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COMMENTARY

Second generation antipsychotics: evolution of scientific knowledge or uncovering fraud

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Second generation antipsychotics (SGAs), beginning with the 'revival' of clozapine in the late 1980s, were hailed throughout the 1990s as a major breakthrough in the treatment of schizophrenia. The 8 July 1992 cover story of the popular US news magazine 'Time' featured clozapine, with a headline that read 'Awakenings, Schizophrenia: A New Drug Brings Patients Back to Life.' As additional SGAs were brought to market, worldwide sales of antipsychotic drugs skyrocketed, growing in successive years to reach US$ 22.8 billion in 2010, 10% higher than all antidepressant sales and the seventh most costly drug class in the world (IMS Health, 2012). However, as early as 2003, the prominent Journal of the American Medical Association published a 12-month trial involving over 300 patients showing that olanzapine, the best selling and most costly of these drugs, was no more effective than haloperidol but incurred significantly greater weight gain and brought no reduction in hospital use or non-drug costs (Rosenheck *et al.* 2003). That initial study was followed by a virtual cascade of trials published between 2005 and 2008 with similar findings. These studies are well reviewed in the paper by Cheng and Jones in this issue of *Epidemiology and Psychiatric Sciences*, who conclude that the clinical superiority of SGAs was modest and that the reduction in neurological side effects was more than offset by adverse metabolic effects.

This story of evolving science is, by now, quite widely known, but, remarkably, the back story, of how and why this happened has received far less attention, especially in the psychiatric literature. We are left to wonder why, given the increased risks and costs in the absence of substantial benefits: (1) sales of these drugs steadily rose, even after the studies reviewed by Cheng and Jones were published, (2) SGAs with limited approved uses came to be prescribed, in a majority of cases, for off-label, non-approved uses without supporting scientific evidence (Leslie et al., 2009; Leslie & Rosenheck, 2012) and (3) why so many physicians who presumably believe in the principles of 'evidence-based practice' continue to favour these drugs in spite of the growing scientific evidence of their risks and limitations? The answers to these questions while not to be found in the pages of psychiatric journals, have been prominently displayed in the headlines of daily newspapers and, more often, in the business sections. Drug companies aggressively, and in some cases illegally, marketed SGAs through virtually every conceivable channel and to every relevant audience in an effort to foster the belief that they represented breakthrough clinical advances. Few, if any, mental health professionals have the expertise to assess these marketing strategies, but US Federal and State governments have been studying them closely and have begun to make their findings public, albeit not in psychiatric journals.

In 2010, the US Public Citizen's Health Research Group published a report on criminal and civil settlements between federal and state governments and pharmaceutical companies showing that between 2006 and 2010 there were 121 settlements totalling over US$ 14 billion (Almashat *et al.* 2010). The report further observed that 'While the defense industry used to be the biggest defrauder of the federal government under the False Claims Act (FCA), a law enacted in 1863 to prevent defense contractor fraud, the pharmaceutical industry has greatly overtaken the defense industry . . .and now tops not only the defense industry, but all other industries in the total amount of fraud payments for actions against the federal government (p. 2).' Altogether 8 of the 20 largest Federal settlements since 1990 involved antipsychotics or antidepressants and all but one of these involved false

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claims (p. 16). From 2007 to 2010, four leading pharmaceutical companies settled federal false claims charges involving, in part, illegal marketing of SGAs for a total of $4.9 billion (p. 16). The US Justice Department's notice of its $1.4 billion settlement with Eli Lilly (US Department of Justice, 2009), which included the largest criminal settlement in US history at the time, stated that 'from Sept. 1999 through at least Nov. 2003, Eli Lilly promoted Zyprexa "for the treatment of agitation, aggression, hostility, dementia, Alzheimer's dementia, depression and generalized sleep disorder", and in so doing "trained its sales force to disregard the law"'. As recently as April 2012, an Arkansas judge fined Johnson & Johnson US $ 1.4 billion in a case intended to send 'a clear signal that big drug companies like Johnson & Johnson and Janssen Pharmaceuticals cannot lie to the (US Food and Drug Administration (FDA)), patients and doctors in order to defraud Arkansas taxpayers of our Medicaid dollars'(Business Week, 2012a). News reports from June 2012 further reported that Johnson & Johnson had agreed to pay as much as $2.2 billion to settle federal suits concerning its marketing of risperidone and payment of kickbacks to a pharmacy benefits management company to promote its product in nursing homes (Business Week, 2012b).

While most recent large lawsuits have involved off-label marketing, claims that SGAs were clinically superior to FGAs for patients with schizophrenia or that SGAs caused less Tardive Dyskinesia (TD) than FGAs were never approved by the US FDA in spite of industry efforts to obtain such approval. An internal FDA memo concerning olanzapine from August 1996 stated that 'It would be reckless…to assume that a drug-haloperidol difference detected on an instrument that registers negative symptoms is actually measuring a difference in antipsychotic effectiveness' (quoted in Rosenheck, 2005, p. 476). Nevertheless, a study authored by employees of the manufacturer of olanzapine appeared in the American Journal of Psychiatry (AJP) 6 months later, asserting the very conclusion that the FDA memo had judged reckless, that 'Olanzapine shows a superior and broader spectrum of efficacy in the treatment of schizophrenic psychopathology…than haloperidol.'(Tollefson *et al.* 1997, p. 457). Ironically it was acceptable to report conclusions in a leading scientific journal that the FDA had deemed reckless as a marketing claim.

Further, while it is widely believed that SGAs reduce the risk of TD, the package insert of every SGA includes a statement to the effect that whether any antipsychotic has a lower risk of TD than any other antipsychotic is unknown. Several SGA manufacturers have sought FDA approval to claim reduced TD risk, but they have been turned down for lack of adequate scientific evidence. Public discourse is not well served when internal FDA scientific conclusions are not made public.

The full story of the marketing of SGAs and its influence on the profession of psychiatry has yet to be told, and may never be told, because many of the settlements cited above include an agreement protecting the privacy of the internal company documents and memos that formed the basis of the settlements, and companies often settle claims before trial, thereby allowing them keeping internal documents from the public while making public claims of no wrongdoing.

Reactions from within the profession have been mixed. On the one hand, the American Psychiatric Association set a high standard for avoiding the perception of conflict by dropping its popular industry sponsored symposia from its annual meetings (Hausman, 2009) and in 2006, an editorial in the AJP vowed to identify and avoid conflicts of interest and warned that 'tolerance of overzealous marketing diminishes everyone's credibility' (Lewis *et al.* 2006).

In 2012, an AJP paper reported that although there is little current evidence to recommend the use of antipsychotics in the treatment of anxiety disorders, the likelihood that an outpatient diagnosed with anxiety disorder would receive an antipsychotic from a psychiatrist doubled between 1996 and 2010, and the likelihood of receiving a SGA quadrupled (Comer *et al.* 2011). The authors concluded that these trends reflect increased acceptance of 'off-label' antipsychotic prescribing but made no mention of the possibility that such prescribing may reflect illegal marketing for indications such as anxiety, as explicitly noted by the US Department of Justice in the announcement of its settlement with Eli Lilly, cited above. An accompanying editorial did acknowledge 'Widespread and inappropriate marketing practices' (Breier, 2011) but considered the use of SGAs in anxiety disorders as a potentially creative clinical response to refractory illness. However, the original paper identified the largest increase in SGA use in new patient visits, and found no significant association between SGA use and concomitant use of antidepressants or anxiolytics, undermining the argument about refractoriness. The AJP disclosure identified the author of the editorial as a former employee of Eli Lilly, but the New York Times had more fully identified the author as the chief scientist on Lilly's Zyprexa program and Lilly's chief medical officer during the time of the activities prosecuted by the Justice Department (Berenson, 2006).

Conflict of Interest

Robert Rosenheck has received research support from Eli Lilly, Janssen Pharmaceutica, Astra-Zeneca and

Wyeth Pharmaceuticals. He has been a consultant to GlaxoSmithKline, Bristol Myers Squibb, Organon, Janssen Pharmaceutica and Otsuka. He provided expert testimony for the plaintiffs in UFCW Local 1776 and Participating Employers Health and Welfare Fund, *et al. v*. Eli Lilly and Company; for the respondent in Eli Lilly Canada Inc *v*. Novapharm Ltd and Minister of Health, respondent; for the Patent Medicines Prices Review Board Canada, in the matter of Janssen Ortho Inc. and 'Risperdal Consta' and was testifying expert in Jones ex rel. the State of Texas *v*. Janssen Phamaceutica *et al*.

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