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The growth of psychopharmacology in the 1990s: Evidence-based practice or irrational exuberance

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Abstract

The rapid growth in sales of psychotropic medications during the late 1980s and 1990s, eventually reaching $20 billion/year, reflected the increased use of seritonin reuptake inhibitors for depression and atypical antipsychotics for schizophrenia. Recently, however, some of the therapeutic claims for these medications have been challenged, and under-appreciated risks have turned out to be significant liabilities. Drug manufacturers increasingly dominate clinical trials research and evidence suggests that study designs and data presentations have been slanted to show products in a favorable light while unfavorable data were suppressed. At the same time, during the 1990s, potentially independent voices did not effectively or consistently present countervailing views. The extensive financial ties between the pharmaceutical industry and academic researchers, professional associations, and consumer groups may also have discouraged expression of critical views. Additionally, the narrow legal mandate of the FDA to evaluate the safety and efficacy of new drugs only in comparison to placebo (rather than in comparison to other treatments) probably limited its contribution. In the absence of reliable, impartial research on the risk and benefits of psychotropic medications, both before and after they are brought to market, pharmacy benefits management cannot achieve its goal of maximizing health care benefits per dollar spent. Further institutional support is needed for independent research, either conducted or funded by the federal government. Published by Elsevier Inc.

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1. New and more costly pharmacotherapy for mental illness

The dramatic growth in sales of psychotropic medications during the late 1980s and 1990s reflected the meteoric rise of two separate drug classes: the seritonin reuptake inhibitors (SRIs) developed for depression, and the atypical antipsychotics for psychotic disorders such as schizophrenia. The first SRI approved for marketing, Prozac® was released in 1987 and the first atypical antipsychotic, Clozaril®, in 1989. By the end of 2001 domestic sales of newer antidepressants topped $12 billion while sales of atypical antipsychotics totaled $4.1 billion (National Institute of Health Care Research and Education Foundation, 2002), reaching $8.5 billion in 2004. Together these medications account for over 10% of all US prescription drug costs.

In 2004, the cost of the most widely used of the older antipsychotics, haloperidol, was about $0.50/day, while the average daily cost of treatment with Zyprexa®, the best selling of the newer drugs, was $11.39/day, over 20 times greater. Differences in the costs of older and newer antidepressants were less dramatic but still substantial. While the older generic tricyclic antidepressants like imipramine cost about $0.50/day, the daily cost of brand-name Prozac® was $2.91/day, over five times more. Two explanations were offered for these high prices. First, the cost of drug development has increased, with one estimate reaching $800 million for the development of each new chemical agent (DeMasi, Hansen, & Grabowski, 2003) although other estimates were as low as $100 million (Goozner, 2003). Secondly, the new agents were said to offer clinical advantages or cost offsets that justified the increased medication costs (Glazer & Johnstone, 1997; Simon et al., 1996).

The expanded use of these new medications reflected both replacement of older agents by newer drugs and expansion to populations that previously would not have taken psychotropic medication at all. Market expansion was especially dramatic in the case of the antidepressants where the advent of managed care and restrictions on reimbursement for psychotherapy may have resulted in substitution of pharmacotherapy for behavioral treatments (Harman, Crystal, Walkup, & Olfson, 2003; Olfson et al., 1998, 2002; Pincus et al., 1998). Although no convincing evidence was ever presented that the SRIs were more efficacious than traditional anti-depressants, they had fewer anticholinergic side effects such as dry mouth, dizziness, or memory impairment, and posed a lower risk of lethality in the event of suicide attempt. Although these drugs sometimes produce sexual dysfunction, their overall safety and tolerability led to their use by a wider spectrum of patients, especially those with less severe disorders and even those with disorders for which the efficacy of these drugs had not been demonstrated (Olfson et al., 2002).

Research on the atypical antipsychotics initially suggested that they had both fewer side effects and greater effectiveness than their predecessors in the treatment of schizophrenia and bi-polar disorder (Brown, Markowitz, Moore, & Parker, 1999; Markowitz, Brown, & Moore, 1999). In addition, some cost studies suggested that reductions in hospital days could offset the high cost of these drugs (Essock, Frisman, Covell, & Hargreaves, 2000; Hamilton, Revicki, Edgell, Genduso, & Tollefson, 1999; Rosenheck et al., 1997), at least in very expensive patients (Rosenheck, Leslie, & Sernyak, 2001). A decade after the first new atypical drug was launched, 82% of VA patients with schizophrenia were using these drugs (Leslie & Rosenheck, 2004). Like the newer antidepressants they were also widely used in the treatment of disorders for which their efficacy was not demonstrated, again because they would, presumably, impose a minimal burden of side effects (Rosenheck, Leslie, & Sernyak, 2001).

Enthusiasm about these medications received popular expression in the 1997 best seller “Listening to Prozac” which reported that SRIs could make people “weller than well” (Kramer, 1997). The optimism about these new drugs was also shared by scientific experts, and was perhaps most authoritatively

expressed by Steven Hyman MD PhD, the Director of the National Institutes of Mental Health, a leading neuroscientist, and a Harvard Professor; in a widely publicized 1998 letter to the Director of the Center for Medicaid State Operations at HCFA (see the full document at http://www.medaccessonline.com/articles/index.php?articleID=5 and artcategoryID1=1) he explicitly linked the two medication classes and expressed concern that their high cost might constrain their use:

> Over the past decade, the serotonin re-uptake inhibitor (SRI) class of antidepressants has largely replaced the older and more problematic tricyclic anti-depressants, based in large part on safety and side effect considerations. There is now clear evidence that a similar shift in the 'state of the science' regarding treatment of schizophrenia is taking place. . . In some parts of the country, we understand that health care systems will not routinely allow new patients to be started on atypical antipsychotic medications until they have failed a course of the standard (less expensive generic) antipsychotic medications. We see no scientific justification for such a practice and consider it particularly ill advised. . . This is a situation in which HCFA and the NIH institutes working in concert can have a substantial beneficial effect on the health care of the American people.

Six years after Hyman's enthusiastic letter, sales of these agents continue to climb, but many of the optimistic claims for them have been challenged in both the scientific literature and in the courts. As these controversies have continued, it is timely to review current information on the clinical and economic value of these medications and to reflect on the sources of the enthusiasm they initially generated. The development of these medications also affords a window into the interaction of key institutions such as pharmaceutical corporations, academic psychiatry, professional organizations, consumer advocates, and the FDA. Any effort of pharmacy benefits managers to maximize medication value, i.e. to obtain the greatest health benefit for each dollar spent, depends on the quality of the available information concerning the effectiveness and net cost impact of such drugs in general clinical practice. Poor or incomplete information, upstream from the benefits management process can thoroughly undermine the success of that enterprise.

2. Newer antidepressants

Since much concern was expressed about the antidepressants in the media, during 2004, we will first review emerging insights into those medications and then turn to the less well publicized developments concerning the atypical antipsychotics.

2.1. Treatment of children and adolescents

In early 2004, several academic reviews of research on the treatment of children and adolescents with antidepressants became international news. In April, a review article in the prestigious *British Medical Journal* (Jureidini, Doecke, Mansfield, Haby, Menkes, & Tonkin, 2004) criticized methods used in many corporate sponsored studies of antidepressant treatment of children and adolescents and charged that the published conclusions were biased. It also drew attention to the fact that a US FDA website noted that 8 of 9 trials that drug companies had not published, showed no benefit for antidepressants in youths. A similar paper published in the *Lancet,* using unpublished data from UK regulatory agencies (Whittington, Kendall, Fonagy, Cottrell, Cotgrove, & Boddington, 2004), found that the addition of unpublished studies to a meta-

analysis reversed the results and suggested that the risks might outweigh their benefits in the treatment of childhood and adolescent depression for all but one of these medications. Only two months later, the Attorney General of New York State sued GlaxoSmithKline PLC, manufaturer of one of the antidepressants, for committing fraud by withholding information from the public about research studies it had conducted, and by August the company had agreed to pay $2.5 million to settle the suit but admitted no wrong doing (http://www.technewsworld.com/story/36159.html).

In addition to the question of whether these medications offered significant clinical benefits to depressed children and adolescents, the long simmering issue of whether they might paradoxically increase suicidal ideation also came to a head. In 2003 the Medicines and Healthcare Products Regulatory Agency of the United Kingdom essentially banned all but one of these antidepressants for use with children because they imposed an unacceptable risk of suicide. By late October, 2004 the US FDA had required manufacturers of SRIs to add a black box warning to their marketing, the most serious kind of public alert, that included a cautionary statement that "while 2% of patients on a 'sugar pill' became suicidal, twice that number, 4% became so on newer antidepressants" (http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm).

Ironically, one month prior to the FDA decision, an independent multi-site study (i.e. one free of drug company control) funded by the NIMH, reported significant reductions in adolescent depression with fluoxetine (the generic ingredient in Prozac®), especially when combined with psychotherapy (March et al., 2004). However the study also found significantly increased "harm-related events" with the medication, but no specific increase in suicidal behavior. While this one study did not alter the consensus of concern about SRI treatment of young people, it confirmed the complex combination of benefits and liabilities associated with these medications.

2.2. SRI treatment of adults

Recent reviews have also raised questions about the benefits of newer antidepressants in adults (Hypericum Depression Trial Study Group, 2002; Khan, Warner, & Brown, 2001; Kirsh, Moore, Scoboria, & Nicholls, 2002; Moncrieff, 2001). Under the Freedom of Information Act, Khan, Warner and Brown (2001) obtained data on 19,639 patients treated in clinical trials submitted to the FDA for approval of seven newer antidepressants. Although suicide rates and attempts were greater among new drugs (0.8%, 2.8%), and active controls (0.7%, 3.4%) than among placebo treated patients (0.4%, 2.7%) these differences were not statistically significant. Symptom reduction was 40.7% with newer drugs, 41.7% with pharmacologically active comparitors (mainly older antidepressants) and 30.9% with placebo. There was clearly no efficacy advantage for newer anti-depressants over the older medications, and the 10% advantage of the antidepressants over placebo was described as "less than impressive."

A further analysis of trials submitted to the FDA focused, specifically, on the comparison of new drugs and placebo and added several methodological refinements (Kirsh et al., 2002). Summary results from 38 trials involving 6944 patients who received either a newer drug or placebo suggested a significantly greater improvement of 1.8 points on active drug ($t=5.0$, $df=18$, $p<.001$) as measured by the 50- and 62-point versions of the Hamilton Depression scale and noted that 82% of the observed improvement with SRIs was attributable to the placebo effect. The authors suggest that these differences, while statistically significant, could reflect unintended unblinding of active cases and resultant rater bias, and contend that drug benefits are both small in magnitude and of questionable clinical significance.

To specifically examine publication bias, Melander, Ahlqvist-Rastad, Meijer, and Beermann (2003) obtained all 42 studies submitted to the Swedish drug regulatory authority between 1983 and 1999 in applications for approval of new anti-depressants. A comparison of studies as submitted to the government with their published versions in medical journals showed that favorable studies tended to be published by themselves, as stand alone studies (three of the studies were even published twice or more) but that data from unfavorable studies tended to be pooled with data from favorable studies, masking their negative results. Half of the 42 submitted studies found the new antidepressant to be more effective than placebo. Nineteen (90%) of these 21 positive studies appeared as stand alone publications. Of the 21 studies that showed no benefits of the new antidepressants only 6 (29%) were published as stand alone publications, 11 (52%) were pooled with data from more favorable studies and 4 (19%) were not published at all.

The studies in their published form were generally more favorable to the new drugs than the versions submitted to the Swedish regulatory agency, and in two cases these differences were substantial. In one case a drug which looked more effective than placebo in the published versions was only marginally so when the original studies were examined. Corporate sponsored studies of newer antidepressants, in both adults and children, have thus come under increasing suspicion of slanting their publications, although no drug has been withdrawn from the market. While biased publications may be used to promote pharmaceutical products by exploiting the authority of the peer reviewed literature, it does not seem that the products they promote fail to meet the minimal regulatory standards for safety and efficacy. Their benefits, however, appear small in magnitude, especially in view of their high price.

Data from major, independent, effectiveness trials, examining the use of antidepressants in "real-world" practice also yield mixed results. System level interventions designed to improve compliance with drug treatment as well as psychotherapy have shown significant benefits for antidepressants (Katon et al., 1995; Wells et al., 2000; Unutzer et al., 2002) although they were not sustained for a full year in one study (Lin et al., 1999), and in another study, where five-year advantages were demonstrable, they were small in magnitude (6%) (Wells et al., 2004). A major 6-month effectiveness study comparing SRIs and tricyclic antidepressants showed better adherence, fewer adverse effects, and no increase in costs with SRIs, but no more improvement in symptoms or quality of life at 3 or 6 months (Simon et al., 1996). Moncrieff (2001) suggested that the most important, large, governmentally sponsored trials have shown generally limited benefits for antidepressants as compared to placebo and that methodological flaws exaggerate the benefits in many cases. Other researchers, however, claim that these trials are credible and valid (Quitkin, Rabkin, Gerald, Davis, & Klein, 2000). At least three studies have found that antidepressant study sponsorship by the manufacturer predicts either reports of superior outcomes or greater cost savings (Baker, Johnsrud, Crismon, Rosenheck, & Woods, 2003; Freemantle, Anderson, & Young, 2000; Melander et al., 2003).

In the only formal study that has attempted to look at the public health impact of the use of antidepressants during the 1990s, Olfson, Shaffer, Marcus, and Greenberg (2003) found greater declines in adolescent suicide rates in regions with greater use of SRIs. Brent (2004) also suggested that the decline in youth suicide in the US since 1994 might correspond to the increased use of these medications, but these studies are subject to the ecological fallacy since their results may be explained by confounding community characteristics. Furthermore, data from the Social Security Administration (SSA) show that between 1994 and 2002 the number of Americans who received SSA disability benefits for affective disorder *increased* by 121%, from 425,138 to 939,711 (or from 0.28% of the adult population to 0.44%) (personal communication, Pamela Mazurski, Associate Commissioner at SSA). Data from the National Health Interview Survey also show that the proportion of working age Americans who report themselves to be *disabled* due to depression increased from 0.10% to 0.30% during the 1990s and that the proportion who

report themselves to be *unable to work* because of depression rose from 0.7% to 0.21% (Burkhauser & Stapleton, 2003). Newer medications thus do not seem to have improved employment among depressed Americans, although it is also possible that these data reflect changes in reporting, i.e. that unemployed Americans have become more likely to cite depression as the reason for their unemployment, perhaps due to the de-stigmatization of mental illness.

While both newer and older antidepressants still pass the regulatory standards for safety and effectiveness and are considered to be invaluable treatments by many psychiatrists and patients, there is limited empirical evidence of a substantial return in public health benefits for the $12 billion annual investment in these drugs. The diminished risk of suicide from overdosing may, in fact, be offset by an increased risk of suicidal ideation.

While the SRIs are safe and effective, it appears that corporate sponsored scientific publications have portrayed them in an unduly positive light whose glow has been magnified by aggressive marketing to both physicians and consumers. Between 1997 and 2000 $8.8 billion was spent on direct-to-consumer (DTC) advertising of six SRIs that were among the top 50 DTC medications (Frank, Berndt, Donohue, Epstein, & Rosenthal, 2002). Additionally, well-known celebrities were recruited in many ads to promote psychotropic agents to the general public (Moynihan, 2002).

3. Atypical antipsychotics

In 1988, a landmark clinical trial showed that clozapine, the first atypical antipsychotic, produced a 30% response rate in patients with previously refractory (i.e. unresponsive) schizophrenia, as compared to a 4% response with an older drug, haloperidol (Kane, Honigfeld, Singer, & Meltzer, 1988). Hailed as the first major step forward in the pharmacotherapy of schizophrenia in over three decades, this study stimulated hopes that newer atypical drugs would bring unprecedented progress, and one book soon heralded a "Return from Madness: Psychotherapy with people taking the new antipsychotic medications and emerging from severe, lifelong, and disabling schizophrenia" (Deegan & Nasper, 1996). As Dr. Hyman indicated in his letter, the new drugs appeared to have virtually no side effects, and to be so much more effective than older drugs that they reduced the need for hospitalization sufficiently to pay for themselves and generate net savings. One prominent NIMH research psychiatrist asserted in a 1996 letter to the *American Journal of Psychiatry* that "between 1990 and 1994, clozapine has saved the United States approximately $2.5 billion in 1993 dollars" (Wyatt & de Saint Ghislain, 1995).

But in 2003, Erica Goode, reporting on the American Psychiatric Association Annual meeting for the *New York Times*, told a quite different story: "They were billed as near wonder drugs, much safer and more effective in treating schizophrenia than anything that had come before... For many years, it seemed that the excitement was fully warranted... There were remarkable stories of recovery... But 14 years after the first of the drugs entered the market, researchers are questioning whether they are quite as miraculous- or benign-as originally advertised." (Goode, 2003).

3.1. Cost savings

Perhaps the first of the hopes to be dashed was that the drugs saved enough to offset their high cost. The early, company-sponsored studies that generated high hopes used pre-post designs or matched control groups and showed savings of $10,000–$50,000 per patient per year. The first of these studies

(Revicki, Luce, Wechsler, Brown, & Adler, 1990) compared clozapine responders (52% of those who started on the drug) with drop outs and found $9011 lower costs in the second year of treatment. However several letters to the editor of the journal that published the study pointed out that the observed cost reduction was far more likely to be attributable the spurious comparison of patients who stayed on the medication with patients who dropped out, and who, by definition, had not responded positively, than to any general beneficial effect of the drug.

A second study reported two sets of analyses: the first showing that among 59 patients who started on clozapine, costs dropped by $8702 from the pre-treatment phase to the treatment phase; and second, that a comparison of costs and outcomes of 37 patients who remained on clozapine treatment and 10 who dropped out revealed $22,936 greater cost reductions among completers (Meltzer et al., 1993). This small and similarly flawed study provided the basis for the $2.5 billion savings estimate in the *American Journal of Psychiatry*, and drew fire from five different letters to the editor that were critical of the study design, observing that regression to the mean and selection bias had been misinterpreted as medication effects. A third study (Reid & Mason, 1998) also used a flawed pre-post design and found savings estimated at $30,000–$50,000 per year among State Hospital patients treated with clozapine, while an updated study from the same group (Reid, Mason, & Hogan, 1998) extended the follow-up to 4.5 years and added a control group which included clozapine drop-outs and found estimated savings of $25,000 per year.

The cost analysis of the International Collaborative Trial (ICT), the large industry-sponsored trial that established the superiority of olanzapine over haloperidol–a study that garnered special praise in Dr. Hyman's letter–showed substantial olanzapine savings of $388 in the first 6 weeks of treatment and $3976 during the remaining 46 weeks in a large experimental study that used haloperidol as the comparitor, (Glazer & Johnstone, 1997; Hamilton et al., 1999). While these savings were far less than those found in non-experimental studies, several design flaws make even these savings suspect. First, while the olanzapine group completed only 34% of the scheduled follow-up interviews over the year of follow-up, the haloperidol group completed even fewer (22%), primarily because patients were not followed-up if they had not responded to treatment by 6 weeks or after they went off study medication. While such low follow-up rates would in themselves weaken the credibility of any study, they are especially problematic because the olanzapine patients were followed for longer periods of time than the haloperidol patients and thus had more time to improve, or to show regression to the mean in monthly costs. Furthermore, the authors used a last-observation-carried-forward (LOCF) analytic technique to deal with the extensive missing data. In the LOCF approach the monthly costs at the time of the last recorded interview were substituted for missing data at all subsequent observations. This approach has been described by one prominent statistician as the least valid approach to the problem of missing data, especially when one group receives treatment for a longer period of time (Lavori, 1992). Since it is clear from the data presented that monthly costs were declining steadily over time in both groups, a major bias was introduced against the haloperidol patients, since they stopped treatment earlier than the olanzapine patients, when their costs were higher. The authors of the study recognized this problem in their discussion of the data, stating "The assumption underlying this approach was that the unobserved costs of patients after withdrawal were equal to their mean cost before drop out" (Hamilton et al., 1999, p. 474). Although it is clear from the data they present that this assumption is false, the authors, virtually all of whom were employees of the manufacturer of olanzapine, credited the drug with savings that substantially exceeded medication costs.

The first two long-term randomized clinical trials involving clozapine (Essock et al., 2000; Rosenheck et al., 1997), showed far more limited savings that were not statistically significant. A 15-site, 12-month VA trial of 423 hospitalized patients (Rosenheck et al., 1997), found $2,441 (4%) lower costs for clozapine

patients than for the controls, a much smaller effect than in any of the non-experimental studies. A further analysis of subgroups in this study found significant savings only in the third of the study sample that showed the greatest reliance on hospital care before entering the study (115–365 days) (Rosenheck et al., 1999). In fact this high use group represented a tiny subgroup, the most costly 0.7% of all VA patients diagnosed with schizophrenia. The vast majority of VA patients with schizophrenia (74%) had no hospitalizations at all and thus had virtually no potential for savings with atypicals (Rosenheck, Leslie, & Sernyak, 2001).

A second major experimental study, of very long stay State Hospital patients in Connecticut, found that although clozapine-treated patients were not more likely to be discharged from the hospital than controls, they were less likely to be readmitted (Essock et al., 2000). However, once drug costs were included there were, again, no significant cost differences between clozapine patients and controls. A third, more recent multi-site experimental VA study comparing olanzapine and haloperidol, found olanzapine to generate *greater* total health care costs, primarily due to greater drug costs, ranging, in a sensitivity analysis, from $4,000–$10,000 per patient per year (Rosenheck, Leslie, & Sernyak, 2001).

There has been only one study of the cost impact of the shift from conventional to atypical antipsychotics in a large healthcare system (Duggan, 2003). That study examined the dissemination of atypicals to 30,000 Medicaid claimants in California from 1993–2002 and found no reduction in hospital use either: a) over time, as atypicals were introduced, or b) in comparing geographic areas with different levels of atypical use, or c) comparing individual practitioners with greater or lesser propensity to use atypicals. In fact total treatment costs steadily increased as atypicals came into wider use. There was no evidence of any cost offset from reduced inpatient or outpatient service use.

3.2. Metabolic side effects

Recent studies have further suggested that while some side effects, especially extrapyramidal side effects, may be less frequent with atypical antipsychotics, others may be more frequent. Most of the atypicals have been associated with substantial weight gain, amounting to 1.7 lbs./week with olanzapine, a significant health risk in itself (Simpson, Goetz, Devlin, Goetz, & Walsh, 2001). But recent data from numerous studies have also demonstrated that use of these medications is associated with onset of diabetes mellitus and hyperlidemia, resulting in increased risk of heart disease (Wirshing, Boyd, Meng, Ballon, Marder, & Wirshing, 2002; Marder et al., 2004; Melkersson, Hulting, & Brismar, 2000). In response to these findings the FDA recently ordered all the manufacturers to add a warning that these drugs pose an added risk of diabetes (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/printer.cfm?id=229). The Association of Clinical Endocrinologists (2004) recently published a consensus statement supporting this assessment and urging close metabolic monitoring of patients who take these medicines.

3.3. Recent independent trials

Two recent, large independent studies (i.e. studies in which data analysis and reporting were not controlled by the manufacturer) that compared atypicals other than clozapine and conventionals, failed to find any benefit in symptoms, quality of life, or even extrapyramidal side effects with atypicals (Rosenheck et al., 2003; Lewis et al., 2005). The lack of substantial advantage for olanzapine in the first of these studies was unexpected, but detailed methodological comparison with the International Collaborative Trial (ICT), which showed marked benefits for olanzapine (Tollefson et al., 1997) suggested that the key methodological

difference was that in the ICT haloperidol patients were *not* given prophylactic anticholinergic medication that would have prevented side effects that can cause early drop out and can be mistaken for symptoms of schizophrenia.

In fact since two-thirds of all randomized clinical trials compared atypicals to haloperidol given *without* this side effect medication, the majority of studies of atypicals and older medications may have all suffered from this same bias (Rosenheck, 2005). A re-examination of recent data from a meta-analysis of 11 studies of treatment failure (Leucht et al., 2003) seems to confirm this view. Data from the two studies that, like the VA trial, used haloperdiol *with* the recommended side effect medication, found a *less* risk of relapse and early drop out with haloperidol than with atypicals. Only in the studies in which haloperidol was used *without* the side effect medication was risk of relapse *greater* with haloperidol.

A second recent independent trial, sponsored by the National (UK) Coordinating Centre for Health Technology Assessment, randomly assigned 227 patients to open treatment with doctor's choice of either an atypical (excepting clozapine) or a conventional antipsychotic (Lewis et al., 2005). A unique advantage of this study is that it allowed the physician to choose which specific agent would be best for each patient as long as they came from the randomly assigned medication class. Because of the open (i.e. non-double blind) study design, ratings were conducted by blind raters who did not know which treatment patients were receiving. Perhaps because of this flexible real-world design an impressive 81% follow-up rate on assigned treatment was achieved at one year (far better than 30% in the ICT and 57% in the VA trial). No differences were observed between treatment conditions in symptoms, quality of life, side effects or subjective satisfaction with medication.

While these two independent long-term studies found few advantages for atypicals, there is still eager anticipation of the results of an important NIMH-funded study, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Stroup et al., 2003) which compares olanzapine, risperidone, quetiapine and ziprasidone, with perphenazine, a medication with less tendency to cause extrapyramidal symptoms than haloperidol. Although anticholinergics were not used prophylactically in CATIE, concerted efforts are being made to follow all 1400 patients for the full 18-month duration of the trial, and LOCF will not be used (Davis, Koch, Davis, & La Vange, 2003). This study will hopefully clarify what has become a contradictory, complex, and possibly biased, scientific literature.

3.4. Tardive dyskinesia

Tardive dyskinesia (TD) is a serious involuntary movement disorder that emerges in as many as 5% of patients receiving long-term conventional antipsychotics annually (Morgenstern & Glazer, 1993). Because the atypicals have less risk of extrapyramidal symptoms, it has been hoped that they would also incur lower risk of TD. But it has been difficult to document this advantage because TD emerges after many years of treatment. A recent review of TD research (Correll, Leucht, & Kane, 2004) found only three well controlled studies, which seemed to suggest lower risk of TD with atypicals. However these three studies have substantial limitations because: a) they were based primarily on 6-week outcome data, b) TD could have been confused with withdrawal dyskinesia as patients changed to haloperidol medication without prophylactic anticholinergics, and c) life time exposure to conventionals was undocumented (Woods, 1999). Avoidance of TD may yet turn out to be a robust advantage of the atypicals, but the evidence, thus far, is not definitive. FDA labeling warns that no antipsychotic has been shown to have lower risk of TD than any other.

3.5. An FDA perspective

It is notable in view of these recent findings, that in August 1996, in an unpublished memo obtained through the freedom of information act, the Director of the Division of Neuropharmacological Drug Products of the FDA, reviewing the ICT of olanzapine concluded that "...the data adduced in the Zyprexa [olanzapine] NDA [New Drug Application] is... insufficient to permit the sponsor to make claims asserting the product's superiority to haloperidol" (Director, Division of Neuropharmacological Drug Products, 1996a). The explanation given for this judgment in a subsequent memo (Director, Division of Neuropharmacological Drug Products, 1996b), is similar to that presented above. The memo reasons, "The problem in schizophrenia outcome assessment is that some of the so-called 'negative' signs and symptoms of that illness are indistinguishable from the pseudoparkinsonian signs and symptoms that are known side effects of antipsychotic drugs like haloperidol. It would be reckless, therefore, to assume that a drug-haloperidol difference detected on an instrument that registers negative symptoms is actually measuring a difference in antipsychotic effectiveness".

It is notable that the published account of the ICT, in which all of the authors were employees of the manufacturer, arrives at the very conclusion that the FDA memo judged to be reckless, "Olanzapine shows a superior and broader spectrum of efficacy in the treatment of schizophrenic psychopathology...than haloperidol" (Tollefson et al., 1997, p. 457). Furthermore, a simultaneously published analysis directly contravened the central argument of the FDA memo, concluding that "These results suggest that the negative symptoms of schizophrenia are directly responsive to treatment" (Tollefson & Sanger, 1997, p. 466). The apparent disagreement between the FDA review and the research findings published by the manufacturer were never made public because FDA is only called upon to determine whether a drug is safe and effective in comparison to placebo, and not how it performs relative to other medications.

4. Evidence based practice or irrational exuberance

This review of the scientific bases for the $20 billion expansion in psychotropic drug sales in the 1990s has shown that new antidepressant and antipsychotic medications met minimal FDA standards for safety, and for greater efficacy than placebo, and thus deserved to be included among the evidence-based practices that are legitimate tools in the medical armamentarium. However, data have accumulated that their advantages over older medications may be more limited than claimed in books like "Listening to Prozac"; in billion dollar, back-of-the-envelope savings estimates; or in NIMH Director Hyman's projection of "substantial beneficial effect on the health care of the American people." The enthusiasm that made these medications billion dollar sellers was only partially justified by scientific evidence and, seems, indeed, to have also reflected a certain "irrational exuberance" of the kind that Alan Greenspan presciently feared had inflated stock prices in the 1990s, and that Robert Schiller, in his book of the same name (2000), found to be at the heart of the "bubble psychology" that led to the stock market boom and bust.

Schiller argues that exuberant "bubbles" occur when many voices reinforce one another, giving false credibility to wishful thinking and to the belief that a "new era" has arrived in which old constraints no longer apply. The factors that Schiller identified as having supported irrational exuberance in the stock market, however remote from the world of psychopharmacology, may have also formed a cultural

backdrop that facilitated the psychopharmacology bubble: Western business had triumphed over communism; information technologies promised access to limitless information; business superstars were idolized as "can't-lose" wizards; and the risk of inflation in a growing economy seemed to have been eliminated.

The more immediate source of irrational exuberance about psycho-pharmacological agents, as we have seen, was overly positive interpretations of research findings based on slanted design, analysis, and reporting by drug companies—findings that were disseminated through vigorous marketing campaigns. The accelerated expansion of drug sales was not limited to psychotropic drugs. From 1997 to 2001 retail spending on prescription drugs in the US increased by an average of 19% *per year*, about 6 times the rate of general medical cost inflation (National Institute of Health Care Research and Education Foundation, 2002). By the end of the century pharmaceutical corporations had become the dominant sponsor of psychopharmacologic clinical trials. Since the primary responsibility of any publicly held corporation is to maximize shareholder value, companies were obligated by law to use their control over the research enterprise to maximize profits in any legal way. According to Abrahmson (p. 94–95), in 1991, 80% of commercially sponsored research was conducted by university researchers who took an independent, active role in the design, analysis and publication of clinical trials of new medications. By 2002, he reports, in a complete reversal, 80% of clinical trial funding came from drug companies whose increasing control over the research enterprise, resulted in overselling of product benefits in the pages of medical journals. David Healy (2004) reports that the first psychiatric research paper authored completely by company employees appeared in print in 1991—a study by Eli Lilly researchers of the risk of suicide in association with Prozac. Just a decade later, in 2001, the editors of 12 leading medical journals jointly proclaimed that "the use of clinical trials primarily for marketing. . .makes a mockery of clinical investigation" and represents a betrayal of patients who participate in such trials altruistically (Davidoff et al., 2001).

As with the stock market, bubble psychology in psychopharmacology appears to have emerged from the reinforcing interactions of multiple stakeholders. Drug company claims found a receptive audience among psychiatrists, whose profession was in the process of re-medicalizing itself, partly in response to stiff competition from lower priced non-medical therapists, and partly from tightening restrictions on psychotherapy by managed care organizations. A new generation of psychotropic wonder drugs offered psychiatrists a unique niche among the crowded mental health professions as stewards of a valuable resource which they, alone, could prescribe.

Professional psychiatric organizations, which received about one-third of their funding from industry, and whose annual meetings became a virtual carnival of marketing activity, were also active champions of the medication stewardship responsibilities of their members. Organizations of family members of people with mental illness, which also received extensive corporate support, were eager to support the idea that mental illness was a brain disease, among other reasons, because it relieved them of a burden of guilt that had been heaped upon them by earlier, psycho-social theories of mental illness. Optimism was further facilitated by the relatively low standards of safety and efficacy by which the FDA is required to evaluate new drugs. Although, as we have seen, a prominent FDA official had come to very different conclusions about the value of the atypicals than researchers employed by one of the manufacturers, there was no forum through which this important difference could enter the public discourse.

As Schiller observes, irrational exuberance is finally cooled by reality, and may even stimulate an irrational backlash in the other direction. Even before more recent studies were published, critical books appeared that described toxic effects of SRIs and belittled their effectiveness (Breggin & Breggin, 1995;

Glenmullen, 2001). These studies had limited impact on either the public opinion, psychiatric practice, or drug sales.

But as the new century began, a series of highly publicized law suits with hundred-million dollar payouts suggested that some of the more brazen payments of drug companies to physicians were actually violations of Federal anti-kickback laws and some marketing efforts violated the False Claims Act, which allows internal whistle blowers to earn vast sums by revealing information that leads to a judgment against their employers (Studdert, Mello, & Brennan, 2004). The manufacturer of Lupron, for example, a prostate cancer drug, paid almost $900 million, in 2001, for offering physicians lucrative rewards for prescribing its drug, and an inside whistleblower triggered a $430 million fine against a company that promoted the use of Neurontin (an anti-epilepsy drug) for purposes not approved by the FDA (Angel, 2004).

In addition to the stock market collapse of 2000, revelations of corporate scandals at Enron, Tyco and elsewhere in the new century, created a climate in which critical consideration of drug company practices was increasingly likely to be taken seriously. Between April and October, 2004, five books were published, (two by the immediate past editors of the New England Journal of Medicine, two by other Harvard faculty members, and one by a Wall Street journal business reporter) that railed against the excesses of corporate drug promotion and the biases of corporate sponsored research (Abramson, 2004; Angel, 2004; Avorn, 2004; Goozner, 2003; Kassirer, 2004). These five critiques were not especially concerned with psychotropic drugs, but focused on misleading marketing and research concerning antihypertensive drugs, statins, weight-loss treatments, non-steroidal anti-inflammatory drugs, hormone replacement therapies, and medical devices. Irrational exuberance for pharmaceuticals appeared to have been widespread in the 1990s as was the turn towards more negative views in the early years of the new century.

Neither the best nor the worst research would have effected sales without aggressive marketing. Corporate gifts and payments to physicians which included pens, mugs, books, meals at fine restaurants, resort trips, and consultant fees for listening to promotional lectures, have all been shown, regardless of their monetary value, to shape physician prescribing behaviors, and thus to violate the ethical precept that a physician's exclusive loyalty in medical decision making must be to the patient (Blumenthal, 2004). As one scholar observed, it is not necessary that the doctors were paid to promote or prescribe specific products through an explicit quid pro quo (Kassirer, 2004). The high fees and adulation are sufficient in themselves to stimulate a reciprocating impulse—a natural inclination to repay those who show one deference and favor (Wazana, 2000).

According to Marcia Angel, former editor of the *New England Journal of Medicine*, in 2001, drug companies spent $11 billion in free samples that were delivered to physicians by 88,000 sale representatives (at a cost of $5.5 billion), and were promoted by $2.7 billion in direct to consumer advertising and another $380 in medical journal advertising. In addition, drug companies reportedly paid for 60% of all continuing medical education (CME) for physicians, education that was often slanted to support their products.

In response to the successful lawsuits and increasingly negative publicity, industry, along with the AMA and several others groups, have established ethical guidelines designed to eliminate the more egregious marketing excesses, and thereby avoid government intervention (Studdert, Mello, & Brennan, 2004). But control over research still rests largely with industry, especially during the early years after a product is launched, before independent trials can be designed, funded, and published. The generation of knowledge is, thus, still more firmly hitched to corporate profit making than to improving public health.

5. Policy perspectives

One institutional corrective for this state of affairs would be an independent scientific agency, either operated or sponsored by the government, that would be charged with: a) conducting the initial evaluations of safety and efficacy for FDA approval, b) performing rigorous long-term cost-effectiveness studies early in the commercial life of "blockbuster" drugs, and c) taking continuing responsibility for monitoring post-marketing safety. While no barrier between commercial interests and research institutions can ever be completely impermeable, such an agency would help disconnect scientific judgment from the corporate mission and, perhaps, better serve the public interest.

Such an agency could be funded, in part, out of tax revenues, like the current FDA, and by fees paid by industry for basic safety and efficacy evaluations of their products. More expensive, long-term cost-effectiveness studies would be mandated only for highly successful drugs and could be funded by imposing a windfall profits tax "blockbuster" drugs.

Such a tax would not be hard to justify, although it might be difficult to promote politically. In the first two years after its release, Zyprexa® sales to Medicaid alone equaled $900 million, beyond the highest estimate of the cost of new drug development (including direct expenditures on pre- and post-clinical research and post-marketing research; the cost of capital; and the cost of failed drugs that never yielded a profit DeMasi et al., 2003). Thus the entire development cost of Zyprexa® was retired by sales to the federal government, after only two years on the market. A 1% tax on subsequent profits would have provided $5–$40 million dollars annually, easily enough to support the independent cost-effectiveness research on this agent and no doubt several others, and hardly enough to suppress future investment in drug development.

Ironically, and consistent with this policy approach, in 1999, NIMH contracted with researchers from several top universities to conduct the $42 million CATIE study of atypical antipsychotics in schizophrenia and Alzheimers disease—the most costly study ever funded by the agency. But because this study was a one-time initiative rather than an institutionalized response to block buster drug sales, by the time the results will become available, in mid-2005, it will have been over a decade since the first of the atypicals was launched. During this time Medicaid expenditures for these medicines, alone, will have totaled almost $17 billion, with total domestic sales exceeding $30 billion.

There will never be universal agreement on the "right" place to draw the line between the public management and private ownership in the development of pharmaceuticals. Giving greater responsibility to government regulators may work against certain kinds of innovation, commercial education, and consumer choice. Giving greater priority to the private sector increases the risk that the profit motive will bias the generation and presentation of scientific data needed to guide medical decision making. The material presented in this review suggests that we have come through a period when the disadvantages of relying on the private sector to guide pharmaceutical evaluation have been amply displayed. A corrective swing of the pendulum towards more independent genesis of medical knowledge seems overdue.

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