of misrepresentation and concealment of data, partied intentionally or unintentionally by regulatory authorities and professionals has now crossed the border of ethical malfeasance.

8. Concluding remarks

Under the current tide of biomedicalization, increasingly more and more aspects of human life are being engulfed under medical jurisdiction and leading to the commodification of health that is illustrated by the growth of the pharmaceutical industry. Even though the pharmaceutical industry owes a moral duty toward the public and the community, a morality that values human beings and their lives, it is being pushed to the backyard as a consequence of placing primacy on profits.

Many would interpret the foregoing commentary as extremely ideological and politically charged. Often this is conflated with an unscientific approach. The author is rather of the view that the interpretation of the ability of science to prosper in a particular economic environment that evaluates value in terms of financial gain in the innovation and by the innovation itself is a biased standpoint. Therefore 'scientific' logic of treating mental disorders amounts to reducing economic burden of diseases. And the business rational for patent rights is to allow economic profits as reinforcement for innovation.

Consequently the conventional responses to these forms of misconduct are more rigorous regulation, legislation and penalty, transparency, formalized accountability, professionals' and public awareness. Yet very few question the abuse of power emanating from accumulating capital that is misused to generate further capital. Any action, legal or regulative, is sure to be constrained by this capitalistic economic relation. It may be so that the answer lies in reevaluating and redoing this economic model of unequal power. Thus a solution lies in a model that values all human lives more than anything else, especially apital.

Contributors

The author has been the soul person responsible in conceptualizing, doing the literature review and preparing the manuscript. The author has no conflict of interest with reference to the contents of this article.

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