Off-Label Prescribing of Antipsychotics to Children: Causes for Concern and Suggestions for Reform

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Introduction

If a doctor recommended that your child be put on an antipsychotic drug, what kinds of questions would you first ask him? Would you want to know whether the doctor owned stock in the company that manufactured that drug? Would you want to know whether that drug maker had paid the doctor to give lectures about the drug? These are precisely the issues confronting parents in light of the recent revelation that three Harvard psychiatrists failed to report millions of dollars in "consulting fees" from drug makers.[1] The media has focused particular attention on Dr. Joseph Biederman, a Harvard child psychiatrist whose work helped spur a 40 percent increase in the diagnosis of bipolar disorder in children from 1994 to 2003.[2] A 2008 investigation by Senator Charles E. Grassley revealed that Dr. Biederman had failed to disclose approximately $1.4 million in consulting fees from drug companies, many of which manufactured medications he prescribed, as required by Harvard Medical School rules.[3] Thus, Dr. Biederman became the center of a controversy involving conflicts of interest in psychiatry, a field where diagnoses are often amorphous and prescribing practices are based on a tenuous game of trial and error.

This paper attempts to identify the precise nature of financial conflicts of interest that motivate physicians to prescribe antipsychotics for children, despite evidence pointing to those products' health risks and efficacy problems. . It will also look at the way in which drug manufacturers have used questionable off-label marketing techniques to sway doctors' medical judgment, as illustrated by several recent settlements by the nation's largest pharmaceutical companies. Furthermore, this paper seeks to examine the manner in which provider

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[1] Gardiner Harris, *Researchers at Harvard Are Named in Subpoena*, NY TIMES, Mar. 27 2009.
[2] *Joseph Biederman*, NY TIMES, Mar. 20, 2009.
[3] Id.

reimbursement for off-label usage and clinical trial design are linked to physicians' prescribing practices and the behavior of pharmaceutical companies. Finally, it will examine several solutions to the conflict of interest problem.

The Problem

During the past decade, doctors have increasingly prescribed powerful antipsychotic medications to children and teenagers. According to research conducted by the FDA's Pediatric Advisory Committee antipsychotic use in the pediatric population (those ages 0 to 17 years) increased 22 percent between 2004 and 2008.[4] Psychiatrists were the number one prescribers of antipsychotics for children, followed by nurse practitioners, and pediatricians.[5] The greatest increase came in the prescription of aripiprazole (brand name Abilify), which is FDA-approved for use in people 13 years of age and older diagnosed with schizophrenia, bipolar disorder, irritability associated with autism, and major depressive disorder in adults.[6] Nonetheless, medications like Abilify are often given off-label to young children for attention deficit disorder, aggression, persistent defiance, and other types of "conduct disorders."[7] Male children are more likely than female children to receive antipsychotics because boys are more frequently diagnosed with behavioral disorders.[8] Likewise, studies suggest that low-income children covered by Medicaid are prescribed antipsychotics at a rate four times greater than privately insured children, most likely because doctors and parents perceive it as the most efficient and cost-

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[4] FOOD AND DRUG ADMINISTRATION, PEDIATRIC ADVISORY COMMITTEE SUMMARY (Dec. 9, 2009).
[5] *Id.*
[6] Abilify —http://www.abilify.com/Default.aspx?client=safari&rls=en&q=aripiprazole+approved+usage&ie=UTF-8&oe=UTF-8
[7] Duff Wilson, *Poor Children Likelier to Get Antipsychotics*, NY TIMES, Dec. 12, 2009.
[8] Mark Olfson, et. al., *Trends in Antipsychotic Drug Use by Very Young, Privately Insured Children*, 49 JOURNAL OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY 13, 17 (Jan. 2010); Mark Moran. *Antipsychotic Use Patterns Surprise Researchers*. PSYCHIATRIC NEWS, May 20, 2005.

effective way to control behavior problems.[9] And following similar logic, foster children also appear to receive antipsychotics at a higher rate than other children.[10] Lastly, only 40 percent of very young children (ages 2 to 5 years old) receive a mental health evaluation before obtaining a prescription for antipsychotics, in violation of the practice standards from the American Academy of Child and Adolescent Psychiatry.[11] Overall, these trends suggest that children who have behavior problems or have parents who, due to time and cost constraints, are unable to try alternative behavioral therapies are more likely to receive antipsychotics.

Such statistics raise several causes for concern. First, very little scientific evidence points to the effectiveness of antipsychotics in young children, and such data as exists is mostly limited to open trials, in which both study subject and doctors know who is receiving what intervention.[12] And, studies suggest that the results of open trials tend to be biased toward finding beneficial effects when the outcomes are subjective, as is the case with determining whether an antipsychotic "worked" for a particular child.[13] Second, studies suggest that antipsychotics may have severe adverse effects on the metabolism and brain development of children.[14] For instance, antipsychotics have been shown to cause children to gain as much as 19 pounds after 11 weeks on the medication, leading to an increased risk of diabetes and heart

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[9] Jean Mercer, Ph.D, *Medicaid and Antipsychotic Drugs for Children: Poverty at Work*, PSYCHOLOGY TODAY, Dec. 12, 2009.
[10] Duff Wilson, *Poor Children Likelier to Get Antipsychotics*, NY TIMES, Dec. 12, 2009.
[11] Mark Olfson, et. al., *Trends in Antipsychotic Drug Use by Very Young, Privately Insured Children*, 49 JOURNAL OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY, Jan. 2010, at 18.
[12] *Id.* at 13.
[13] Wood L, Egger M, et. al 336 *Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study*. BRITISH MEDICAL JOURNAL 601–5 (2008).
[14] *Id.*

disease in the very young.[15] Third, because children's rate of development varies substantially, doctors may have difficulty gauging appropriate drug dosing standards and rates of absorption.[16] Fourth, because the validity of children's psychiatric disorders is still being debated no clear standards exist for diagnosing them with such conditions.[17]

Thus, despite serious concerns from experts regarding the safety and efficacy of antipsychotics in children, physicians are prescribing such drugs at ever-increasing rates. Why? Financial conflicts of interest among doctors and illegal drug marketing practices among pharmaceutical companies are certainly part of the problem. Additionally, social conditions have also played a role in fostering increased antipsychotic use among children. For instance, because many children toady grow up in single-parent homes, where time and money are tight, putting a child on an antipsychotic for a behavior problem instead of attending counseling sessions is often viewed as the most feasible option.[18] Likewise, as today's public schools increase their focus on meeting academic standards set by the federal government, while eliminating activities involving creativity and play time, schools often push parents to place children with behavior problems on medications as a matter of administrative convenience. One thing is clear, however; very few experts believe that psychosis in children has increased in recent years. Rather, social conditions, combined with drug company profit motives and conflicts of interests among doctors, are likely to blame for the rise in antipsychotic use among children.

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[15] Jonathan D. Rockoff, *Antipsychotics Cause Weight Gain in Kids*, WALL STREET JOURNAL, Oct. 28, 2009.
[16] Mark Olfson, et. al., *Trends in Antipsychotic Drug Use by Very Young, Privately Insured Children*, 49 JOURNAL OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY, Jan. 2010, at 13.
[17] Jennifer Thomas, *More toddlers, Young Children Given Antipsychotics*, BLOOMBERG BUSINESS WEEK, Jan. 4, 2010.
[18] Duff Wilson, *Poor Children Likelier to Get Antipsychotics*, NY TIMES, Dec. 12, 2009.

Applicable Federal Law

The FDA requires drugs to be approved for an "intended use" before a manufacturer can ship them in interstate commerce.[19] Once the drug has been approved for treatment of a specific condition within a certain population, the manufacturer can market that product for that "intended use." However, after the FDA has approved a drug, physicians are permitted to prescribe it for any medically appropriate use they choose.[20] Likewise, the *Physicians' Desk Reference* states that, "Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling."[21] This practice of prescribing drugs for uses other than those for which they are approved is referred to as off-label prescribing. Off-label prescribing is a common practice. A 2003 report showed that for the 3 leading drugs in each of the 15 top drug classes, 21% of all prescriptions were for off-label use.[22] Moreover, the study found that 60 percent of antipsychotics are prescribed off-label.[23] Likewise, studies show that 80 percent of all drugs prescribed for children had FDA-required disclaimers highlighting the lack of research demonstrating safety or effectiveness in children.[24]

The Food, Drug and Cosmetic Act (FDCA) of 1938 regulates drug company promotional materials, including print, broadcast, and Internet advertisements. In addition, the FDCA

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[19] Gregory Gentry, *Criminalizing Knowledge: The Perverse Implications of the Intended Use Regulations for Off-Label Promotion Prosecutions*, 64 FOOD & DRUG L.J., 441, 443 (2009).
[20] Food, Drug and Cosmetics Act, 21 U.S.C. § 396 (1994) (stating that "Nothing in this Act shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship.")
[21] PHYSICIAN'S DESK REFERENCE (2008), FORWARD (62nd ed. (2007)).
[22] Randall S. Stafford, M.D., Ph.D., *Regulating Off-Label Drug Use — Rethinking the Role of the FDA*, 358 NEW ENG. J. OF MED. 1427, 1427 (2008).
[23] *Id.*
[24] Gregory Gentry, *Criminalizing Knowledge: The Perverse Implications of the Intended Use Regulations for Off-Label Promotion Prosecutions*, 64 FOOD & DRUG L.J., (2009) at 441-442.

regulates the materials that pharmaceutical companies can distribute to health care professionals and patients.[25] The FDCA does not explicitly forbid off-label promotion of drugs, but two provisions do so implicitly. One provision prohibits pharmaceutical companies from "introducing into interstate commerce any new drug" unless the FDA has approved the drug and its label.[26] Marketing a drug in a way that differs from its approved use violates this provision. The second provision prohibits manufacturers from introducing "misbranded drugs" into interstate commerce.[27] The FDA considers a drug to be "misbranded" if its label contains misleading information, omits information supporting its safe use, or contains information about unapproved uses.[28] If the manufacturer distributes printed materials in order to explain the uses of the drug, they are considered part of the drug's labeling even if they are not packaged with the drug.[29] Nonetheless, drug makers are allowed to respond to unsolicited inquiries from health care professionals regarding off-label uses of a product.[30] The company's medical affairs office, not its sales staff, must handle these inquiries, and the responses must be strictly limited to the question asked.[31] In practice, this means that pharmaceutical companies cannot send

[25] Michelle M. Mello, J.D., Ph.D., M.Phil., et. al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, NEW ENG. J. OF MED. 1557, 1557 (Apr. 9, 2009).
[26] Food, Drug and Cosmetics Act, 21 U.S.C. § 355(a) (2008).
[27] Food, Drug and Cosmetics Act, 21 U.S.C. § 331 (2008).
[28] Michelle M. Mello, J.D., Ph.D., M.Phil., et. al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, NEW ENG. J. OF MED. (Apr. 9, 2009) at 1557.
[29] *Id.*
[30] Food and Drug Administration, *Citizen petition regarding the Food and Drug Administration's Policy on promotion of unapproved uses of approved drugs and devices, request for comments,* 59: 59820-59826 (1994).
[31] Michelle M. Mello, J.D., Ph.D., M.Phil., et. al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, NEW ENG. J. OF MED. (Apr. 9, 2009) at 1558.

promotional materials in response to unsolicited inquiries—instead they usually send journal articles or formulary advice.[32]

Because FDA regulates drug promotional materials strictly for, pharmaceutical companies have sought to elude the prohibition on off-label promotion two ways—by distributing scientific articles and sponsoring Continuing Medical Education (CME) programs.[33] The FDA published regulatory guidance in 1992 that established some restrictions on the promotion of off-label uses during CME programs.[34] Around the same time, the FDA also began to send warning letters to manufacturers regarding their distribution of article reprints. In 1996 and 1997, the FDA issued more guidance documents that formally recognized that CME programs and dissemination of journal article reprints could constitute off-label promotion.[35] Under these rules, manufacturers were allowed to send out reprints of scientific articles or portions of textbooks describing off-label uses, but only if the "principal subject" of the written material was an approved use and the manufacturer included a prominent disclosure stating that other uses were unapproved.[36]

Furthermore, under the FDA Modernization Act of 1997 (FDAMA), drug companies were permitted to distribute peer-reviewed articles from scientific journals if the off-label uses described were included in a filed or soon-to-be-filed supplemental new drug application.[37] In September 2006, Congress allowed the FDAMA provisions on off-label promotion to expire,

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[32] Rumore M. *Legal aspects of drug information practice*. DRUG INFORMATION: A GUIDE FOR PHARMACISTS. 3rd ed. New York: McGraw-Hill Professional; 2006. p. 448.
[33] *Id.*
[34] Food and Drug Administration. *Draft policy statement on industry-supported scientific and educational activities: notice*, 57: 56412-56414 (1992).
[35] Food and Drug Administration. *Advertising and promotion; guidances*; 61: 52800-52801 (1996); Food and Drug Administration. *Final guidance on industry-supported scientific and educational activities*.62: 64073-64073 (1997).
[36] *Id.*
[37] 21 C.F.R. § 99 (2008).

thus technically restoring the ban on disseminating journal reprints detailing off-label uses. However, 2009 guidance from the FDA again allowed drug companies to distribute peer-reviewed scientific texts describing off-label uses, this time under less scrutinizing conditions.[38] Under the new rules, drug companies can distribute peer-reviewed articles describing off-label uses even if they have not or do not intend to file a supplemental new drug application, and they are not required to submit the disseminated materials to the FDA in advance.[39]

While federal law governs the regulation of drug promotion and the designation of "approved uses," state laws also influence the general standard of care applicable to physicians. State laws regulate prescribing practices and the licensing of physicians, which in turn influence the standard of care when doctors are sued for malpractice. In certain instances, off-label promotion can even become the standard of care. For instance, in the realm of cancer treatments, tricyclic antidepressants have become the standard of care for pain management, although this class of drugs has only been approved for the treatment of depression.[40]

Furthermore, the fact that a manufacturer follows FDA regulations in securing approval for its medications does not absolve it from a finding of negligence.[41] In its landmark case, *Wyeth v. Levine*, the United States Supreme Court held that FDA approval of a medication's labeling did not prevent a plaintiff from suing the manufacturer under a common law tort theory.[42] Because a drug company can change its label to strengthen or add a warning without waiting for FDA approval, the Court held that the plaintiff's state failure-to-warn tort claim was

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[38] Michelle M. Mello, J.D., Ph.D., M.Phil., et. al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, NEW ENG. J. OF MED. (Apr. 9, 2009) at 1560.
[39] *Id.*
[40] National Cancer Institute. *Why is off-label use of drugs so common in cancer treatment?* http://www.cancer.gov/clinicaltrials/learning/approval-process-for-cancer-drugs/allpages#Anchor-Wh-36735.
[41] Wyeth v. Levine, 129 S. Ct. 1187, 1187 (2009).
[42] *Id.* at 1190.

not preempted.[43] Thus, drug companies can be held liable both under federal law, for violations of off-label promotion laws, and under state laws, for negligence in designing warning labels.

Given the concerning trends regarding off-label prescribing of antipsychotics to children, should the FDA increase its scope of regulation in this realm, or should reform mechanisms be left to medical professionals and state law? The FDA's 2009 guidance seems to be moving toward a more minimal role in the oversight of off-label prescribing.[44] This backward shift in oversight appears inconsistent with the FDA's growing concern about post-market drug evaluation—if there is increasing concern about safety concerns associated with approved uses, surely there are even greater concerns with the safety of off-label uses, especially in children.[45] Why, then, has the FDA chosen to no longer require the filing of a supplemental new drug application or review of journal articles on off-label uses before drug makers can distribute them?

The FDA most likely fears that further regulation of off-label promotion would constitute an impermissible infringement on commercial free speech. Under the framework established in *Central Hudson Gas & Electric Corp v. Public Service Comm'n*, a government prohibition on commercial speech violates the First Amendment if four conditions are met.[46] First, the speech must concern lawful activity and not be misleading.[47] Second, the government can only restrict commercial speech to advance a "substantial" interest.[48] Third, the restriction must directly

[43] *Id.* at 1189.
[44] Randall S. Stafford, M.D., Ph.D., *Regulating Off-Label Drug Use — Rethinking the Role of the FDA*, 358 NEW ENG. J. OF MED. at 1428.
[45] *Id.*
[46] *Central Hudson Gas & Electric Corp v. Public Service Comm'n*, 447 U.S. 557 (1980).
[47] *Id.*
[48] *Id.*

touch upon the interest the government asserts.[49] Fourth, the restriction cannot be more extensive than is necessary to serve the interest advanced.[50] Under this standard then, an absolute prohibition of off-label promotion by the FDA would likely violate the First Amendment. If, as FDA regulations currently permit, a drug company circulates a journal article that speaks truthfully about an off-label use, and the article does not mislead the public, then it is likely permissible commercial speech under the First Amendment.

Thus, because the FDA's current regulations strike a delicate balance between protecting public safety and infringing on commercial free speech, it seems more promising to encourage medical professionals to adopt a higher standard of care when it comes to prescribing antipsychotics off-label to children. Through CME classes, the medical profession itself could encourage its members to recommend other courses of treatment or interventions before prescribing antipsychotics for a child. These classes could serve to better educate doctors about the difference between chemically based mental illnesses in children and behavioral problems resulting from unfortunate family circumstances. Likewise, CME classes could educate doctors about the potential adverse effects of antipsychotics in children, particularly weight gain and heart disease. By simply alerting the medical to the worrisome trends regarding off-label prescribing of antipsychotics to children, individual doctors may become more conscious of their own prescribing practices and think twice before prescribing these powerful medications to young patients.

Conflicts of Interest

Despite laws prohibiting off-label promotion, conflicts of interest between drug companies and physicians have contributed to the stark increase in off-label prescription of

[49] *Id.*
[50] *Id.*

antipsychotics for children.[51] One way in which drug manufacturers can circumvent the prohibition on off-label promotion is to pay doctors to give educational lectures where they can, if asked, discuss unapproved uses of drugs.[52] Between 2000 and 2005, drug company lecture fee payments to Minnesota psychiatrists rose more than sixfold to $1.6 million.[53] Not surprisingly, prescriptions of antipsychotics for Minnesota's children rose ninefold during this period.[54] The data also suggests that those doctors who accepted the most money from drug makers were most likely to prescribe antipsychotics for children.[55] In fact, Minnesota psychiatrists who received $5,000 or more in lecture fees from the manufacturers of antipsychotics between 2000 and 2005 wrote three times as many prescriptions of antipsychotics for children as psychiatrists who did not receive such payments.[56]

The drug industry argues that such physician-lead lectures are an important educational tool designed to keep physicians abreast of the latest developments in the field. Likewise, industry representatives also assert that no one has proven a causational link between money paid to physicians for lectures and prescribing practices.[57] Still, critics assert that consultant and lecture fees paid to physicians are actually kickbacks in disguise, and that they dangerously sway physicians' judgment. Such concerns are particularly magnified in the field of psychiatry, where causation of mental problems is not well understood and treatment often involves a game of trial

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[51] Gardner Harris, et. al. *Psychiatrists, Children and Drug Industry's Role.* NY TIMES, May 10, 2007.
[52] *Id.*
[53] *Id.*
[54] *Id.*
[55] *Id.*
[56] *Id.*
[57] Lorna Benson, *Minnesota doctors defend payments from drug companies*, MINNESOTA PUBLIC RADIO, October 19, 2010.

and error.[58] In fact, the best screening tests for psychosis have a 98 percent false-positive rate in the general population and a 66 percent false-positive rate in a select group of highly disturbed pediatric patients.[59]

The increased diagnosis of bipolar disorder in pediatric patients is a prime example of the way in which an amorphous diagnosis combined with physicians' monetary incentives can result in children receiving potentially dangerous drugs. Between 1994 and 1995, 25 children in a population of 100,000 youths received a diagnosis of bipolar disorder, whereas between 2002 and 2003, this number skyrocketed to 1,003 children per 100,000.[60] At the same time, the treatment of bipolar disorder shifted markedly—physicians largely abandoned antidepressants like Prozac in favor of much more expensive antipsychotic drugs, such as Risperdal.[61] In 2000, for example, the Minnesota state government spent more than $521,000 on antipsychotics drugs for children on Medicaid.[62] By 2005, the cost had risen to $7.1 million annually.[63] Unfortunately, the data does not reveal the breakdown of exactly how much Medicaid money is spent on Risperdal or other drugs prescribed for pediatric bipolar disorder.

In addition to influencing physicians' medical judgment with regard to individual patients, lecture and consulting fees from drug companies may also influence the results of scholarly studies and guidelines issued by professional societies. For example, Dr. Melissa DelBello, a child psychiatrist at the University of Cincinnati, has published well-regarded

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[58] *Id.*
[59] Richard Warner, M.B., D.P.M., et. al., *Ethical Problems in the Relationship of Psychiatry to the Pharmaceutical Industry.* JOURNAL OF ETHICS IN MENTAL HEALTH, April 2009.
[60] Carmen Moreno, MD, et al., *National Trends in the Outpatient Diagnosis and Treatment of Bipolar Disorder in Youth,* 64 ARCH GEN PSYCHIATRY, 1032-1039, 1032 (2007).
[61] Gardner Harris, et. al. *Psychiatrists, Children and Drug Industry's Role.* NY TIMES, May 10, 2007.
[62] *Id.*
[63] *Id.*

research on the drug Seroquel for use in treating bipolar disorder in children.[64] Her 2002 study concluded that Seroquel was effective in children, and a committee of prominent experts published guidelines in the Journal of American Academy of Child and Adolescent Psychiatry deeming it a first-line treatment for some children.[65] However, an investigation by Senator Charles Grassley revealed that between 2005 and 2007 Dr. DelBello had failed to report a portion of the $238,000 she earned from AstraZeneca, the manufacturer of Seroquel.[66] Once her total drug company earnings were revealed, the university became concerned that DelBello's research, which had served as the underpinnings of important recommendations in the field of child psychiatry, might be biased or potentially misleading.

The off-label promotion of drugs has, according to some experts, resulted in disease-mongering, whereby drug manufacturers push for the increased diagnosis of a particular illness in order to expand new uses for a drug going off patent.[67] A prime example of this phenomenon could be the 40-fold increase in the diagnosis of bipolar disorder between 1994 and 2003.[68] During this period, researchers at Harvard, including Dr. Joseph Biederman, pushed to expand Johnson & Johnson's market for antipsychotics to pediatric patients, a lucrative untapped population.[69] The work of these opinion-leader researchers paid off—today, more than a quarter of prescriptions for Johnson & Johnson's antipsychotic, Risperdal, are for children and

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[64] Jacob Goldstein, *Univ. of Cincinnati Psychiatrist Under More Scrutiny Over Funding*, WALL STREET JOURNAL, Apr. 21, 2008.
[65] Gardner Harris, et. al. *Psychiatrists, Children and Drug Industry's Role.* NY TIMES, May 10, 2007.
[66] Jacob Goldstein, *Univ. of Cincinnati Psychiatrist Under More Scrutiny Over Funding*, WALL STREET JOURNAL, Apr. 21, 2008.
[67] Richard Warner, M.B., D.P.M., et. al., *Ethical Problems in the Relationship of Psychiatry to the Pharmaceutical Industry.* JOURNAL OF ETHICS IN MENTAL HEALTH, April 2009.
[68] *Id.*
[69] *Id.*

teens.[70] Despite such statistics, only a minute percentage of this patient population would be expected to have such a serious psychotic disorder.[71] This concern over "disease-mongering" is also fueled by psychiatrists' recent interest in "preventing" psychosis through the use of drugs and other interventions before a condition is fully manifested.[72]

In order to remedy some of the conflicts of interest that arise when antipsychotics are prescribed off-label to children, the doctrine of informed consent should be revised to increase the amount of disclosure required of physicians. Although off-label use is remarkably common, a majority of patients believe that doctors always prescribe drugs for FDA-approved purposes.[73] Additionally, many patients are unaware of drug industry marketing practices that may create conflicts of interest when their physicians are deciding what medications to prescribe.[74] Because off-label prescribing of drugs, and in particular antipsychotics for children, can have potentially severe adverse effects and little proven benefit, patients should have full knowledge of the conflicts of interest that may cloud a doctor's judgment when prescribing off-label.

Under current tort law, the doctrine of informed consent requires doctors to disclose information that would be material to a reasonable patient's decision to consent to a recommended course of treatment, including the risks of treatment.[75] Thus, the question is whether the off-label use and potential drug company influences on a provider are "material." Because prescribing a drug for a use not approved by the FDA can carry a risk that it is less safe or effective than an on-label alternative, doctors should disclose the off-label nature of a

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[70] *Id.*
[71] *Id.*
[72] *Id.*
[73] Margaret Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L.J. 967, 968 (2006-2007).
[74] *Id.* at 970.
[75] *Id.* at 1012.

prescription to a patient. In fact, the off-label use may prove harmful to a patient. Nonetheless, courts have yet to find that an off-label disclosure was required. In a series of cases involving injurious bone screws, several state courts held that the off-label use of the screws was not a required disclosure because the off-label status of the medical device was not a material fact bearing on medical judgment.[76] Nonetheless, several considerations distinguish those cases, from the proposal regarding disclosure of off-label drug use. First, the bone screw cases involved medical devices, which are the FDA regulates under a more lenient standard than drugs. Second, because there is a greater concern that off-label marketing of drugs will unlawfully influence physicians' judgment, courts are more likely to find that off-label use of drugs, but not medical devices, requires disclosure to patients.

Under the proposed informed consent standard, a doctor should also disclose his receipt of lecture or consulting fees from a drug company to patients. Even if they are unaware of its influence on their prescribing practices, doctors may be swayed by such payments to prescribe certain medications or to recommend certain courses of treatment. Most famously, in *Moore v. Regents of the University of California*, the California Supreme Court held that doctors had a duty to disclose their research and monetary interest in developing a cell line from the patient's removed spleen cells.[77] The court reasoned that the doctors' financial and research interests may have biased their treatment recommendations to the patient, and that the patient has a right to

[76] See *Alvarez v. Smith*, 714 So.2d 652, 654-655 (Fla. Dist. Ct. App. 1998) (stating that disclosure of off-label nature of bone screws was not required because it was not a medical risk); *Blazoski v. Cook*, 787 A.2d 910, 922 (N.J. Super. Ct. App. Div. 2002) (holding that FDA status of bone screws did not bear on medical judgment); *Klein v. Biscup*, 673 N.E. 2d 225, 231 (Ohio Ct. App. 1996) (holding that disclosure was not required because off-label use was not a material risk and the FDA does not regulate the practice of medicine).

[77] *Moore v. Regents of the University of California*, 793 P.2d 479, 485 (Cal. 1990).

trust that his doctor's judgment is not influenced by a profit motive.[78] As in *Moore*, patients would want to know whether the doctor's opportunity to benefit financially is influencing his decision to prescribe a certain drug.[79]

Despite the apparent benefits to patient safety and autonomy, critics may argue that requiring disclosure to patients of doctors' conflicts of interest and off-label prescribing is either unnecessary or harmful. For instance, some might argue that such disclosures would unnecessarily frighten patients who might believe that lack of FDA approval is equivalent to FDA disapproval.[80] Others might assert that requiring disclosure to patients places an undue burden on doctors to pay close attention to FDA law, rather than the latest developments in medical literature.[81] These concerns, though, do not trump the value of patient autonomy contained within the doctrine of informed consent. A patient's possible misunderstanding of important information is not a sufficient reason for withholding it from him. Likewise, because the information about approved uses is contained in drug package inserts or on the manufacturer's website, doctors will not be overly burdened if they are required to disclose off-label uses.

In addition to revising informed consent doctrine, individual research hospitals could help to prevent conflicts of interest from tainting research in the field of psychiatry by prohibiting their physicians from receiving lecture or consulting fees from drug makers. For instance, in 2009, Partners HealthCare adopted a rule prohibited its physicians from accepting gifts and

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[78] *Id.* at 483.
[79] Margaret Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L.J. AT 1021.
[80] *Id.* at 1014.
[81] *Id. at 1015.*

meals from drug and device companies or serving as paid speakers for them.[82] Such a policy would give patients more confidence that their physicians were not "hired guns" being paid to prescribe certain drugs to their patients.[83] Likewise, it would help insurers and patients to save money because doctors would be less likely to prescribe an expensive drug manufactured by a company that is paying the doctor to promote it. A hospital's policy might go even one step further, as at Stanford University School of Medicine's hospitals, by prohibiting drug companies from paying for CME classes for doctors working at their facilities.[84] Overall, by strengthening the doctrine of informed consent and urging hospitals to restrict receipt of funds from drug companies, patients could have greater confidence that their providers' judgment was not being clouded by financial conflicts of interest.

Provider Reimbursement for Off-Label Prescribing

As off-label prescription of antipsychotics increases, both government and private insurers have grown concerned about the cost, safety, and efficacy of off-label drugs, especially in children.[85] Policymakers are particularly worried about freely reimbursing patients for off-label uses when little data supports the effectiveness of the particular drug for the off-label use.[86] In fact, 15 percent of off-label uses lack any scientific evidence at all, and less then 30 percent of off-label uses are bolstered by strong clinical findings.[87] On the other hand, especially in the field of oncology, providers argue that off-label uses have proven value and may even represent

[82] Liz Kowalczyk, *Partners Curbs Doctors' Drug Industry Ties*, THE BOSTON GLOBE (April 10, 2009).
[83] *Id.*
[84] *Id.*
[85] Joshua Cohen, et. al., *Off-Label Use Reimbursement,* 64 FOOD & DRUG L.J. 391, 393 (2009).
[86] *Id.*
[87] *Id.*

a patient's only treatment option.[88] Thus, stricter restrictions on off-label reimbursement might negatively impact patient health outcomes.[89] Nonetheless, because insurers' resources are limited, liberal reimbursement for off-label uses involves an opportunity cost—the more off-label uses they reimburse, the less on-label uses they can afford to cover without raising premiums.[90] States also exhibit growing concerns about the portion of state Medicaid budgets devoted to reimbursement for antipsychotic drugs.[91] In fact, almost every state government spends more on antipsychotics than any other class of drugs.[92] As of 2009, Massachusetts Medicaid spent over $93 million, or 18.5% of the pharmacy budget, on antipsychotics.[93] Thus, with little evidence proving the effectiveness of such drugs in children, and the potential conflicts of interest that exist in the field of psychiatry, insurers have begun to implement cost-containment mechanisms.

In an attempt to find the proper balance regarding off-label reimbursement of antipsychotics, a study conducted by the Food and Drug Law Institute suggests that payers administering Medicare and Medicaid plans have taken several approaches. Typically, insurance contracts exclude experimental or investigational drugs from reimbursement, and such a provision can often be used to exclude coverage for certain off-label uses.[94] Likewise, some payers require prior authorization before reimbursing a patient for an off-label use.[95] Other

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[88] *Id.* at 394.
[89] *Id.*
[90] *Id.*
[91] Ed Silverman, *Antipsychotics & Kids: States are Cracking Down*, http://www.pharmalot.com/2008/09/antipsychotics-kids-states-are-cracking-down/ (Sept. 10, 2008).
[92] *Id.*
[93] The Commonwealth of Massachusetts Executive Office of Health and Human Services, Office of Medicaid, *Letter Regarding MassHealth Pharmacy Program*, April 2009.
[94] Joshua Cohen, et. al., *Off-Label Use Reimbursement,* 64 FOOD & DRUG L.J. at 395.
[95] *Id.* at 394.

payers employ "step therapy," whereby an insurer requires the patient first to try using the least expensive drug in a given class before progressing to more expensive options.[96] Likewise payers commonly place limits on drug quantities or impose cost-sharing mechanisms for off-label uses.[97] Whether an off-label use is reimbursable in the first place often depends on its inclusion in a recognized pharmaceutical compendia, a collection of published evidence and expert opinion on the benefits of particular drugs.[98] If an off-label use is not included in a recognized compendium, payers then look for published clinical evidence in support of the use either in a peer-reviewed journal or clinical practice guidelines.[99]

State legislatures, too, have passed laws aimed at off-label reimbursement in an effort to strike the appropriate balance between payments for on-label prescriptions and off-label prescriptions. Currently, due to intense lobbying efforts by patient interest groups and oncologists, 32 states require all payers to reimburse patients for FDA-approved cancer drugs prescribed off-label.[100] Meanwhile, other states have implemented restrictions on off-label reimbursement for certain medications in particular age groups. Currently, ten states have implemented prior-authorization requirements before an antipsychotic can be prescribed for a child.[101] In Florida, for example, the state government has mandated that prior authorization is required before a provider can prescribe an atypical antipsychotic to a child younger than age

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[96] *Id.*
[97] *Id.*
[98] *Id.*
[99] *Id.* at 396.
[100] National Cancer Institute, *State laws requiring third-party reimbursement for off-label uses of prescription drugs for the treatment of cancer*, http://www.scld-nci.net/Data/off-label_use_09_30_07.pdf (Sept. 30, 2007).
[101] Michael R. Law, M.Sc., et. al., *Effect of Prior Authorization of Second-Generation Antipsychotic Agents on Pharmacy Utilization and Reimbursements*, 59 PSYCHIATRIC SERV 540, 540 (May 2008).

six.[102] As a result of this restriction, Florida Medicaid reports that the doses of antipsychotic medication to this age group have declined by 75 percent, and the overall number of Medicaid claims for antipsychotics for young children has declined by 40 percent.[103]

Ultimately, given the results achieved once Florida required prior authorization before a children could receive an antipsychotic, it seems advisable for other states' Medicaid programs to adopt a similar requirement. Such a requirement would aim to control the rising cost of antipsychotics for Medicaid, while also seeking to ensure that only those children with a serious medical need for these powerful medications receive them. The concern, however, is that prior authorization requirements will unnecessarily hinder the treatment of mentally ill children who legitimately need antipsychotic drugs in order to function in a school setting.[104] Also, at what age should a prior authorization requirement cease? Should state law require physicians prescribing antipsychotics for all minors to obtain prior-authorization, or should the rule apply only to the youngest children, as in Florida? Luckily, the age requirement for prior authorization does not seem to be a key factor in decreasing the number of prescriptions given to children for off-label antipsychotics –the Florida rule shows that any prior authorization rule will have a blanket affect on overall antipsychotic prescribing practices. Perhaps the mere existence of a prior authorization rule simply makes providers think twice before prescribing such powerful drugs to those for whom valid alternative treatments exist.

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[102] Florida Medicaid Program, *Medicaid Prescribed Drug Program: Oversight of Off-Label Prescribing of Atypical Antipsychotic Medications for Children Under Six Years of Age Covered by Florida Medicaid Program*, http://www.scribd.com/doc/33914034/Medicaid-Prescribed-Drug-Program-Oversight-of-Off-Label-Prescribing-of-Atypical-Antipsychotic-Medications-for-Children-Under-Six-Years-of-Age-Covered (Mar. 27, 2009).

[103] Kris Hundley, *Approval process lowers the number of kids on atypical prescriptions*, ST. PETERSBURG TIMES (Mar. 29, 2009).

[104] Michael R. Law, M.Sc., et. al., *Effect of Prior Authorization of Second-Generation Antipsychotic Agents on Pharmacy Utilization and Reimbursements*, 59 PSYCHIATRIC SERV at 545.

The Role of Clinical Trial Design

In seeking to expand the market for an antipsychotic already approved for use in adults, drug companies must weigh the costs and benefits of filing for a new drug application (NDA) to include children. On the one hand, if the medication gains a second FDA approval because it is shown to be safe and effective in children, the company can promote its use in children and reap additional profits. However, the clinical trials associated with gaining an NDA are extremely costly, and a company must judge whether to spend millions of dollars in testing the drug on children when only a few years of exclusivity may remain on the patent.[105] Likewise, a drug manufacturer might risk millions on clinical trials, only to discover that an antipsychotic is not safe or effective in children. And, worse still — the FDA might require a company to place a warning label on the drug's packaging indicating its potential for adverse reactions in children. For instance, during the early 2000s, as evidence accumulated regarding a possible increased risk of suicidal thoughts and behaviors associated with antidepressants in children, the FDA began to review such data in 2003.[106] After collecting data from health care providers across the nation, On October 15, 2004, the FDA announced that it was issuing a black box warning that all antidepressants posed a significant risk of suicide and suicidal ideation in children and adolescents.[107] Immediately after this announcement, and much to the drug makers' detriment, antidepressant use by pediatric patients decreased.

Some experts argue that the Better Pharmaceuticals for Children Act, which was incorporated in the FDAMA, offered a huge incentive for drug companies to test new or patented

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[105] Michael R. Ward, *Drug Approval Overregulation*, 15 REGULATION MAGAZINE (Fall 1992).
[106] Mark Olfson, MD, et. al., *Effects of Food and Drug Administration Warnings on Antidepressant Use in a National Sample*, 65 ARCH GEN PSYCHIATRY 94, 95 (2008).
[107] *Id.*

drugs in pediatric patients.[108] Enacted under heavy lobbying pressure from pharmaceutical companies, the FDAMA extends the length of market exclusivity by six months for any patented drug or one under development that has been tested on children in controlled clinical trials.[109] However, the FDAMA did not explicitly require pediatric studies to show safety and efficacy to gain a patent extension, creating a perverse incentive to value potential monetary rewards over the protection of public health.[110] The *Wall Street Journal* reported in 2001 that six months of market exclusivity for a top selling drug could equal anywhere between $284 million and $975 million, a strong financial incentive,.[111] Nonetheless, drug makers argue that the increase in pediatric clinical trials was beneficial. They insisted that without information on children's drug dosages, children were put at risk of adverse reactions, and that financial incentives were necessary to push manufacturers to conduct pediatric trials.[112] On the other hand, skeptics argued that dosage handbooks already provided sufficient guidelines regarding pediatric dosages, and that clinical trials are more often conducted solely to gain FDA approval rather than to guide practicing clinicians.[113]

The financial incentive to test antipsychotic medications in children is uniquely problematic. Currently, the FDA's "Pediatric Rule" authorizes the FDA to require drug companies to conduct clinical trials on children for drugs currently in use by adult patients

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[108] Vera Hassner Sharav, *Children in Clinical Research: A Conflict of Moral Values*, 3 AMERICAN JOURNAL OF BIOETHICS 12, 19 (2003).
[109] *Id.*
[110] *Id.*
[111] R. Zimmerman, *Drug makers find a windfall testing adult drugs on kids*, WALL STREET JOURNAL, Feb. 5, 2001.
[112] Vera Hassner Sharav, *Children in Clinical Research: A Conflict of Moral Values*, 3 AMERICAN JOURNAL OF BIOETHICS (2003) at 19.
[113] *Id.*

"whenever a potential use in children can be anticipated."[114] However, the FDA gives drug companies the authority to determine when this potential use in children can be anticipated.[115] Furthermore, the FDAMA's general policy shift toward increasing pediatric clinical trials encourages drug makers to apply a broad standard when determining if an anticipated need or research benefit for healthy children might arise in the future.[116] Therefore, such a loose standard has motivated drug companies to recruit "risk bearing" children for clinical trials involving medications that have the potential to cause serious developmental problems.[117] Likewise, a strong motivation also exists for researchers to diagnose children with psychiatric disorders in order to facilitate their participation in a study.[118] The danger here is that healthy children are being exposed to potentially debilitating drugs with very little potential for personal benefit solely in order to bolster drug company profits.

A prime example of such questionable recruitment of young children into clinical trials occurred in 2000, when the NIMH set out to test Ritalin in three to five year old children.[119] Although Dr. Lawrence Greenhill, the study's principal investigator, stated that ADHD is "not a well-defined psychiatric disorder in this age group," the NIMH administered Ritalin to 312 previously untreated three-year-olds to test the safety and efficacy of the drug.[120] Some experts questioned the ethics of doing such a study, especially because investigators could not confirm any scientific abnormality in the children being recruited to participate.[121] Moreover, parents

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[114] R. Steinbrook, *Testing Medications in Children*, 347 NEW ENG. J. MED 1462, 1468 (2003).
[115] *Id.*
[116] Vera Hassner Sharav, *Children in Clinical Research: A Conflict of Moral Values*, 3 AMERICAN JOURNAL OF BIOETHICS (2003) at 28.
[117] *Id.*
[118] *Id.*
[119] *Id.*
[120] *Id.*
[121] *Id.*

were paid $645 if their child completed the requisite 43 study visits, and teachers were paid $340 for completing study forms.[122] Likewise, Ritalin was administered to young children despite the fact that evidence suggested its use increased the subsequent likelihood of cocaine and tobacco addiction in adults by more than 20 percent.[123] Ultimately, as financial incentives under the FDAMA spur researchers to identify new uses or new populations for which to market a drug, physicians' judgments may be inappropriately swayed toward over-diagnosis and overtreatment.

What can be done to better protect child subjects in clinical trials of antipsychotic drugs? First, the current provision under the FDAMA that allows for a six-month extension on a patent should be amended such that drug companies would only receive the patent extension if their pediatric trials made a showing of safety and efficacy. Instituting a safety and efficacy requirement for a patent extension would require drug makers to weigh more heavily the cost of conducting potentially ineffective or unsafe clinical trials in children. Thus, this would create an incentive for drug companies to only test those antipsychotics on children that they feel are most likely to be safe and efficacious.

Second, when conducting clinical trials of antipsychotics on children, only children previously diagnosed with a psychiatric disorder by a physician who is not conducting the particular clinical trial should be allowed to enroll in the study. Such a rule would lessen the likelihood that study investigators would be able to diagnose children with a psychiatric disorder solely in order to make that child eligible for the trial. Similarly, because psychiatric disorders are so difficult to diagnose in children, study investigators should limit pediatric trials of antipsychotics to narrowly defined class of disorders with clear characteristics, such as schizophrenia, as opposed to a more amorphous disease, such as oppositional defiant disorder.

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[122] *Id.*
[123] *Id.*

Third, many experts in the field of biomedical ethics recommend that for clinical trials in children, parents and caretakers should receive only minimal compensation for the participation of their children.[124] For instance, parents might be reimbursed for the cost of public transportation to the trial site or for parking, but not a general incentive payment. Limiting incentive payments to caretakers would help to prevent researchers from disproportionately recruited lower income children for their trials. In fact, researchers should be encouraged to include children from a broad range of social and ethnic backgrounds in their studies of psychiatric drugs in order to make their subject populations more representative of the potential patient base nationwide.[125]

Aside from fashioning rules to alter patient and drug company incentives, the medical community should work to develop better tools for diagnosing psychiatric disorders in children. Because current diagnostic tools have a 66 percent false positive rate among pediatric populations, physicians should continue to investigate better methods of distinguishing chemically based brain disorders from environmental factors, such as difficult family situations, that might account for behavior problems in children.[126] Thus, with the implementation of some or all of the above suggestions, clinical trials of psychiatric drugs in children would likely become more ethical and accurate means of determining safety and effectiveness of medications.

Litigation Concerning Off-Label Promotion

Recently, a flurry of litigation surrounding off-label promotion of antipsychotics for children has arisen. These lawsuits vary, however, in the statutes under which plaintiffs have chosen to bring suit. Under the Food, Drug and Cosmetic Act, a drug manufacturer can be held

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[124] *Id.* at 47.
[125] *Id.*
[126] Richard Warner, M.B., D.P.M., et. al., *Ethical Problems in the Relationship of Psychiatry to the Pharmaceutical Industry.* JOURNAL OF ETHICS IN MENTAL HEALTH, April 2009.

liable for promoting a drug for uses other than those approved by the FDA.[127] Private individuals, or *qui tam* plaintiffs, have also sued manufacturers under the False Claims Act, alleging that a drug company has given physicians false or misleading information, which in turn has lead them to submit claims to Medicare/Medicaid that are not for "medically accepted indications."[128] *Qui tam* suits allow for private individuals to share in any recovery they obtain on behalf of the United States government.[129] Under the Federal Health Care Program Anti-Kickback Statute, a pharmaceutical company may be held liable for providing financial compensation to a physician as a quid pro quo for the doctor increasing his off-label prescriptions of the company's drug.[130]

Just recently, in September of 2010, Forest Pharmaceuticals, pleaded guilty to one criminal misdemeanor count of distributing an unapproved new drug in interstate commerce, one criminal felony count of obstructing justice, and one criminal misdemeanor count of distributing a misbranded drug.[131] Under the plea agreement, Forest Pharmaceuticals agreed to pay more than $313 million to resolve claims relating to Celexa and Lexapro, both anti-depressants, and Levothroid, a medication for the treatment of hypothyroidism.[132] Regarding Celexa and Lexapro, the complaint alleged that Forest Pharmaceuticals promoted these drugs for pediatric use, despite the fact that they were only approved for use in adults at the time.[133] For instance,

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[127] 21 U.S.C. § 355(a) (2008); 21 U.S.C. § 331 (2008).
[128] 31 U.S.C. § 3729-33
[129] The United States Attorney's Office, District of Massachusetts, *Drug Maker Forest Pleada Guilty; Will Pay More than $313 Million to Resolve Criminal Charges and False Claims Act Allegations*, Sept. 10, 2010.
[130] 42 U.S.C. § 1320a-7b(a)
[131] The United States Attorney's Office, District of Massachusetts, *Drug Maker Forest Pleada Guilty; Will Pay More than $313 Million to Resolve Criminal Charges and False Claims Act Allegations*, Sept. 10, 2010.
[132] *Id.*
[133] *Id.*

Forest Pharmaceuticals allegedly circulated the positive results of a double-blind, placebo-controlled study on the use of Celexa in adolescents, while at the same time neglecting to disclose the negative results of a similar European study on Celexa in adolescents.[134] Additionally, the government alleged that Forest Pharmaceuticals directed its sales representatives to promote Celexa for pediatric use via sales calls to physicians and by hiring outside speakers to speak with pediatricians about the advantages of using Celexa to treat children and adolescents.[135] Moreover, the government's complaint also alleged that Forest used illegal kickbacks, such as lavish meals, entertainment, and cash payments disguised as "consulting fees," to persuade physicians to prescribe Celexa and Lexapro off-label for their patients.[136]

In April of 2010, AstraZeneca paid out $520 million to settle similar charges that it had engaged in off-label marketing of its blockbuster antipsychotic Seroquel.[137] As with the lawsuits against Forest, the government accused AstraZeneca of paying illegal kickbacks to doctors, and in particular to pediatricians.[138] Additionally, AstraZeneca allegedly promoted Seroquel for unapproved uses, such as Alzheimer's disease, ADHD, post-traumatic stress disorder, and insomnia.[139] Similar to the charges against Forest, the government also accused AstraZeneca of covering up negative studies, such as those revealing the risk of diabetes, while actively touting only positive studies [of off-label use?].[140] Additionally, two of the largest settlements occurred in 2009, when Pfizer agreed to pay out $2.3 billion in fines for the off-label promotion of

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[134] *Id.*
[135] *Id.*
[136] *Id.*
[137] Duff Wilson, *For $520 Million, AstraZeneca Settles Case Over Marketing of a Drug*, NY TIMES, April 27, 2010.
[138] *Id.*
[139] *Id.*
[140] *Id.*

painkillers, and Eli Lilly agreed to pay $1.4 billion for the off-label promotion of Zyprexa, a medication approved for the treatment of schizophrenia.[141] Overall, Attorney General Eric Holder has stated that the government won more than $2.8 billion in health care fraud cases between 2009 and 2010.[142]

Recently, under the False Claims Act, *qui tam* plaintiffs have begun to directly sue providers for the prescription of off-label psychiatric drugs to children. In *United States ex rel Linda Nicholson v. Lilian Spigelman, M.D., Hephzibah Children's Association, and Sears Pharmacy*, filed in June 2010, a mother sued on behalf of her daughter, a Medicaid recipient.[143] The mother alleged that her daughter's doctor prescribed antipsychotic drugs to her daughter and other minors that were not for "medically accepted indications," and then caused such claims for prescriptions to be submitted to Medicaid for reimbursement.[144] The complaint alleges that the antipsychotics prescribed for her daughter were not for indications approved by the FDA or supported by a recognized Compendia, making them false claims under the False Claims Act.[145] If this case succeeds, it is likely that other parents of children harmed by the use of off-label antipsychotics may increasingly bring suit against providers. However, because drug companies have deeper pockets than individual providers, *qui tam* plaintiffs unlikely to abandon suit against drug manufacturers.

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[141] Michael Conner, *AstraZeneca to pay $520 million to settle illegal marketing charges,* BUSINESS ETHICS, April 27, 2010.
[142] *Id.*
[143] *United States ex rel Linda Nicholson v. Lilian Spigelman, M.D., Hephzibah Children's Association, and Sears Pharmacy*, Complaint, June 2, 2010, Northern District of Illinois, Eastern Division. http://psychrights.org/states/Illinois/ExRelNicholson/1-100602Complaint.pdf
[144] *Id.* at. 7.
[145] *Id.* at 9.

Conclusion

Today, more and more children are receiving powerful antipsychotics to treat perceived behavior problems, while very little evidence demonstrates their safety, effectiveness, or long-term effects in the pediatric population. Meanwhile, many parents are unaware of the potential conflicts of interests that arise when pharmaceutical companies pay physicians lecture and consulting fees to promote and research the very antipsychotics they later prescribe to children. Thus, via enhanced informed consent standards, parents should be told the facts about off-label prescribing and conflicts of interest so that they can make well-informed decisions regarding their children's health care. Research hospitals, too, can play a role in controlling costs and enhancing patient safety by prohibiting their doctors from receiving lecture and consulting fees from drug makers. Because of the direct control they assert over reimbursement for off-label drugs, both public and private insurers can help to limit the unnecessary and often dangerous prescription of antipsychotics to children, most notably by implementing prior authorization requirements. Lastly, in order to better protect pediatric subjects of clinical trials involving antipsychotics, studies should be limited only to children previously diagnosed with a psychiatric disorder, improved diagnostic tools should be developed, and efforts should be made to recruit children from more diverse socioeconomic and ethnic backgrounds. Ultimately, tightening restrictions on reimbursement, expanding informed consent, restricting consulting fees disguised as kickbacks, and improving standards for pediatric clinical trials could help reverse the worrisome trend that has allowed doctors and drug companies to line their pockets at the expense of children's health and safety.