Restoring the Integrity of the Pharmaceutical Science Record: Two Tales of Transparency

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- Jon N. Jureidini, Jay D. Amsterdam & Leemon B. McHenry, The Citalopram CIT-MD-18 Pediatric Depression on Trial: Deconstruction of Medical Ghostwriting, Data Mischaracterisation and Academic Malfeasance, 28 **Int'l J. Risk & Safety Med.** 33 (2016)
- Joanna Le Noury et al., Restoring Study 329: Efficacy and Harms of Paroxetine and Imipramine in Treatment of Major Depression in Adolescence, 351 **Brit. Med. J.** 4320 (2015)

Inappropriate prescription and overconsumption of pharmaceuticals is one of the most pressing public health concerns in North America. Aggressive pharmaceutical promotion practices are widely recognized as a major contributing factor. Two recent medical journal articles provide further evidence of serious problems with the scientific record that has become an intrinsic part of pharmaceutical marketing. They document each in their own way the corruption of scientific practices in which academic scientists appear to play a significant role, but also indicate how the scientific community and civil society can help correct the record and expose misconduct. The papers further illustrate how legal tools can enable them to do so. They both affirm the importance of transparency, which many in the medical and health policy community increasingly support as essential to restore confidence in the science surrounding pharmaceuticals.

Jon N. Jureidini, Jay D. Amsterdam, and Leemon B. McHenry's paper in the International Journal of Risk and Safety in Medicine is a case study of how the pharmaceutical company Foster used a scientific publication to boost prescription of its blockbuster anti-depressant citalopram. A paper by Joanna Le Noury and colleagues in the British Medical Journal is the first publication produced as part of an innovative initiative by the scientific community aimed at correcting the scientific record on a host of pharmaceutical products. The study involves a reanalysis of the raw data of a Smithkline Beecham (now GSK)-sponsored published study on the efficacy of paroxetine and imipramine for the treatment of depression in adolescents.

That both publications deal with anti-depressants is not entirely surprising. They have been among the most prescribed—in fact overprescribed—drugs of the last decades. The vagueness of diagnostic criteria and the subjective nature of efficacy measurements in relation to most mental health conditions further facilitate data manipulation. Yet it should not lull us into thinking that the problems are restricted to psychiatric drugs. Both papers confirm what has been exposed in the medical and increasingly also the health law and policy literature for some time, and in relation to a variety of products: that industry control over the design, conduct, analysis, and reporting of clinical drug trials has turned many scientific publications into marketing tools. It has enabled the industry to selectively report positive results, hide negative results, manipulate statistical tools for favorable outcomes, and underplay problems.

The Jureidini et al. analysis, based on data unsealed by a U.S. court as part of a court-approved settlement in a class action litigation procedure, provides fascinating evidence of how a company can conspire with a medical writing agency and—certainly indirectly—academic scientists, to use flawed scientific publications as marketing tools. The authors obtained access to a host of documents, including correspondence, e-mail exchanges, protocols, trial results, and drafts of ghostwritten documents. They examined the original protocol and clinical trials data of a study on citalopram's efficacy and safety for

the treatment of major depression with the final published outcome. Their unsurprising conclusion is that the published paper mischaracterized primary outcomes and adverse events, hid negative secondary outcomes, and added post hoc outcomes that put a more positive spin on the data. Their analysis of the correspondence and e-mails between the medical communications agency and company marketing officials interestingly reveals that the paper was entirely written in-house and explicitly approached as a PR document. Yet, 18 academic scientists became authors of the paper, including the elected president of the American Academy of Child and Adolescent Psychiatry as the first author. The paper quotes some remarkable exchanges that should make any academic author on the paper blush, if not outright fear sanctions for violation of authorship standards. Correspondence reveals that a full draft was produced before the authors were even contacted. Yet, the academic authors later maintained that they didn't know that a guest writer of a medical communications firm had been involved.

The Le Noury et al. study is the first study to come out of the so-called RIAT initiative: Restoring Incomplete and Abandoned Trials. The RIAT initiative was launched in 2013 with a high profile publication in the British Medical Journal. With this initiative, prominent scientists launched a public call to sponsors and investigators of unpublished (abandoned) studies to correct the published record on pharmaceutical products. They pointed out that increasing amounts of previously hidden information had become publicly available, including through access-to-information requests with the European Medicines Agency (EMA). A preliminary analysis of these data already suggested, according to the RIAT authors, that several clinical trial publications related to widely prescribed pharmaceuticals were questionable and might be in need of correction. The RIAT proposal put the sponsors and authors of these publications before an awkward dilemma: either they correct their publication themselves within a year—likely having to admit that they made "errors"—or the RIAT initiative would invite volunteers in the scientific community to conduct their own analysis based on the full data set, and submit these "restorative" publications to correct the scientific record. Several leading international medical journals explicitly supported this initiative and announced they were interested in publishing the outcomes of these studies. The 2015 Le Noury et al. article is the first of these restorative publications, written by independent authors not involved in the first study. Not surprisingly, their thorough analysis of the full data set confirms what many had already been arguing for years, namely that paroxetine is no better than placebo for the treatment of depression in children and adolescents, and is associated with a risk of serious side effects, including suicidal ideation and self-harm. Publications by leading psychiatrists had come to the opposite conclusion at the time. Also not surprisingly, these authors still maintain that their original publication remains valid.

Several commentators, including myself, have argued for a complete overhaul of the drug regulatory review system because of the significant impact of the discussed problems on public health and health care expenditures. The two papers both uniquely show what can and should be done in the absence of such reform and how legal tools can empower the scientific community to counter problems that have been created to a significant extent by ill-conceived regulatory and legal rules. The drug regulations requiring the submission of detailed clinical trials data are indeed responsible for the creation of a billion-dollar pharmaceutical knowledge industry. And trade secret rules are increasingly invoked to keep some of the data underlying regulatory submissions and scientific publications hidden. It is precisely the existence of this knowledge production industry, protected by legal rules, that has given the pharmaceutical industry enormous power over the creation, analysis, and selective distribution of research results. Since the U.S. or other governments will not likely take over the conduct of clinical trials or set up a very different and more independent clinical trials structure anytime soon, transparency can help restore the scientific record, expose problems, and provide tools for civil society to hold regulatory agencies accountable for their decision-making.

The papers also show what works best for what purpose. Both papers relied on transparency, but they obtained their data through different legal mechanisms. Jureidini et al. were dependent on a court order,

and thereby had access to communications among the company, a medical writing agency, and academics for their analysis. Their paper gives unique insight into the concrete involvement of, and collaboration between, medical writers and academics in these marketing schemes. Yet, as the authors rightly point out, pharmaceutical litigation often ends up in settlements where confidentiality agreements are a part of the deal. As plaintiff lawyers may offer confidentiality of the data to obtain better compensation, a potential conflict of interest exists between plaintiffs' lawyers and their clients, on the one hand, and the public interest in access to data, on the other. Moreover, this form of disclosure obviously happens only when someone has made the effort to go to court for the alleged harms caused by a pharmaceutical product. Court-ordered unsealing therefore cannot be relied upon as a systematic tool for public health.

Le Noury et al. obtained most of their data as a result of the EMA's data access policy, arguably the most comprehensive data access policy by a drug regulatory agency. The new data policy starts from the premises that disclosure is the rule, clinical data submitted to the drug regulator are generally not confidential commercial information, and that exceptions to disclosure have to be justified. (This is in contrast to other countries, such as Canada, where drug regulators appear to have accepted industry's argument that most of these data constitute confidential commercial information and that regulators are therefore under specific obligations to keep the data secret.) The EMA policy is not perfect and its implementation may often face difficulties. But the EMA's more flexible approach to data sharing, which is reflected in this new policy but was also already present in the data sharing practices it has been following in the last couple of years, resulted in the release of more than 1.5 million pages of previously hidden data. A strong data disclosure policy, clear rules for disclosure, and a regulatory affirmation that these clinical data should generally not be considered confidential, are indeed the preferred approach to promote public health. They are not a panacea, since it still requires a significant mobilization of the scientific community and civil society to conduct these analyses. But they are an important means to restore the scientific record and to hold drug regulatory agencies also potentially accountable for their decisions.

Let me add a final note from an academic integrity perspective. Both papers reveal problems of scientific integrity in pharmaceutical industry-sponsored publications and raise serious questions about the collaboration of academic scientists. In light of what is being exposed in these and in many other related publications, it is remarkable how academic institutions remain silent about the alleged scientific misconduct by some of their researchers.

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