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Diagnosing Conflict-of-Interest Disorder

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Big Pharma works in subtle but powerful ways inside the pages of the Diagnostic and Statistical Manual of Mental Disorders.
By Lisa Cosgrove

In June 2010, the Association of American Medical Colleges issued the third and final portion of its conflict-of-interest policy initiatives. The task force on "Conflicts of Interest in Clinical Care" did not mince words when it described the impetus for these initiatives: "It is imperative that the possibility or perception of [financial conflict of interest] be advertently examined and appropriately evaluated to ensure that academic medicine in all of its missions is fundamentally dedicated to the welfare of patients and the improvement of public health."

This report is especially timely because of recent questions raised by investigative journalists and policy makers about the extent of industry influence on the diagnostic guidelines of the American Psychiatric Association (APA). Much is at stake: the APA's *Diagnostic and Statistical Manual of Mental Disorders (DSM)* is often referred to as the bible of psychiatric disorders because of its enormous influence on clinical practice, affecting such disparate domains as jurisprudence and insurance claims. The APA also produces and disseminates clinical-practice guidelines directly tied to *DSM* diagnoses. Thus, publication of the *DSM-V*, scheduled for 2013, will not only generate millions in additional revenue to the APA but also affect what health practitioners prescribe to patients. The people responsible for determining whether a new diagnosis should be added to the *DSM*, or whether the *DSM*'s descriptions of symptoms for current disorders need revision, should not benefit financially from their recommendations. For example, if a *DSM* panel member is a major stockholder in a pharmaceutical company that manufactures a drug used to treat a disorder, a clear conflict of interest exists.

In response to concerns about conflicts of interest expressed by researchers, clinicians, patient groups, and even people who served on committees for previous revisions to the DSM, the APA has increased transparency. Specifically, the APA has required all taskforce and panel members to post disclosure statements in which they identify financial ties to industry. The transparency provides an opportunity to assess the subtle but powerful ways pharmaceutical-industry influence may continue to play a role. It is critical not only to look at the proposed changes but also to examine what remains unchanged sixteen years after the *DSM-IV* and a decade after the *DSM-IV-Text Revision* was published.

What Increased Transparency Reveals

At least three areas of concern emerge from a review of the first draft of the DSM-V.

1. *Despite transparency, financial associations with industry remain robust.* In May 2009, Harold Bursztajn, Sheldon Krimsky, and I described the results of our research on financial ties between *DSM-V* panel members and the pharmaceutical industry in the *New England Journal of Medicine*. Our research showed that nearly 70 percent of the DSM-V task-force members report having ties to the pharmaceutical industry. This represents a relative increase of 20 percent over the proportion of *DSM-IV* task-force members with such ties just a decade ago. But it is not only task-force members who have financial relationships with Big Pharma. Of the 137 *DSM-V* panel members (that is, workgroup members) who have posted disclosure statements, 77 (56 percent) reported industry ties, such as holding stock in pharmaceutical companies, serving as consultants to industry, or serving on company boards—no improvement over the 56 percent of *DSM-IV* panel members who were found to have such industry relationships. Some *DSM-V* panels still have a majority of members with industry ties. If financial conflicts of interest are not reduced, private-sponsor bias in research will be exacerbated.

2. *Attention to adverse side effects of medications is virtually nonexistent.* Previous editions of the *DSM*, including the latest text revision published in 2000, glossed over the side effects of psychotropic medications. Only two of more than seven hundred pages of the main body of the *DSM-IV-Text Revision* deal with diagnosing side effects of psychotropic medication, and there the focus is on movement disorders, such as Neuroleptic- Induced Tardive Dyskinesia (a disorder that may occur in patients taking antipsychotic medications). According to the *DSM*, Neuroleptic Malignant Syndrome (a severe neurological disorder that may occur in patients taking antipsychotic medications) includes symptoms such as "severe muscle rigidity, elevated temperature, and other related findings . . . [such as] incontinence, changes in consciousness ranging from confusion to coma, mutism . . ." However, discussion of this syndrome is limited to one paragraph.

Absent entirely is a discussion of life-threatening side effects of medication, such as diabetes and other metabolic conditions. A review of the recently proposed changes to the *DSM* at www.dsm5.org indicates that these omissions will be continued in the next edition. Information made publicly available by the APA suggests that the proposed revisions continue to be relatively silent on the issue of iatrogenic harm (that is, the harms or adverse effects that may result from the treatment). In fact, many of the revisions seem only to reinforce and expand the primacy of medications in the management of psychiatric disease. As noted in a 2010 paper, "The Public Health Consequences of an Industry-Influenced Psychiatric Taxonomy: Psychotic Risk Syndrome as a Case Example," in the journal *Accountability in Research*, a diagnostic manual that touts indications for medications but does not address their associated risks is on its face unbalanced and raises questions about industry influence. This omission is especially disconcerting given the extreme profitability of the psychotropic drug market and the burgeoning data regarding the highly problematic, even potentially deadly side effects— hyperglycemia, diabetes, metabolic syndrome, cardiac problems, sexual dysfunction— of commonly prescribed psychiatric medications, such as antidepressants and atypical (or "secondgeneration") antipsychotics. It is of additional concern that antidepressants are increasingly being prescribed for conditions other than depression—from hot flashes to headaches and back pain. Similarly, prescriptions of atypical antipsychotics have significantly increased since the U.S. Food and Drug Administration (FDA) approved

their use not only for schizophrenia but also for bipolar disorder and depression. More people than ever before are being exposed to these agents, including children and adolescents.

3. *There are significant gaps in the disclosure policy*. Unrestricted research grants were excluded from the APA's disclosure requirements, even though the monies from such grants can total hundreds of thousands of dollars or more. There also are no policies for managing indirect financial ties, such as industry funds that are pooled and given to academic departments, hospitals, and medical schools. Moreover, *DSM* panel members are allowed to resume their financial relationships with industry as soon as their tenure on the DSM panels is over. As Krimsky, Manisha Vijayraghavan, Lisa Schneider, and I discussed in our 2006 study "Financial Ties between *DSM-IV* Panel Members and the Pharmaceutical Industry," continuing (or resuming) these relationships after serving on a *DSM* panel raises ethical concerns. If an association with the pharmaceutical industry occurs after work on the panel is completed, panel members might be perceived as using, or might actually use, their prestige to leverage lucrative consulting arrangements with the pharmaceutical industry. Indeed, public trust in the independence of medical science is eroded when former panel members, who are valued highly (and paid handsomely) as "thought leaders," exert their influence on prescription practices through consulting, public speaking, and participation in industry-sponsored educational workshops.

The DSM, a Patent, and Big Pharma

Eli Lilly was originally scheduled to lose its patent on its blockbuster drug Prozac in 1999. Lilly was able to get another extension (by patenting a new formulation) six months before its original patent was about to expire. However, the pharmaceutical company had no way of knowing ahead of time that the FDA would grant approval for the new formulation and thus was certainly motivated to find another way to continue to enjoy Prozac's multibillion-dollar profits. In November 1999, Lilly submitted, and the FDA subsequently approved, its application for fluoxetine hydrochloride (Prozac) for the treatment of Premenstrual Dysphonic Disorder (PMDD). Shortly thereafter, women were inundated with direct-to-consumer advertisements encouraging them to consider the possibility that they might have PMDD. One of the most widely run TV ads showed a frustrated and irritated woman outside a supermarket trying to pull a stuck shopping cart out of its lineup. The voice-over in the ad states, "Think it's PMS? It could be PMDD. PMDD affects millions of women . . . but the good news is that your doctor can treat PMDD with a new treatment called Sarafem." What women were not told in these ads was that the psychotropic medication produced by Eli Lilly to treat PMDD was Prozac, relabeled as Sarafem and manufactured in pink and lavender pills. (Marcia Angell provides an illuminating history of what she calls "patent-extending games" in her 2004 book, *The Truth about Drug Companies: How They Deceive Us and What We Can Do about It*.)

The *DSM* can play a subtle but key role in the FDA's decision about whether to approve a new psychotropic drug. This is because, as Angell points out, the FDA does not simply grant approval of new medications; it grants approval based on a particular use or condition. When the FDA considers a new indication for a drug, there must be empirical support or well-accepted diagnostic criteria for that indication. For example, the minutes from the November 1999 FDA meeting show that Lilly had to provide evidence that PMDD was "distinct from other disorders that are characterized by affective symptoms such as, for example, major depressive disorder."

The design and structure of the *DSM*—what has been referred to as a "checklist" approach—not only conflates mental health treatment with psychopharmacology but also may create an industry-friendly situation. As prominent neuroscientist and psychiatrist Nancy Andreasen pointed out in her seminal 2007 paper "*DSM* and the Death of Phenomenology in America: An Example of Unintended Consequences," this checklist approach sacrifices validity for reliability: "*DSM* diagnoses have given researchers a common nomenclature—but probably the wrong one. . . . *DSM* diagnoses are not useful for research because of their lack of validity."

In an industry-dominated climate, assessing the validity of new *DSM* disorders becomes even more complex. As the Sarafem story makes clear, the lack of biological markers for psychiatric illnesses may set the stage for patentextending possibilities or approval of "me-too" psychotropic drugs that are not necessarily in the public's best interest. It is noteworthy that, in December 2000, the FDA sent a warning letter to Eli Lilly, mandating that Lilly cease using this ad for the following reasons: "The imagery and audio presentation of the advertisement never completely define or accurately illustrate premenstrual dysphoric disorder (PMDD) and *there is no clear distinction between premenstrual syndrome (PMS) and PMDD communicated*. . . . The advertisement is lacking fair balance because the graphics accompanying the audio presentation of the risk information are very distracting and minimize the important risk information." (Emphasis added.)

Conclusion

Revising the *DSM* is certainly an arduous task; panel members need to review carefully the *DSM*'s current design and structure, address conceptual issues, and make decisions about the validity and reliability of psychiatric diagnoses. The public's trust in psychiatry has been weakened by the many lawsuits against psychotropic drug manufacturers for, among other things, failure to report adverse side effects.

The medical field is at a critical juncture in terms of its professionalism and integrity. Although the APA has increased transparency of the *DSM-V*'s development over the last three years, transparency is a partial solution at best. As Carl Elliot, a professor in the Center for Bioethics at the University of Minnesota, astutely noted in 2009, improving public trust will require a focus on eliminating *practices* that allow for corruption rather than a focus on requiring *individuals* to disclose industry ties. That is, we have a social and systemic problem requiring a significant change in the current rules of the game. The rule changes include breaking what some have referred to as the "unholy alliance" among the FDA, the APA, and Big Pharma. In addition, the APA should institute a policy ensuring that no panel is dominated by members with ties to the pharmaceutical industry and that critics of industry are actively recruited on the various panels. If these changes are not implemented, questions will remain about whether organized psychiatry can be trusted to protect the public's health.

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