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Design and Reporting Modifications in Industry-Sponsored Comparative Psychopharmacology Trials

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This review of recently published pharmaceutical industry–sponsored comparative psychotropic drug trials aims to classify apparent design and reporting modifications that favor the sponsor's product. The modifications have been grouped into 13 discrete categories, and representative examples of each are presented. Strong circumstantial evidence suggests that marketing goals led to these adjustments. The consequences of marketing influences on comparative psychopharmacology trials are discussed in terms of conflicts of interest, the integrity of the scientific literature, and costs to consumers, as well as their impact on physician practice.

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Occasionally, a pharmaceutical product enters the market that has some distinct advantages over its predecessors. Soon thereafter, other companies manufacture and patent a similar drug, referred to as a me-too drug. Then, an intense competition for market share develops for which the drug's price is not the central issue (Kessler et al., 1994; Tarabusi and Vickery, 1998). An important aspect of this competition is the publication of clinical trials showing the superiority of one drug over another that has a niche in the same market. The purpose of that research is not only to show the relative superiority of the company's product, but also to show the drawbacks of the competing drug.

The resulting publication of pharmaceutical company–sponsored comparative drug research now occupies a big share of the medical literature. It is fueled by marketing aims, so it is no wonder that an estimated 89 to 98% of comparative drug treatment studies funded by pharmaceutical companies yield results that are favorable to their company's product (Cho and Bero, 1996; Davidson,1986). Furthermore, such sponsored research generally shows their product to be safer than its rival (Mandelkern, 1999; Rochon et al., 1994b).

To achieve the aim of demonstrating comparative superiority, certain design adjustments and reporting modifications are frequently utilized. These can include the following: 1) using a dose of the comparable drug that is outside of the standard clinical range, 2) altering the usual dosing schedule of the competing drug, 3) using misleading research measurement scales, 4) picking endpoints post hoc, 5) masking unfavorable side effects, 6) repeatedly publishing the same or similar findings for impact, 7) selectively highlighting findings favorable to the sponsor, 8) editorializing in the abstract, 9) publishing the obvious, 10) statistical obfuscation, 11) selecting subjects and a time frame designed to achieve a favorable outcome, 12) withholding unfavorable results, and 13) masked sponsorship.

These research modifications will be presented in this review in more detail with examples. Then, the broader and untoward ramifications of competitive drug company–sponsored clinical research will be presented.

This review of the psychopharmacology literature, primarily from the U.S., is selective and does not aim to present a comprehensive or a balanced perspective of all pharmaceutical company–sponsored psychotropic research. Some have argued that bias in the literature is not infrequent and includes placebo-controlled registration trials and some government-sponsored research (Conley, 2001; Gorelick,1998; Moynihan, 2002). Nonetheless, this report focuses on industry-sponsored comparative trials because these contain far more numerous and prominent examples of design and reporting modifications and because industry-sponsored studies now dominate the comparative drug trial literature (Angell, 2001; Davidoff, 2002).

Design Adjustments and Reporting Modifications

Using Doses Outside the Usual Range for Competitive Advantage

An obvious example of drug company–sponsored research designed to prove a point is that of a sec-

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ond-generation neuroleptic compared to a relatively high dose of haloperidol. At least eight studies sponsored by three different drug companies have compared their second-generation neuroleptic drug to a fixed high dose of haloperidol of 20 mg per day (Chouinard et al., 1993; Deo et al., 1990; Emsley 1999; Goldstein et al., 1999; Marder and Meibach, 1994; Simpson and Lindenmeyer, 1997) or to an average haloperidol dose greater than 20 mg per day (Lapierre et al., 1990; Patris et al., 1990). Using such an unusually high dose virtually ensures that the second-generation product will have fewer extrapyramidal side effects (EPS) than haloperidol. In comparative studies between second-generation neuroleptics, unusually high fixed or average doses of risperidone (7.2 and 8 mg/day) have also been used to achieve similar results (Peuskens et al., 1999; Tran et al., 1997b).

Doses of haloperidol exceeding the customary levels of 4 to 10 mg/day produce no better clinical results than do doses above that range (Baldessarini et al., 1988; Mc Evoy et al., 1991; Rifkin et al., 1991), but they induce more EPS (Mc Evoy et al., 1991; Rosebush and Mazurek, 1999: Stone et al., 1995; Wong et al., 1999) and lead to far more treatment drop-outs (Beasley et al., 1999; Chouinard et al., 1993; Tollefson et al., 1997b; Van Putten et al., 1990). Likewise, doses of risperidone above 6 mg/day produce more side effects and no greater therapeutic results than standard doses of 4 to 5 mg/day (Love et al., 1999; Nyberg et al., 1999). Furthermore, a recent meta-analysis clearly revealed that doses of haloperidol greater than 12 mg/day produced significantly fewer favorable symptom scores than haloperidol at doses of less than 12 mg/day (Geddes et al., 2000).

Substantially Altering the Dose Schedule of the Comparison Drug for Competitive Advantage

Commercially sponsored studies comparing two antidepressant drugs often schedule an unusually rapid and substantial dose increase in the one not manufactured by the sponsoring company. For example, in comparative studies of antidepressants, the dose of fluoxetine was increased to 40 mg/day in over one half of the subjects at 3 weeks (Geerts et al., 1999), to an average of 47 mg/day during weeks 4 to 8 (Rudolph and Feiger, 1999), and to an average of 40 mg/day in 10 of the 21 subjects at 4 weeks (Armitage et al., 1997). Likewise, sertraline was increased to an average of 148 mg/day at 6 weeks (Feiger et al., 1996), and paroxetine was increased to 50 mg/day in one third of the cases by 7 weeks (Kiev and Feiger, 1997). Doses and dose schedules beyond the usual range, particularly early in treatment, characteristically bring an increased rate of side effects—as was the case in the studies referred to above.

Sometimes in comparative studies, the company-supported protocol used a relatively low dose of its own sponsored drug or the competing drug to accentuate efficacy or side effect differences from its rival. Examples include a slightly high but reasonable mean dose of 15.7 mg/day of olanzapine compared with a clearly substandard mean dose of 201 mg/day of clozapine for weeks 2 through 18 (Bitter et al., 2000), and a low mean dose of 102 mg/day of fluvoxamine compared to a moderately high mean dose of 34 mg/day of fluoxetine after week 7 (Rapaport et al., 1996). Another skewed design can be achieved by altering the customary timing of the drug administration. For example, in one study comparing paroxetine with amitriptyline, the amitriptyline was administered twice daily, which led to a prominent degree of daytime sleepiness (Christiansen et al., 1996).

Using Self-Serving Measurement Scales and Making Misleading Conclusions From Measurement Findings

Some researchers use unpublished rating scales, and as a group, these are said to constitute "a major source of bias in randomized controlled clinical trials" (Marshall et al., 2000). Clearly, industry-sponsored researchers use rating scales that will attain the most favorable result for their product (Sheehan, 1999).

In studies of risperidone versus placebo and haloperidol, drug company–sponsored researchers utilized the "worst EPS score" to compare differential EPS changes (Chouinard et al., 1993; Lemmens et al., 1999; Marder and Meibach, 1994; Simpson and Lindenmeyer, 1997). They reported that after a brief washout period, risperidone at doses of 2 to 6 mg/day given to chronically medicated schizophrenic patients evidenced the same degree of EPS as placebo. The company's marketing personnel widely circulated this result (Janssen Pharmaceutica Research Foundation, 1996; Borison et al., 1992), which misled many to assume that risperidone at doses of 2 to 6 mg/day did not cause EPS, because obviously a placebo given to treatment-naive subjects would not cause them. However, risperidone can indeed cause EPS in customary doses (Ho et al., 1999; Lane et al., 2000; Mullen et al., 1999; Rosebush and Mazurek, 1999). Using a "worst EPS score" can give quite different and potentially misleading results compared to final total EPS scores or last recorded

observations (Tollefson et al., 1997a). Fortunately, most investigators at this time now use total and last observation scores to evaluate EPS rating changes from baseline (Bondolfi et al., 1998; Marder et al., 1997; Wirshing et al., 1999).

Another example involves defining treatment success using a 20% or greater decline in a symptom severity rating score. Patients with schizophrenia may achieve a 20% decline in the Brief Psychiatric Rating Scale scores and yet remain "profoundly disabled" (Gilbody et al., 2002). A further example involves defining treatment success as at least a 25% decline from baseline on a rating scale score for symptom severity for youths with attention deficit hyperactivity disorder (ADHD). In an industry-sponsored study, the majority of the groups that received the company product and methylphenidate achieved this goal and were thus deemed equivalent in their response. However, the cutoff score was so modest that 32% of the placebo subjects also met this standard (Heilgenstein et al., 2000), which was more than double the customary placebo response in ADHD stimulant studies (Greenhill et al., 2001). Presumably, if a standard symptom reduction cutoff score had been used, the reported drug equivalency would not have been achieved.

Selecting the Major Findings and Endpoints Post Hoc

Kessler (1992) refers to comparative drug studies wherein "the putative advantage is related to an endpoint that was not the primary hypothesis tested by the study" (p. 950). He adds, "such claims of superiority often depend on an analysis of multiple endpoints, a practice often referred to as *data dredging*." Thus, it is unclear whether a seven-week study had been originally designed to be an eight-week study. More suggestive is the side effect comparison of venlafaxine and fluoxetine that was done one week into treatment (Silva, 1998), which suggests that something was left out that would apply to a more meaningful assessment period.

As Schooler (2000) pointed out in her review of two industry-sponsored comparative drug trials, "perhaps in each case the researchers examined all the scores and reported only those that looked best for their drug" (p. 13). Carpenter (2001) likewise noted that industry studies "showing a superior effect of the sponsor's drug may be the result of scores of analyses searching multiple variables and reporting those that show an advantage" (p. 13). Tamminga (2000) similarly observed that in industry-sponsored studies "the distinction between the a priori hypothesis and the secondary analyses is often lost" and a "whole rash of secondary analyses are used to present the results" (p. 5).

Masking Unfavorable Side Effects

Reports of sexual side effects from selective serotonin reuptake inhibitor (SSRI) antidepressants range from 2% to 73% depending primarily on whether side effects were elicited merely by open-ended questioning or by a detailed inquiry (Modell et al., 1997; Montejo-Gonzalez et al., 1997; Zajecka et al., 1999). Reports by sponsoring pharmaceutical companies tend to downplay sexual side effects of SSRIs by using open-ended or nonspecific questions about side effects (Zajecka et al., 1999). In one instance, a drug company–sponsored review covering over 3,000 subjects treated with SSRIs simply did not list any sexual side effects on its 23-item side effect table (Preskorn, 1997). At the opposite extreme, researchers from competing companies emphasize the high rate of sexual side effects with SSRIs when their drug has a lower rate. These investigators ask specific questions in order to bring out the high rate of sexual side effects that characterize SSRI treatment so as to favor their product's side effect profile (Croft et al., 1999).

Repeatedly Publishing the Same or Similar Positive Studies to Increase the Impact

Obviously, pharmaceutical manufacturers want to make sure that reports of their drug's advantage over competing drugs in sponsored research receive wide circulation. Their supported researchers consequently submit relatively similar findings to different journals, each with a slightly different emphasis but stressing the main themes. They also publish reviews of these same findings (Gilbody and Song; 2000; Huston and Moher, 1996). Examples repeatedly showing an EPS advantage with one second-generation neuroleptic over high-dose haloperidol include prominently overlapping articles by one pharmaceutical company–supported team (Beasley et al., 1999; Lane et al., 2000; Tollefson et al., 1997b; Tran et al., 1997a,1998) and a very similar duplication of articles from another firm's second-generation neuroleptic—which is well described by Huston and Moher (1996). Still another pharmaceutical company followed this same pattern, sponsoring five studies comparing sertraline or fluoxetine with bupropion SR in order to reiterate the point about their drug having fewer sexual side effects than SSRI drugs (Coleman et al., 1999; Gil-

body and Song, 2000; Kavoussi et al., 1997; Segraves et al., 2000; Walker et al., 1993). An editorial in *JAMA* by Rennie (1999) discussed in depth this problem of publication duplication.

Selectively Highlighting Findings Favorable to the Sponsor

The selective reporting of the findings in industry-sponsored trials has merited criticism from experienced investigators (Carpenter, 2002; Davidoff et al., 2001). In this regard, Schooler is quoted as follows: "They emphasize those parts of the data that are most favorable to their drug" (Moukheiber, 2001, p. 268). As an example, in the placebo-controlled clinical trial comparing the effect of two antidepressants with each other to reduce anxiety symptoms, the abstract totally ignored the fact that the placebo effect for anxiety was in most respects comparable to that of the two antidepressants and that it resulted in far fewer side effects (Trivedi et al., 2001). Likewise, two studies mentioned an early treatment response of the sponsor's drug in their abstract but did not mention that this relative benefit was no longer present by the end of the study (Claus et al., 1992; Wheatley et al., 1998).

Editorializing for the Sponsor in the Abstract

In the seven-week study comparing fluvoxamine and paroxetine, the patients receiving paroxetine were given (at week 7) a substantial mean dose of 36 mg/day, whereas patients receiving fluvoxamine were given a relatively low mean dose (at week 7) of 102 mg/day. Certain side effects were understandably higher in the paroxetine group. In their conclusions, the authors advised, "when a patient has difficulty tolerating one SSRI, the clinician may choose to change to a different agent within the same class" (Kiev and Feiger, 1997).

In another study, risperidone treatment was shown to be comparable in efficacy and side effects to pimozide in the treatment of Tourette's disorder. Two relatively minor differences favored risperidone, leading the authors to conclude that "risperidone may become the first-line treatment of Tourette's disorder, owing to a more favorable efficacy and tolerability profile" (Bruggeman et al., 2001, p. 50).

Publishing the Obvious to Emphasize a Point

It is known from placebo-controlled clinical trials that certain second-generation antidepressants have far fewer sexual side effects than SSRIs. Thus, it is not necessary to repeatedly compare that side effect between these drugs; the result is obvious beforehand. Likewise, it has long been known that tricyclic antidepressants (TCAs) are a risk for older adults with heart disease (Roose, 1992). Thus, the comparison of paroxetine with nortriptyline in older adults showing more cardiovascular problems with the latter drug (Nelson et al., 1999) does not add new information to the literature. In this respect, Shimm and Spece (1991) express concern about "scientifically uninteresting and inconsequential clinical trials" (p. 150). Kessler et al. (1994) view such scientifically unnecessary trials as "thinly veiled attempts to entice doctors to prescribe a new drug being marketed by the company. . ." (p. 1351).

Touting Nonsignificant but Favorable Differences and Negating Dropout Differences Statistically

Medical journal supplements provide numerous other examples of studies with small and modest-sized samples that report an advantage of one drug over another but avoid analyzing the difference statistically (Bero et al., 1992; Greene et al., 2000; Hotopf et al., 1997; Rochon et al., 1994a). One example of this frequent pattern is from a paroxetine-clomipramine comparative study. A statistically insignificant difference was used to justify the author's conclusion that paroxetine was "better tolerated" (Lecrubier and Judge, 1997).

One technique to accentuate a nonsignificant but supposedly favorable finding in a comparative study is to view it only in terms of relative risk (without presenting a range or confidence interval). This technique applied to a small sample often misleads and has reportedly influenced physician prescribing patterns (Bobbio et al., 1994; Brett, 1989, Feinstein, 1992).

When there is a substantial dropout of subjects before the end of a clinical trial, industry-sponsored researchers commonly use the last observation carried forward method to include the dropout data in the total results. This approach assumes a steady trajectory of the available findings from the dropouts—which is seldom the case (Allison and Casey, 2001). Consequently, it is usually preferable to avoid this form of statistical analysis (Schooler, 2000).

Selecting Subjects and Altering the Duration of Trials to Achieve a Favorable Outcome

Treatment resistance in schizophrenia research is not well defined (Brenner et al., 1990). Comparisons of

second-generation neuroleptics with one another and with haloperidol in short-term drug company–sponsored clinical trials of so-called treatment-resistant schizophrenic patients have resulted in findings that suggest that a number of second-generation neuroleptics (aside from clozapine) are very beneficial for these patients. Surprisingly, after only 6 and 8 weeks of treatment, 35% to 65% of patients so identified were found to respond to each of the new medications. However, these studies included a sizable number of patients whose treatment resistance was highly questionable (Marder, 1999). Bondolfi et al. (1998), for example, included both treatment-resistant and treatment-"intolerant" patients, and one half of the patients studied by Breier and Hamilton (1999) were outpatients (presumably less emotionally disturbed than inpatients).

The relatively brief clinical trials with olanzapine and risperidone suggested that these drugs were as effective with treatment-resistant patients as clozapine, the present "gold standard" of such treatment (Conley et al., 1999a). However, it must be noted that clozapine treatment may take up to one year to achieve maximum benefit (Lieberman et al., 1994). When drug treatment comparisons of an even longer duration (1 to 2 years) are made with chronically impaired schizophrenic patients, clozapine to an even greater extent produces the best results (Conley et al., 1999b).

Withholding Unfavorable Results

Drug company–sponsored clinical drug trials are for the most part not publicly recorded (Rennie, 1999), so that unfavorable trials can be kept from publication (Friedberg et al., 1999; Goldberg, 1999; Gwynne, 1999; Hillman et al., 1991; Lauritsen et al., 1987). This unfortunately is still a fairly common practice (Quick, 2001). The sponsoring company's control of publication is aided by confidentiality agreements signed by the investigators before any project is financed (Goldberg, 1999; Gwynne, 1999; Dickersin et al., 1987; Rennie, 1997; Shenk, 1999).

Masking Sponsorship

In multisite clinical trial studies, the pharmaceutical company designs the research—usually in consultation with some of the outside team—and then all the clinical investigators carry out the protocol (Council on Scientific Affairs, 1990). In some instances, the designers of the research do not put their names on the study, which makes the role of the pharmaceutical company less clear. This practice has been referred to as "ghost authorship" (Flanagin et al., 1998; Rennie and Flanagin, 1994). Related to this concern is the fact that some authors still do not disclose the financial sponsorship of the research (Krimsky et al., 1998).

Broader Drawbacks of Research Linked to Promotion

Lowers the Scientific Quality of Published Research

Friis (1999), in a lead editorial for *Acta Psychiatrica Scandinavica*, wrote that "the need of a company to increase sales of a new drug easily creates a climate in which it is virtually impossible for the company's own research department to produce unbiased studies of that drug" (p. 157). The research department, in the view of some, might then ". . .represent a subgroup of the marketing division, with the aim of producing scientific arguments for promoting sales."

Drug company–sponsored symposia (published as supplements) are far less carefully peer reviewed than standard research reports, and their papers are consistently appraised as more misleading than are others in the published medical literature (Bero et al., 1992; Cho and Bero, 1996; Rochon et al., 1994a).

Leads Physicians to Alter Their Prescribing Options

Studies show that drug company promotion of their own sponsored published research findings—often containing a selective presentation of the relative merits of their products and the drawbacks of competitive products—successfully influences physician prescribing practices (Chren and Landefeld, 1994; Spingarn et al., 1996; Ziegler et al., 1995). The use of "design-adjusted," drug company–sponsored medical publications that superficially appear like more scientifically solid research has been shown specifically to mislead physicians, resulting often in the prescription of relatively expensive and sometimes less appropriate drugs (Bero et al., 1992; Caudill et al., 1996; Spingarn et al., 1996).

Drug company–sponsored articles reporting positive clinical trials in medical journals frequently convey to physicians the impression that their prescribed pharmaceuticals produce more favorable results than is the case in community practice. For example, studies of brief and extended drug company–sponsored clinical trials with olanzapine ($N > 2000$) report a dropout rate due to weight gain of less than one half of one percent (Littrell et al., 2000; Tollefson et al., 1997b; Tran et al., 1999), which suggests that it was not a problem. Yet a

nationwide survey of 277 psychotic outpatients treated primarily with atypical neuroleptics reported that weight gain caused at least 25% of the medication nonadherence (Weiden et al., 2000), particularly for the obese, who were three times more nonadherent for this reason than were those of normal weight (Weiden, 2001). A second example of a misleading dependence on sponsored clinical trial data pertains to desmopressin for the treatment of nocturnal enuresis. In a company-supported comparative clinical trial, both a bedwetting alarm and desmopressin had relatively similar results during the treatment period, but no follow-up assessments were made (Longstaffe et al., 2000). However, two independent studies reporting the aftermath of similar comparative trials revealed that 3 to 12 months after the treatment ended only 10% to 18% who were treated with desmopressin ceased their enuresis, versus 42% to 56% who had been treated with the alarm (Monda and Husmann, 1995: Schulman et al., 2000; Wille, 1986).

Adds Unnecessarily to the Cost of Prescription Drugs

A me-too drug is a drug that has slight chemical differences from a frequently prescribed innovator drug so that the latter's patent is not infringed. Me-too drugs represent over 75% of all new drugs and are among the most heavily marketed (Garattini, 1997). The cost of marketing prescribed drugs in the U.S. was over 12 billion dollars in 1993, which exceeds the pharmaceutical industry's expenditure for basic research (Woosley, 1994). The cost of pharmaceuticals has risen far more than other products in the U.S. economy and is a particular burden for those senior citizens whose only medical coverage is Medicare (Soumerai and Ross-Degnan, 1999).

Tends to Have a Corrupting Effect on Researchers

The enticement of making a large amount of money by participating in drug company–sponsored clinical trials is not to be underestimated (Eichenwald and Kolata, 1999a; Eichenwald and Kolata, 1999b). Along with this involvement and financial aid go ever-present pressures to endorse or support the company's product (Nemeroff, 1998).

Tends to Distort the Knowledge Base and the Terminology in the Field

The findings from a large number of comparative clinical trials that are financed by pharmaceutical companies are commonly included in literature reviews and meta-analyses. Many are scientifically weak. Their inclusion in a review may well alter the conclusions of a reviewer (and therefore the reader). For example, Stahl (1999) and Ho et al. (1999), citing a drug company–sponsored study, accept the reported but misleading finding that "low"-dose risperidone has the same likelihood as placebo to induce EPS.

Likewise, certain terms that reflect a drug company's claim may enter into common medical usage. For example, the term 'mood stabilizer' is commonly applied in pharmaceutical company–sponsored studies to certain anticonvulsant and neuroleptic drugs as though they benefited mood beyond their acute and short-term anti-manic effects (Sobo, 1999).

The sheer weight of the company's many supposedly favorable studies has its own impact. The positive comparative findings of company-financed clinical trial research are widely disseminated and aggressively promoted. The fact that these findings are published in nationally circulating medical journals suggests to physicians and to the public that they have high-level approval from within the medical establishment.

Limits Research Autonomy

Confidentiality agreements between the researcher and the sponsor delay research reporting and occasionally impede publication of findings deemed undesirable by the sponsoring company (Blumenthal, 1996; Chalmers, 1990; Dickersin et al., 1987; Phillips and Hoey, 1998; Rennie, 1997, Shuchman, 1998).

Influences Physicians to Decrease Their Prescriptions of Less Costly Medications That Have Equivalent Efficacy

Once second-generation neuroleptics became viewed as first-line medication treatments, physicians increasingly bypassed their neuroleptic predecessors—ones that, though still very useful, are no longer promoted. First-generation neuroleptics as a group cause far less weight gain than their successors (Allison et al., 1999) and their side effect profiles are much better established. A recent meta-analysis of available data comparing conventional with second-generation neuroleptics by the National Schizophrenia Guideline Development Group of Great Britain concluded that they had equivalent efficacy and tolerability. Therefore, the group rec-

ommended that "conventional antipsychotics should usually be used in the initial treatment of an episode of schizophrenia unless the patient has previously not responded to these drugs or has unacceptable extrapyramidal side effects" (Geddes et al., 2000). In support of this, a four-week, independently funded study recently revealed that modest average doses of haloperidol (3.7 mg/day; $N = 212$) were equally as effective as average doses of risperidone (3.2 mg/day; $N = 34$) for neuroleptic-naive psychotic patients, and that at these doses, the two neuroleptics had similar results on the development of EPS (Rosebush and Mazurek, 1999).

In like manner, independent reviewers have concluded that tricyclic antidepressants—whose proportional use has prominently decreased in the 1990s (Hirshfeld, 1998)—are as efficacious for the treatment of depression as SSRIs (Anderson, 2000), although they are far more hazardous in overdose. Furthermore, for certain depressive subtypes (*e.g.*, melancholia), the first-generation antidepressants appear to be more effective than SSRIs (Parker et al., 2001). Nonetheless, both second-generation antidepressants and second-generation neuroleptics are routinely reported to be "first-line agents" by opinion leaders who wield great influence when they present industry-sponsored studies at professional meetings.

Conclusion

The concerns raised herein relate largely to the very expensive, often misleading, and commonly wasteful drug trial comparisons of similarly effective drugs that are sponsored by major pharmaceutical companies. In response to these concerns, numerous articles and editorials written over the last two decades in medical journals have focused on: "conflicts of interest," "scientific misconduct" (Chalmers, 1990), "is medicine for sale?" (Angell, 2000a), "commercial sources of influence" (Avorn et al., 1982), and "the industrialization of clinical research" (Rettig, 2000). Furthermore, ethical practice guidelines have been written by the Food and Drug Administration and professional medical organizations to limit conflicts of interest between physicians and pharmaceutical company representatives (Goldfinger, 1990; Zappala, 1998).

Although legal restraints have curtailed some excessive industry financial incentives to physicians, the financial power of the big pharmaceutical companies continues to make them far and away the dominant vendors of clinical research (Bodenheimer, 2000; Silversides, 1998). So, however forceful, the overall influence of the editorials and guidelines of organized medicine appears to be meager.

The major pharmaceutical companies are extremely successful financially (Angell, 2000b), such that they can afford to spend an average of 23 to 30 cents of every dollar of the wholesale cost of trade name prescription medications on promotional marketing (Barry, 2000; Stolberg and Gerth, 2000; Wolfe, 1996). Likewise, fully one third of the American Psychiatric Association's annual income is derived from pharmaceutical companies (Borenstein, 2000). Such financial resources allow the industry to succeed handily in influencing physician practice and determining the bulk of the U.S. drug research agenda (Avorn et al., 1982; Lexchin, 1993; Peterson et al., 2000). With these financial advantages, the adage continues to apply: those who pay the piper call the tune.

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