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Commentary

How the Doctor Can Counter Commercial Bias in the Dissemination of Pharmacotherapeutic Knowledge

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There are many issues and much concern with the methods by which pharmaceutical companies seek to influence clinical decisions and increase market shares for their products. Safer (2002) cites key articles in the professional literature and criticizes 13 aspects of commercial influence. He argues that this influence creates a substantial bias in the creation and dissemination of drug treatment knowledge and notes adverse effects on scientific knowledge, clinical practice, and health economics. The issues are general to medicine, but are presented in the context of pharmacotherapy for mental disorders. This is timely in that the number of patients, the number of drugs, and the number of dollars in this marketplace is rapidly expanding. So, too, is the knowledge base, but the lion's share of data and opinion which inform and influence physicians is developed and disseminated by the entities which make and sell the drugs, or, as Safer notes, in collaboration with opinion leaders drawn from academia and clinical practice. From the commercial side, this is legitimate business practice. But it is also a matter of public concern (DeAngelis 2000; Press and Washburn 2000; Peterson 2000; Cohen 2000). Patients are entitled to informed and objective therapeutic advice, and physicians should meet this responsibility. This is difficult to achieve when vast sums are spent influencing physician decision-making combined with direct marketing to the public and substantial commercial support of professional societies, medical journals, advocacy organizations, academic opinion leaders, and practitioners. The public is justified in questioning the profession's ability to deliver evidenced-based therapeutics based on objective and critical evaluation of relevant data.

It is easier to share Safer's concern than to propose solutions. Angell (2000) seems to call for a "just say no" strategy, but even the *NEJM* has trouble finding authors for drug updates when requiring the requisite expertise and the absence of financial ties with industry. Safer increases sensitivity to the issues, but does not propose remedial actions. Bodenheimer, in particular, has identified how commercial bias influences clinical trials' results (Bodenheimer 2000) and Klein has made recommendations to improve the quality of clinical trials and proposed methods to address the dual problem of data mining and suppression of negative findings (Klein et al., 2002). Leading medical journals have recently adopted rules that will reduce ghost-authored reports and academic authors fronting for analyses without full access to commercial data or an unfettered right to make public all findings. I have commented elsewhere on aspects of this problem (Carpenter 2002; Carpenter and Conley 2001), and believe each of the stakeholders in evidence-based pharmacotherapy can improve the quality of knowledge dissemination.

Post-marketing phase IV studies rarely address issues most important to clinicians, but routinely report "our drug is better than their drug" analyses using clinical trials as marketing devices. Journal editors and reviewers appear to give a soft ride to manuscripts that report the sponsor's advantages without disclosing data-mining techniques and which unhelpful findings were suppressed. In the absence of clinically and statistically meaningful findings, terms such as "numerical superiority" and "the possibility of superior efficacy requires further study" are used to describe advantages of the sponsor's drug. Academic investigators sometimes participate in commercial science without the authority

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to make data public regardless of findings. Some academic leaders receive very substantial incomes from industry, and neither universities nor federal research agencies have established rules of engagement which would satisfy the public that broad and effective procedures are in place to assure reasonable independence of academicians as they address drug therapy issues. Recent activity by the Department of Health and Human Services' Office for Human Research Protection and the American Association of Medical Colleges is encouraging and may lead to new guidelines addressing potential conflict of interest issues as individuals and their institutions engage with commercial entities (Agnew 2000; Korn 2000). It seems less likely that professional societies and health advocacy groups, which find their financial affairs importantly dependent on industry support, will be effective in addressing these issues. The term "drug fair" is increasingly used to describe professional meetings under the auspices of learned societies.

Each of the many issues raised by Safer, including those noted above, requires remedial action. However, in this commentary I will suggest that the doctors can improve the situation by becoming more critical recipients of information. Several suggestions as to how this can be accomplished are put forward. These suggestions also may be helpful to patients and their families as they become increasing knowledgeable. Illustrations are drawn from experience with antipsychotic drug trials in patient subjects with schizophrenia.

1. Doctors receive much continuing education as passive recipients of industry-sponsored material. This can be balanced with access to objective sources of information. There is far too much literature for busy clinicians to master. Study design and analytic strategies may require extensive expertise for critically appreciation. The Cochrane Group regularly and systematically evaluates therapies in several medical fields. In mental disorders, they summarize findings and apply sophisticated meta-analytic approaches to data from drug and interpersonal therapeutic studies. Internet access facilitates use (http://www.ihs.ox.ac.uk/csg.html). Doctors need to contrast this source of information with the often far more favorable evaluation of drug treatment contained in sponsored educational activities. Adis (http://www.adis.com) provides another source of peer-reviewed academic reviews of effects of psychotropic drugs. Findings from these sources on efficacy and effectiveness of new generation antipsychotic drugs stand as a conservative contrast to the more enthusiastic assessments in sponsored dissemination activities.

2. Study the reports and conclusions of experts who independently evaluate clinical trials data. This will sometimes be in federal- or foundation-supported clinical trials. But the large data sets are usually industry multicenter trials. Two approaches have particular merit in interpreting industry studies. One is a systematic and independent analysis such as conducted in the Schizophrenia PORT (patient outcomes research team) and reported by Lehman and colleagues (Lehman et al., 1995). In this instance, experts and various stakeholders were supported with a federal grant to assess all relevant data relating to drug and psychosocial treatment of schizophrenia. Another approach has been taken by Davis and Chen (Davis and Chen, 2001; Davis and Chen 2002). These academicians gained unrestricted access to large, commercial data sets and were able to conduct their own analysis and report results without industry supervision or capacity to suppress findings. Such access is difficult to arrange, and I have personally failed each time I have attempted to access data sets from industry to conduct an independent analysis on negative symptom efficacy of new antipsychotic drugs. But the Davis and Chen success could become routine if Klein's recommendations for improving the quality of information from clinical trials is accepted. Look for refereed drug treatment reviews in high quality journals prepared by experts you trust. Kane's drug therapy update in the *New England Journal of Medicine* is an example (Kane 1996), and an academic work group addressed key issues in schizophrenia therapeutics and reported in a recent issue of the *Schizophrenia Bulletin* (Marder et al., 2002).

3. Stay familiar with treatment guidelines developed by independent work groups. The American Psychiatric Association develops consensus guidelines including one for schizophrenia (APA 1997). Miller has led a group of experts in formulating the Texas treatment guidelines with a process for continuing updates (Miller 1999; Rush, et al., 1999).

4. Ask questions. Whether a dinner talk, a symposium, or private visit from a sales representative, be skeptical and ask for the information you need to judge the issues. When hearing about a side effect advantage of a drug, ask about the full profile of adverse effects. If an EPS advantage is reported, say "great" and ask about sexual dysfunction, weight gain, alteration of risk profiles for diabetes and cardiovascular disease, and prolongation of the Q-T interval. If it is reported that "our drug has superior efficacy," then ask if the FDA has approved the claim. In any comparison study, ask what drug and at what dose. It is difficult to design a level playing field when comparing two drugs. Optimal dose is

usually not known, especially at the time comparative trials are being conducted for marketing purposes. Five to 10 mg/day haloperidol is usually better than 20 mg/day, and 4 mg/day risperidone is better than 8 to 10 mg/day. With the dosing issue in mind, it is easy to see how the impression of superior efficacy can be created by the study design rather than efficacy differences innate to the compounds.

5. Sometimes related to dose, another design contribution to the appearance of superiority is the Last Observation Carried Forward (LOCF). This is a common analytic strategy to deal with the problem of subjects dropping prematurely from a study. But if attrition rates are not random between the drugs being studied, a bias is common which usually favors the new or experimental drug. This, perhaps more than any other factor, has fueled the claims of superior antipsychotic efficacy of second generation "atypical" drugs. Keeping in mind that the FDA has approved a superiority claim only for clozapine in treatment refractory patients, how has LOCF supported the "new drugs are superior" message? Patients agreeing to be subjects in a new drug study have some relevant attributes. They are not likely to be doing well on their first generation drug (note how the playing field is already tilted when comparing first and second generation drugs—imagine comparing aspirin to ibuprofen for pain selecting patients who are dissatisfied with aspirin). Both patient subject and doctor will be hoping the new drug is better, and hoping the patient receives the new drug. With a substantial dose of haloperidol, EPS and dysphoria quickly suggest that the coded medication is not the hoped-for new drug. The subject may simply stop participating from disappointment, but the experimental drug may be made available open-label once study participation ends. These sorts of issues lead to a nonrandom attrition, with subjects leaving the study earlier on the first generation comparison drug. A subject who stops a 10-week study at the third week will have their 3-week symptom scores carried forward to be the end point rating [LOCF]. We know that antipsychotic drug effects gradually accumulate over time, and that 10 weeks of haloperidol is superior to 3 weeks of haloperidol. Therefore, a LOCF analysis will favor the drug condition with the lower and slower attrition rate. This is not proof of superior efficacy. It may reflect important effectiveness advantages if the same medication adherence advantage is associated with real clinical care experience. However, if it reflects patient and doctor desire for the experimental drug, the results will do more for marketing than for evidence-based clinical therapeutics.

Geddes et al. (2000) report that antipsychotic advantages of new generation drugs depend importantly on the dose of haloperidol used in the control group. The higher the haloperidol dose, the greater the new drug's advantages. If high dose haloperidol drives subjects to early attrition, it is apparent that LOCF analysis will reveal superior outcome for the experimental drug. Davis and Chen (2001, 2002), however, take a broader view of clinical outcome data and reach a somewhat different conclusion on advantages of new generation antipsychotic drugs. It is not important that these experts agree. Rather, it is important that doctors can access expert and dispassionate analysis of drug treatment data and appreciate the points of controversy and uncertainty and synthesize this information in their clinical decision-making process.

Keep in mind that reporting clinical trials data is similar to giving race results ("the winner is...") and guidelines are formulated to guide caravans with alternative routes if a dead end is encountered. The doctor is informed by study data and guidelines, but has a very different challenge. He or she must synthesize complex data and judge the best approach for one person. Doctors do not treat cohorts, they treat individuals. The slender schizophrenia patient with good health habits and an active sex life should not receive the same antipsychotic drug as the overweight, sedate, and nicotine-addicted schizophrenia patient who has a schizoid lifestyle.

I share many of Safer's views, but expect the pharmaceutical industry to continue as a major influence in educating physicians on the use of medications. The role of industry in education is legitimate from a business standpoint, and many of the educational activities are substantial contributions to the field. The challenge is to maximize the relevance and objectivity of industry sponsored clinical studies and dissemination of study results. I suggest that assertive, well-informed doctors will raise expectations of their "educators." But regardless of success in that venture, the physician has a professional and moral obligation to serve only the best interest of the patient. This requires a well-informed and critical clinician. Suggestions for high quality sources of information are noted above, and a few points of bias in study designs are noted in the hope that this information can be useful in balancing commercial influences.

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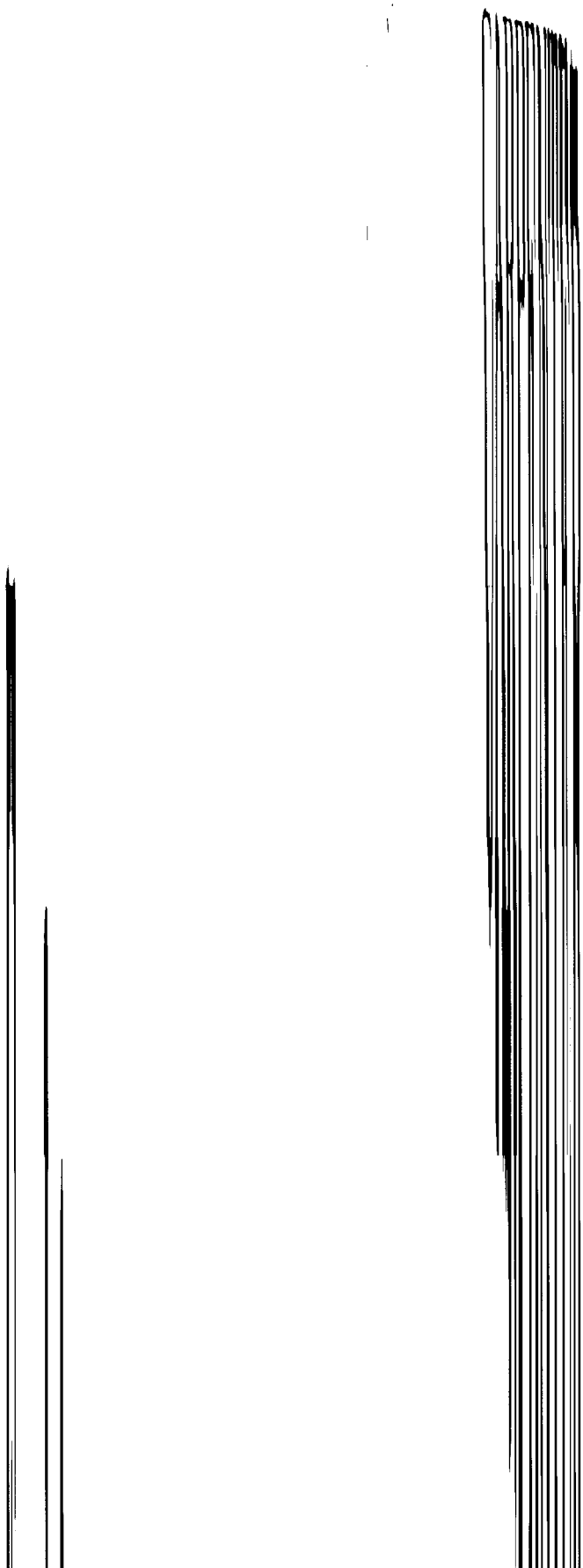

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