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The Hidden Costs of Financial Conflicts of Interest in Medicine

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A series of three articles by Lisa Rosenbaum [1–3] in the *New England Journal of Medicine* called for a reexamination of the views and regulations of financial conflicts of interest in medicine. Her conclusions appeared to be clear: 'The bad behavior of the few has facilitated impugning of the many' [3, p. 2067]. The effects of this behavior were amplified by journalists who fed a vicious cycle in which each story generates more distrust in the public. Dr. Rosenbaum suggested that current restrictive rules may 'undermine potentially productive research collaborations, dissemination of expertise, and public trust' [3, p. 2068]. She acknowledged that studies by pharmaceutical companies are more likely to have outcomes favorable to the sponsor [4] and that physicians who attend events funded by pharmaceutical companies tend to prescribe the featured drugs [5]. However, she claimed that these interactions might actually be beneficial to the patient and that much of the harm was 'invented'. Dr. Rosenbaum's views were in sharp contrast with the history of the journal where they were published. The *New England Journal of Medicine* pioneered the need of disclosure of financial conflicts of interests [6] and the importance of having authors of editorials and review articles free from commercial ties [7], yet time seems to be ripe for getting rid of these worries and to return to business as usual.

A recent viewpoint published in the *JAMA* [8] moves toward this direction. Also, these authors complain of the policies on conflicts of interest that were developed in reaction to a limited number of investigators but, once introduced, applied to all. They suggested substituting the pejorative term of 'conflict of interest' with 'confluence of interest'. A name change can be important. When withdrawal reactions started being described following the discontinuation of second-generation antidepressant drugs (selective serotonin reuptake inhibitors, SSRI) they were promptly labeled as 'discontinuation syndromes' [9]. The name successfully conferred a harmless nature, which was in sharp contrast with the withdrawal reactions that occurred with other drugs like benzodiazepines [10]. SSRI thus replaced benzodiazepines in the treatment of anxiety disorders, even though discontinuation syndromes of SSRI are actually withdrawal reactions [10], and the clinical evidence was pointing to just the opposite (benzodiazepines are more effective, with fewer side effects) [11]. The shift from benzodiazepines to SSRI has probably been the most successful achievement of pharmaceutical propaganda in psychiatry, with full endorsement of guidelines and professional societies [12]. Will the term 'confluence of interest' achieve the same success?

Let us examine the development of the problem, its implications and what can be done about it.

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The Development of the Problem

The term 'conflict of interest' is widely used but may entail different meanings. Margolis [13] distinguishes between conflicting interests and conflicts of interest. The former occur in any situation where competing considerations are presumed to be legitimate. Conflicts of interest, on the other hand, are characterized by individuals occupying dual roles which should not be performed simultaneously. Which roles? For instance, being a researcher and holding a financial interest in an area related to the research in which one is involved. Because of the potential for abuse, performing both roles at the same time is considered to be inappropriate. Conflicts of interest may be financial (such as being paid by a private firm or deriving a financial benefit from owning a relevant patent) or nonfinancial (such as allegiance to a school of thought or political commitment).

In the nineties, an impressive body of facts pointed to the dangers of conflicts of interest in medicine [14]. However, as with many cultural and scientific phenomena, these dangers tended to be overlooked, if not deliberately denied. The medical community was substantially unprepared to deal with the problem. Not surprisingly, appropriate regulations occurred in a comprehensive form only at the end of the subsequent decade [15], as an attempt to restore credibility after an endless series of scandals and not as a spontaneous development of professional societies for preventing biased research and corporate indoctrination.

At the beginning, the issue was whether specific episodes that emerged were the unavoidable drawbacks of a scientific system that functioned in a substantially independent way or whether they were simply the tip of the iceberg. Books such as Jerome P. Kassirer's *On the Take* [16] and John Abramson's *Overdosed America* [17] illustrated how corporate interest manipulated science, misled doctors and threatened the health of the community, and how medical journals and medical societies had a role in this. These and many other subsequent publications, such as Whitaker and Cosgrove's *Psychiatry under the Influence* [18], documented a systematic, even though not universal, phenomenon in clinical medicine. Jerome P. Kassirer, a former editor-in-chief of the *New England Journal of Medicine*, unlike Lisa Rosenbaum [1–3] acknowledged the positive role of investigative journalists in the public interest [16]. The iceberg started to become evident: corporate interest which results in self-selected academic oligarchies (special interest groups) that influence clinical and scientific information. Members of special interest groups, by virtue of their financial power and close ties with other members of the group, have the task of systematically preventing the dissemination of data which may be in conflict with their interests [14]. It is certainly not because of a few bad apples or the behavior of journalists that the medical field is being discredited in the general public.

The mechanisms of propaganda of Chomsky [19] may illustrate what has occurred in medicine in the past decades. Corporate interests have fused with academic medicine to create an unhealthy alliance that works against the objective reporting of clinical research (censorship), sets up meetings and symposia with the specific purpose of selling the participants to the sponsors (engineering opinions), gets its prodigal experts into leading roles in journals, medical associations and nonprofit research organizations (using the public relations industry) and provides the appropriate degree of retaliation to outliers (marginalizing dissident cultures).

When, in the early nineties, these mechanisms became operational in medicine there were several important obstacles: the presence of independent studies that could challenge sponsored findings, the potential influence of critical review articles and opinions by researchers devoid of financial conflicts of interest and the stubborn reliance of physicians on clinical judgment.

All these aspects were taken care of, and the clinician who wanted to retain a cautious and balanced attitude (for instance believing that the judicious use of benzodiazepines may be warranted) felt like the person whom Chomsky depicts as sitting alone in front of the TV, thinking he/she must be crazy or outdated for not buying what comes out of the tube [19].

The Growth of Evidence-Based Medicine: Meta-Analyses as the Marketing Arm of the Pharmaceutical Industry

The growth of evidence-based medicine (EBM) provided an ideal ground for multiplying the effects of financial conflicts of interest in medicine. Feinstein and Horwitz [20] were among the first to warn about the dangers of excessive reliance on randomized controlled trials and meta-analyses. It is not simply that trials sponsored by drug firms are more likely to report positive outcomes [4]. Selective publication, overstatements of benefits and minimization of risk appear to characterize clinical trial reporting funded by the industry, whether of drugs or medical devices [21]. In review articles or

textbook chapters, these effects could be much larger than publishing a single trial. It is a common belief that meta-analyses provide an objective appraisal of the state of the art in a specific field. Actually, during the developments of these analyses there are many steps that may involve highly subjective choices [22–24]: formulation of the question, collection of studies (published vs. unpublished, databases, key words, etc.), criteria for eligibility and selection of studies, evaluation of risk of bias, methods of data extraction and analysis, choice of assessment criteria, presentation of results and interpretation of data. All these issues may be affected by conflict of interest [23]. However, authors of meta-analyses are only required to disclose their financial interests and are unlikely to detail the source of funding of the studies that were included. In a recent paper, Ebrahim et al. [25] examined conflicts of interest in meta-analyses concerned with antidepressant drugs. In nearly two thirds of cases, the authors were either employees of the assessed drug manufacturer or had some industry links. In these cases, negative or simply cautionary statements in the concluding statement of the abstract were unlikely to appear [25]. EBM, with its emphasis on systematic reviews and guidelines, offered an unprecedented marketing arm to special interest groups [26]. The risk is particularly serious in view of the fact that financial conflicts of interest are substantial in medical societies and guidelines for authors [27, 28]. A major hidden cost is entailed by the influence of financial conflicts of interest in textbook chapters, reviews and guidelines: physicians are forced into prescribing patterns that are detrimental, costly and that clash with clinical reality, as portrayed by the substitution of benzodiazepines with antidepressant drugs in anxiety disorders [9–12].

The Rise of Censorship

Special interest groups have thus been using EBM to enforce treatment through guidelines, advocating what can be subsumed under the German language term of 'Leitkultur', which connotes the cultural superiority of a culture, with policies of compulsory cultural assimilation [29]. Pluralism is threatened by the 'Leitkultur' of EBM, as well by the increasing weight of open access publications, which set a financial threshold for contributions and hinder the type of research (such as that concerned with the reporting of side effects) that is not funded [29]. Not surprisingly, ghostwriting has become an increasingly common practice in medical publishing [30]. Presentation of data and use of words may be more effective than having or not having significant results.

Traditionally, financial conflicts of interest have been viewed in relation to the pharmaceutical corporations [1–3]. The booming of the biotechnology industry (including genetic and imaging research) has created unprecedented opportunities for investigators to become entrepreneurs and pursue commercialization of their discoveries and/or skills. At times, this occurs while remaining within the academia – at other times by moving directly to the private sector, as exemplified in the case of the head of the National Institute of Mental Health leaving for a major corporation [31]. Such partnerships entail major challenges in terms of regulations.

Intellectual freedom is required to balance and interpret conflicting interests and viewpoints that are an integral part of reviews of scientific developments. The presence of financial conflicts of interest may be a threat to such freedom and the risk is most increased in operations of knowledge synthesis, such as reviews and editorials. As suggested by a survey of journalists [32], it is self-censorship which may yield the most dangerous effects. In journalism it is rather common and eliminates the need for formal cuts and modifications [32]. In the medical literature it occurs when an investigator omits raising questions and criticism for fear of swimming against the tide. Intellectual independence requires psychological autonomy, defined as the capacity of being self-determining and able to resist social pressures [33], which in a grant-seeking environment may be difficult for investigators. This is another hidden cost of financial conflicts of interest and 'Leitkultur' in medical research.

The End of the Journal Era?

In a recent editorial, Harlan M. Krumholz [34] described the end of medical journals as the main vehicle of dissemination of knowledge in medicine. In current terms of communications technology, journals are obsolete: they are too slow, expensive, limited in the configuration of articles despite online supplementary information, arbitrary in their peer review processes and too parochial [34]. Further, the journal publication is a static product: it can be corrected or retracted, but it is not interactive and has no capacity for iterative changes stimulated by input from audiences. Finally, open access publications, from the author's perspective, are like 'a restaurant in which the customers cook the meal and then pay the bill' [34]. Will a new world that is flat, digital and

transparent provide the answer, as Krumholz suggests, or will it facilitate the influence of corporate interest in medical information and lead to increasing costs for the society?

In the same vein, medical conferences still follow an obsolete, antiecological pattern. Society meetings are still held on an annual basis, with thousands of people travelling to reach the sites to hear medical news that is already available [29]. They reflect a 20th century communication paradigm, where meetings were the main source of scientific novelties compared to printed journals. Most meetings are a waste of energy and time, with minimal opportunities for professional growth and reflections.

What Can Be Done?

The hidden costs to the society of financial conflicts of interest in medicine need to be addressed at various levels.

Definition of Financial Conflict of Interest

A quantitative threshold for financial conflicts of interest is claimed to be difficult: a bagel or one million dollars does not seem to make a difference [1–3]. However, a qualitative differentiation based on the work by Krimsky et al. [35] appears to be possible and was indeed tested. This definition of a substantial conflict of interest is based on the dangers of the continuity of a financial relationship with a private corporation, as outlined in table 1. Occasional consultancies, grants for performing an investigation or receiving honoraria or refunds in specific occasions would not be a source of substantial conflict of interest. Indeed, it would be perfectly legitimate and essential for the progress of science for an academic physician to collaborate with the industry on specific scientific projects. Researchers with substantial conflicts of interest are not suitable for writing and participating in reviews, editorials, meta-analyses and guidelines, since the continuity of their ties may affect their knowledge synthesis. In this sense, the long-standing policy of the *New England Journal of Medicine* [6, 7] still finds a justification and represents a protection of intellectual freedom that should characterize the most influential papers.

Alternative Modalities of Academia-Industry Collaboration

An issue that was not discussed in Rosenbaum's update [1–3] concerned some new modalities of academic-industry interaction. For instance, the industry may interact with academic investigators through consulting agreements that benefit the university but not the investigator, eliminating any source of direct financial benefit for the individual from the company. This form of interaction is quite different from the marketing collaborations disguised as scientific consultations that have characterized academic medicine [14]. A definition of conflict of interest based on qualitative criteria (table 1) and new modalities of interactions between industry and academic researchers may thus yield improvements in clinical science.

Table 1. Criteria for the presence of substantial conflict of interest of a researcher

The researcher meets at least one of the following:
(1) Being an employee of a private firm
(2) Being a regular consultant or on the board of directors of a firm
(3) Being a stockholder of a firm related to the field of research
(4) Owning a patent directly related to the published work

The Pursuit of Critical Thinking in Clinical Practice and Research

Preserving intellectual freedom in the setting of proliferating connections between pharmaceutical and biotechnology industries and the physicians is a major ethical challenge of medicine today. Loosening rules that were developed over an incredible sequence of scandals and jeopardized the credibility of medicine would not offer a suitable solution. Unfortunately, in the past decades mainstream major journals have published faulty meta-analyses, industry-financed reviews and ghostwritten articles. As Wilkes [36] commented on the consequences of inappropriate industry-physician interactions: 'When trust goes, so does the healing power of physicians.' Similarly, medical journals do not lose their function to the extent that they foster critical thinking as to clinical matters and do not lose their credibility. Such critical thinking may also be increased by the opportunity at scientific meetings for in-depth discussions among clinical scientists with no substantial conflicts of interest – a pause from information overload [29].

The Inadequacy of EBM

Recently, Richardson and Doster [37] suggested the consideration of three dimensions in the process of evidence-based decision: *baseline risk* of poor outcomes from an index disorder without treatment, *responsiveness*

to the treatment option and *vulnerability* to the adverse effects of treatment. EBM is focused on the potential benefits that therapy may entail as to baseline risk, but it is likely to neglect the other two dimensions. A rational approach to treatment takes into account the balance between potential benefits and adverse effects applied to the individual patient [26]. The achievement of such balance is hindered by the difficult integration of different sources of information. Guidelines tend to place emphasis on systematic reviews and meta-analyses of RCT, which are uniquely geared to highlighting benefits. The clinician needs to have a clear account of the potential benefits of a specific treatment, as well as of the predictors of responsiveness and of the potential adverse events that may be triggered by the therapeutic act. The conceptual model that has generated EBM and guidelines clashes with clinical reality and fosters a dichotomy between medical science and clinical judgment. EBM certainly made an important contribution to questioning unsubstantiated therapeutic claims. Time has come, however, to become more aware of its considerable limitations, including overall reductionism, disregard of patient-physician relationships and patient preferences, and insufficient consideration of problems related to financial conflicts of interest [26].

Support of Researchers Free from Substantial Conflict of Interest

At the same time, researchers without substantial conflicts of interest need support. Otherwise, the scientific community would soon drain itself of a reservoir of truly independent experts who can be called upon to advise policy makers on the safety and efficacy of treatments, the hazards of chemicals and the safety of technology [35]. Lines of support for independent researchers, including priority for obtaining grants from public agencies supported by taxpayers' money and for editorship positions in medical journals, have been outlined [38].

Boycotting Commercial Medical Education and Professional Societies

The process of regaining intellectual independence does not only involve researchers but also each clinician and society member. Fugh-Berman and Hogenmiller [39] suggested that, in many cases, CME stands for Commercial Medical Education and argued that avoidance of industry-sponsored CME is associated with more rational prescribing [40]. The misleading indications of Commercial Medical Education are more dangerous when sponsoring is subtle and not clearly disclosed. Similar considerations may apply to certain professional societies that are inadequate in handling issues related to conflicts of interest and produce guidelines that are biased. Boycotting such initiatives and societies may yield important effects. Such stands have personal costs but are in line with the expression of intellectual freedom.

These concerted actions may not only address many of the problems entailed by the presence of researchers with conflicts of interest in medicine; they may also foster an intellectual renewal of medical research and thinking.

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