



Antipsychotic Medications Are Spelling Legal Trouble for Drugmakers

Robert I. Field, JD, MPH, PhD



Dr. Field is Professor of Law at the Earle Mack School of Law and Professor of Health Management and Policy at the School of Public Health at Drexel University in Philadelphia, Pennsylvania.

Antipsychotic medications are now the largest-selling class of drugs in the U.S. They have grown from a niche product to the king of blockbusters, accounting for more than \$14.6 billion in annual sales. However, they have also recently become the most common subject of major enforcement actions. Every manufacturer of antipsychotics has faced legal challenges over their marketing.

HISTORY OF ANTIPSYCHOTIC AGENTS

The saga of the antipsychotics began in the 1950s, when the first drugs in this class, including chlorpromazine (Thorazine, GlaxoSmithKline) and haloperidol (Haldol, Ortho-McNeil), were introduced. These products offered the ability to control symptoms of severe psychiatric disorders, such as schizophrenia, pharmacologically. Previously, patients had been treated with either long-term institutionalization, including frequent use of physical restraints or invasive surgery, such as lobotomy, with devastating effects.¹

With the introduction of antipsychotic drugs, many patients could be discharged from institutions back into communities. However, drugs control symptoms only when patients take them, and many patients stopped taking their medications because of severe side effects, such as involuntary muscle movements and tics. This led drug companies to search for ways to control psychotic symptoms with fewer adverse reactions.

This research produced a new class of medications known as “atypical” antipsychotic agents, which were intro-

duced in the 1990s. Examples include quetiapine (Seroquel, AstraZeneca), olanzapine (Zyprexa, Eli Lilly), ziprasidone (Geodon, Pfizer), aripiprazole (Abilify, Bristol-Myers Squibb/Otsuka), and risperidone (Risperdal, Janssen). These “second-generation” agents are less likely to cause muscular disorders, but studies indicated that they could lead to different and potentially more serious adverse effects, including weight gain and diabetes.²

ECONOMIC CONSIDERATIONS

Makers of the new antipsychotic drugs also faced an economic challenge. Because schizophrenia affects a relatively small percentage of the population, medications to treat it reach a limited market. As a result, although the drugs were expensive to develop, the upside (in terms of sales) was restricted, at least in comparison to drugs addressing more widespread conditions, such as statins for high cholesterol.

Although schizophrenia is limited in prevalence, psychiatric conditions in general are not. There are many kinds of behavioral disorders, and they can affect all segments of the population. For the most part, these disorders are less serious than schizophrenia, but many are severe nonetheless, including hyperactivity in children and agitation in elderly patients. Marketing atypical antipsychotic agents to patients with this broader category of disorders held the promise of sales reaching blockbuster levels.

However, broader promotion of these drugs faced two obstacles. The first problem was their safety profile. Serious adverse reactions may be acceptable in treating a severe disorder such as schizophrenia, but the risk-benefit calculus is much less favorable when milder conditions are involved. The second obstacle was their approval status. The FDA approved these drugs only for the treatment of severe psychosis in adults; thus,

their use in treating other ailments is considered “off-label.” FDA regulations prohibit companies from promoting drugs for such additional applications.

LEGAL ENFORCEMENT AGAINST ALLEGED MARKETING ABUSES

Despite these obstacles, the lure of a wider market was too much for the manufacturers of atypical antipsychotics to resist. A number of lawsuits filed over the past several years have alleged that the drugs were marketed in ways that violated the law. Specifically, the suits claim that manufacturers hid or downplayed known risks and that they actively promoted uses beyond those that the FDA had approved. Some of the promotions were also alleged to have involved paying indirect bribes to prescribing physicians.

Legal actions over pharmaceutical marketing practices can take several forms. Among the most common, the federal government can sue under the False Claims Act for deceptive practices that lead to payment for a product or service under a government program, such as Medicare or Medicaid.³ Private whistleblowers can report perceived abuses to the government and can sue on their own if the government decides not to pursue the case. These are known as *qui tam* actions.⁴ Individual patients can bring product liability claims for harm caused by undisclosed side effects.

Manufacturers of the atypical antipsychotic medications have been the targets of all of these kinds of lawsuits, resulting in some of the largest settlements ever seen in pharmaceutical litigation. Pfizer holds the dubious record, paying \$2.3 billion in 2009 to settle an enforcement action involving Geodon as well as other drugs. Of this total, \$1.3 billion was assessed as a criminal fine, an unusually severe penalty in a case of corporate misconduct.⁵

The same year, Eli Lilly paid a \$1.4-billion settlement for a suit involving

Zyprexa, including a \$515 million criminal assessment. Beyond these blockbuster settlements, Bristol-Myers Squibb paid \$515 million in 2007 to settle charges concerning the promotion of Abilify. More recently, Novartis agreed in 2010 to pay \$422.5 million in an enforcement action involving the epilepsy drug oxcarbazepine (Trileptal, Novartis).⁶ Also in 2010, AstraZeneca paid \$520 million to settle charges related to the marketing of Seroquel.

In addition to these federal actions, several states have sued makers of atypical antipsychotic agents. Some of these suits claim that undisclosed side effects imposed costs on their Medicaid programs; other suits allege violations of consumer protection laws.⁷ Patients have also sued claiming harm from the drugs.⁸ These proceedings have resulted in numerous additional settlements, although not as large as those in the federal prosecutions.

NATURE OF THE ALLEGED ABUSES

What did the drug companies do to warrant these draconian penalties?

The government alleged that Pfizer made indirect payments to physicians who were frequent prescribers of Geodon through funding of their research, speaking fees, meals, and gifts, and it characterized such payments as kickbacks. Pfizer was also said to have promoted Geodon to family physicians, pediatricians, and geriatricians when it was approved only for treating several psychiatric illnesses in adults. Eli Lilly, it was claimed, trained sales representatives to rebut a growing body of research revealing adverse reactions caused by Zyprexa and promoting the drug's use to calm elderly patients in nursing homes even after the FDA had warned that this could lead to the development of heart failure and pneumonia.

Bristol-Myers Squibb was charged with marketing Abilify for use in children and the elderly, in contravention of FDA-approved labeling. Novartis was charged with paying physicians to prescribe Trileptal through speaker fees, compensating them for serving on advisory boards, providing expenses for travel and meals, and training and rewarding its sales staff for promoting off-label uses. AstraZeneca was alleged to have pro-

moted Seroquel for off-label use in children and the elderly.

These settlements amount to big money, not to mention bad publicity for the manufacturers involved. Will the companies now begin to mend their ways? The answer is uncertain. As large as the settlements are, they represent only a fraction of the revenues that have been earned from these drugs. AstraZeneca made \$21.6 billion from Seroquel between 1997 and 2009. Its \$520 million payment is only 2.4% of that sum.

ANTIPSYCHOTIC AGENTS AND THE DYNAMICS OF PHARMACEUTICAL SALES

The saga of antipsychotic drugs reflects the dynamics of the larger pharmaceutical market. For the last several decades, drug companies have relied on the blockbuster model to derive most of their profits. Blockbuster drugs are those with more than \$1 billion in annual sales. That kind of return is possible only with a large market. Therefore, manufacturers have tended either to focus on common conditions when they develop new products or to seek the widest possible market for products that have already been approved. The latter approach was the strategy behind the marketing of the newer-generation atypicals.

Adding to the pressure to seek wider markets is the growing cost of developing new drugs—estimated at nearly \$1 billion.⁹ This has magnified the imperative to gain the highest level of sales for each product.

In the not-too-distant future, the blockbuster model will become increasingly challenging to maintain. As advances in genomics make it possible to pinpoint how individual patients might react to a specific drug, it will become more difficult to promote a medication as a one-size-fits-all solution to common ailments. A more segmented market means that drugs will gradually be relegated back into niches. The challenge for manufacturers will be to earn the highest return for the drugs in each niche rather than to spread sales across as many niches as possible.

Moreover, psychiatric conditions are extremely varied in their causes and symptoms. A milder symptom such as agitation in an elderly patient does not

warrant the same intensity of medical intervention as a severe symptom such as a hallucination in a schizophrenic patient. The tendency of these drugs to cause powerful adverse reactions is a particular threat to medically vulnerable groups, like the very young and the very old. As a result, the newer antipsychotic drugs are not the kind of product that should have lent itself to broad marketing to begin with.

NEXT STEPS

In light of the large number of successful enforcement actions and the continued potential for abuses, prosecutors are likely to remain vigilant concerning the marketing of atypical antipsychotic agents. Repeated violations could generate even larger penalties. Publicity over the large settlements has put physicians and the public on notice about the hazards of indiscriminate use of this class of drugs. In the future, regulators, clinicians and patients should view atypical antipsychotics and marketing claims concerning them with caution.

REFERENCES

1. Jibson MD, Tandon R. New atypical antipsychotic medications. *J Psychiatr Res* 2008;32(3-4):215-228.
2. Wilson D. Weight gain associated with antipsychotic drugs. *The New York Times*, October 27, 2009, p B1.
3. False Claims Act, 31 U.S.C. §3729.
4. 31 U.S.C. §3730.
5. Wilson D. Side effects may include lawsuits. *The New York Times*, October 2, 2010, p BU1.
6. Kendall B, Brin DW. Novartis unit to pay \$422.5 million in marketing case. *The Wall Street Journal*, October 2, 2010.
7. Eli Lilly agrees to settle Zyprexa marketing cases. *The Wall Street Journal*, January 15, 2009, p B4.
8. Zekaria S. Astra settles claims related to Seroquel. *The Wall Street Journal*, August 10, 2010.
9. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: New estimates of drug development costs. *J Health Economics* 2003;22(2):151-185. ■