



**DIVISION OF PHARMACOEPIDEMOLOGY AND PHARMACOECONOMICS AT BRIGHAM AND  
WOMEN'S HOSPITAL, HARVARD MEDICAL SCHOOL**

**POLICY EDUCATION INITIATIVE**



**POST-APPROVAL MEDICATION SURVEILLANCE: THE CASE OF  
ANTIDEPRESSANTS IN CHILDREN**

**Case Author:**

Lauren Gold HMS '08

**Case Consultants:**

Katherine Elizabeth Grimes, M.D.  
Psychiatry-Cambridge Hospital  
Assistant Clinical Professor of Psychiatry, Harvard Medical School

Aaron S. Kesselheim, M.D., J.D., M.P.H.  
Instructor in Medicine at Harvard Medical School  
Division of Pharmacoepidemiology and Pharmacoeconomics  
Brigham and Women's Hospital

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With thanks to Jerry Avorn, M.D. for his comments on an earlier draft.

Case 2-1

Your 15-year-old daughter Alexis has always been a solid student. She is also a star player on her high school's tennis team, has a large group of friends, and helps take good care of her younger brother Joshua (age 6). Since she began her sophomore year of high school, however, you've been noticing some changes in Alexis. She sulked her way through the end-of-summer family vacation. You see her less, as she's more often in her room with the door closed and music playing. She is more secretive about whom she goes out with and where she goes on the weekends. She seems fidgety and tired, and you've seen her light on at 2 and 3 am – she claims she was “reading.” Her grades during the first marking period suffered, with Bs and Cs appearing for the first time instead of her usual A- and B+ grades. Recently, Alexis announced that she wants to skip the upcoming regional tennis championship match. “I'm sick of Coach McIntyre and all those stupid practices. I think I'm going to sit out the rest of the season,” she said.

Though your husband thinks this may just be a phase, you both decide that a visit with her pediatrician is reasonable, and Alexis comes reluctantly to see Dr. Shah.

Dr. Shah asks Alexis how she's been feeling, to which she replies, “Fine. I'm just sick of tennis, and no one listens to me.” She denies any systemic complaints other than some difficulty sleeping and trouble focusing in school. She asks whether Ritalin, which her friend Rosie takes for ADD, might help her study. Then you explain what you have observed. Dr. Shah asks you to leave the room while she speaks with Alexis in private and examines her. Afterwards, Dr. Shah gives you and Alexis her assessment:

“Alexis, as your pediatrician for the last 15 years, I know you pretty well. And I can tell you that I share your parents' concerns about these recent changes in your behavior. It is not unusual for teenagers to go through rough patches, but I'm afraid this is more serious than that. I am glad to hear that you have not been engaging in any dangerous activities. But loss of interest in your hobbies, difficulty sleeping, and trouble paying attention in school are all signs that you are suffering from depression. I see this often in teenagers your age, and I've seen medications significantly improve the situation. I want you to try taking Paxil, an antidepressant, every day for 6 months. I also want you to speak with a therapist on a regular basis. This medication can take several weeks to take effect, and there may be some side effects. Come back in four weeks so we can see how the medication is working and monitor for any side effects.”

Discussion

- 1) *How would you describe this patient's problems? Whose decision should it be to medicate this patient? What is the role of the patient, parents, and primary care physician in this decision? Should she be referred to a child psychiatrist before medication is initiated?*
- 2) *What is the prescription drug “label”? What does it contain? Who writes it? How do the contents of the warnings in the label affect prescribing practices?*
- 3) *How has use of psychotropic medications changed over the past twenty years?*
- 4) *What is off-label medication use, and how does this relate to treatment of this patient? Are all off-label uses inherently inappropriate? What are the restrictions about pharmaceutical promotion and off-label use, and why are they in place? What are some considerations regarding the quality of published data about off-label uses?*

Case 2-2

One month later

Your worry about Alexis continues, though you draw some comfort from your visit with Dr. Shah and knowing that medication might help her. A friend from the PTA confides that her son has been taking Paxil for months, and has had more energy and is more participatory in school and family functions. You help Alexis take the medication daily. Within a week, Alexis states that she thinks it is helping, and although you've heard it can take several weeks for such drugs to work, you are encouraged by her reports. Alexis does seem to have more energy, but her energy is hardly constant; she has bouts of giddiness, dancing with Joshua and tapping her foot incessantly at the dinner table, alternating with times you can hardly get her off the couch to set the table or walk the dog.

One night you have a small fight with Alexis at dinner when she asks to go out with Rosie instead finishing an important homework assignment. She storms off to her room, and your husband urges you not to chase her. "Let her decompress," he argues. After putting Joshua to bed, you knock on Alexis' closed door. You don't hear an answer. You check the bathroom and living room, with no luck. Nervous, you enter her room. Alexis is perched near the open window of her second story room, face moist with tears. "Honey," you say, "what's the matter?"

"I just ruin everything," she answers. "I can't do school and I can't play tennis. You and Dad hate me because I'm not your perfect child like Joshua, because I have problems. It would be easier for everybody if I wasn't here at all. It would be so much easier if I just jumped out this window and died right now."

Discussion

- 1) *How would you characterize this patient's risk of suicide? What are some safety concerns surrounding SSRIs in children?*
- 2) *What is appropriate monitoring for children on SSRIs?*
- 3) *What is the difference between a side effect, an adverse event, and an allergic reaction? What are some reasons that medication side effects may be under-diagnosed?*
- 4) *What is the current system for post-approval surveillance of pharmaceutical agents? What are the advantages and the liabilities of this system?*
- 5) *To whom can physicians report adverse events of medications prescribed to patients? How often does such reporting occur? What is the role of the pharmaceutical company?*

Case 2-3

Two weeks later

You've hardly slept in weeks. You took Alexis to the hospital the night you found her in her window. You and Dr. Shah, along with her new therapist Tracy, agree that she should take several weeks off from school, and she is starting the day program for children with emotional and behavioral problems at the nearby Children's Hospital. She seems calmer after stopping Paxil, with fewer mood swings and less impulsive behavior. You've arranged with your boss to cut down your hours at work so that you can be home more often during this time.

You've also begun reading about SSRIs in children and the risk of suicidal behavior. You have joined an online support group for parents of children with behavioral problems, and through this group have found some of the understanding and emotional support that you need. As you are preparing dinner one day, the phone rings.

"Mrs. Harris? This is Ed Rogers calling. I'm a lawyer with the DeValeck group. I got your name and number from the online group you joined. I want to make you aware of a class action lawsuit we are filing on behalf of parents such as yourself against the pharmaceutical companies who have duped parents and the FDA into believing that SSRIs are safe in children...."

Although you decide that participation in the case would cause your family additional undue stress, you begin to think more critically about the role of the drug companies, the FDA, and your own pediatrician in the "adverse event" your daughter suffered.

Discussion

- 1) *Isn't the FDA supposed to prevent distribution of drugs for which the risk exceeds the benefit? Or is that the role of your pediatrician? Whose fault is this, anyway?*
- 2) *What are the advantages and liabilities of the current system of drug safety assessment?*
- 3) *What are the options when the FDA learns that a product it has already approved may potentially be inherently unsafe, or be used in unsafe ways? What is a "black box" warning and how effective is it in changing prescribing behavior?*
- 4) *Do pharmaceutical companies contribute to overuse of unsafe medications? How have lawsuits and other such threats contributed to improving public awareness about medication risks?*
- 5) *How does and should the public hear about emerging medication risks and what is the role of the media?*

Case 2-4

Five days later

Alexis' appointment with Dr. Chase, the child psychiatrist, has finally arrived. You feel relieved that her care will finally be managed by a specialist, and despite her protests that she is fine now that she is off of the "crazy pills."

Dr. Chase speaks with you, your husband, and Alexis about her mood, family dynamics, and the events of the last month. He does not label Alexis as depressed and he accepts her assertion that she was not trying to commit suicide. He does not blame anyone for the events which have transpired. You explain why you believe, based on your research, that SSRIs should be banned in children. Dr. Chase replies, "I've long suspected that there's more to these medications than meets the eye, and I have not been alone in my concerns. While I do prescribe these drugs to young people, I conduct a rigorous weekly surveillance program for all patients taking these medications, particularly in the beginning stages of therapy. I've also been involved in an effort by several child psychiatrists to formalize and mandate a surveillance system like the one I've set up for my patients."

Dr. Chase describes how he communicates with a patient's primary care physician to avoid medication interactions and errors. He explains that while he does not believe that SSRIs are the right medication for everybody and particularly for Alexis, he does prescribe drugs like Paxil to patients for whom he believes the medications are indicated. He adds that he's afraid the current backlash against psychotropic medication use in children could result in under-treatment of children with serious mental health problems. He shows you and your husband a recent NY Times article suggesting that a recent increase in suicide rate in children may be related to this undertreatment. He assures you again, however, that in Alexis' case therapy and lifestyle change rather than medication are the best treatment.

Discussion

- 1) *Can there be a backlash to concerns about medication safety? How do we define overmedication vs. undermedication?*
- 2) *What is pharmacovigilance, and how is it employed? Whose role is it to define surveillance systems for medications? Is it ethical to mandate patient compliance with surveillance guidelines?*
- 3) *How do and should a patient's physicians communicate?*

Case 2-5

Six months later

With the help of Tracy and Dr. Chase, Alexis seems to be nearing her baseline again. She's been more interested in school, has been seeing her old friends again, and has begun to write for the school's literary magazine about some of her feelings. She has not changed her mind about tennis, but you have let that issue pass. You've had some good conversations in the time you've taken off of work, as well as some typical family disagreements. She has started to open up about her "rough times" and the thoughts which drove her to contemplate suicide, and has stopped fighting you each time you drive her to Dr. Chase's office. You decided to be more open with Alexis about any thoughts you have for her treatment, and she recently shared with you the rough draft of an article for the LitMag on being a teenager on antidepressant medication. You tell her how proud you are of her.

Meanwhile, through your support group, you've heard some encouraging news about attempts by government agencies and medical groups to increase regulation of medication approval and monitoring, as well as transparency regarding the results of medication trials. You decide to join the Council for Drug Safety demonstration in Washington next month for increased regulation of psychiatric medications in children. You are proud to tell Alexis you are doing something important for this cause which has come so close to your heart.

Discussion

- 1) *Who should regulate medication approval and post-approval monitoring, and whose job is it to oversee and amend this process?*
- 2) *What are some changes you would propose to change the current system of medication approval and post-approval monitoring?*
- 3) *What are some changes that have been proposed recently and what impact have these had?*
- 4) *How can patients and doctors influence the process of medication approval, monitoring, and drug surveillance?*



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## Case 2-1 (Day 1)

### Psychotropic medication use patterns in the past 20 years

Given recent controversy over the safety and efficacy of psychotropic medications in children and adolescents, there has been an increase of public and scientific literature on the pharmacoepidemiology of psychoactive medications in youth. Studies have found, for instance, that the overall rate of psychotropic medications in children increased threefold from 1987 to 1996, and the rate of co-prescription in children increased 7-fold during this time (Olfson 2002). Co-prescription was defined as a patient being prescribed medication from more than one drug class (i.e. antidepressant, anxiolytics, mood stabilizers) over the course of one year. The *New York Times* reported that over 86% of children treated with antipsychotic medication simultaneously received another psychotropic drug. Certainly, these type of medications are indicated in some circumstances, given the 5-9% of children who have serious emotional disturbances (Hogan 1999), but these trends raise questions about overmedication and cost, particularly now that the efficacy and safety of certain psychotropic medications in children has been called into question.

Over this same period, changes in health care delivery systems and reimbursement strategies have led to changes in the provider who were prescribing these medications; in one study, over 80% of psychotropic medications for children were prescribed by non-psychiatrists (Goodwin 2001). This change has contributed to the change in patterns of medication use for children. The antidepressants used by primary care physicians and psychiatrists to treat common psychiatric conditions in children can vary significantly. Primary care physicians are likely to use older medications such as tricyclic antidepressants (Zito 2001, Tinsley 1998). This change carries important ramifications for the nearly 4% of children currently being treated pharmacologically for emotional and behavioral problems and for their families, physicians, and teachers.

### The Decision to Medicate and Refer to Child Psychiatry

The decision to medicate this patient is a difficult one given the spectrum of “normal” behavior and the often changing behavior of adolescents struggling to forge an identity, separate themselves from parents, and express themselves. It should be a collaborative decision between patient, parent, primary care physician, therapist, and in certain cases psychiatric specialist.

Referral is indicated in patients with recurrent, chronic depression, depression complicated by comorbidities, suicidal intent or ideation, depression which limits functionality, and if the presentation is unclear. Referral is also appropriate if the primary care physician is unfamiliar or uncomfortable with prescribing psychotropic medications, but feels that a patient deserves treatment with antidepressants. However, the majority of psychotropic medication prescription is nonetheless handled in the primary care setting (Goodwin, 2001). Over 50% of prescriptions for psychiatric medications in children in 2005 were used to treat attention deficit-hyperactivity disorder (ADHD) and another 25% were used to treat depression (Harris, 2006).

An uncomfortable tension underlies the growing use of psychotropic medications in children. The number of child and adolescent psychiatry residents has not increased in the past decade; there were 712 in 1990 and 657 in 2001. The number of child and adolescent psychiatry training programs has decreased from 120 to 113 in the same period, and more than 20% of child and adolescent psychiatry residency positions go unfilled each year

(American Academy of Child and Adolescent Psychiatrists, 2005). Financial, logistical, and geographical barriers prevent many children and adolescents from accessing specialty psychiatric services. According to the Surgeon General's Report (2003), "This places a burden on pediatricians, family physicians, and other gatekeepers to identify children for referral and treatment decisions."

## **Case 2-2 (One Month Later)**

### **Medication Labels**

The FDA has a number of requirements for drug labels, including dosing information, monitoring requirements, dose modifications in specific clinical situations or patient populations, drug interactions, administration information, and warnings on drug safety and adverse events, including type of events, frequency, and severity. Drug labels are written by the pharmaceutical companies in accordance with these requirements of the FDA, and must be approved by the FDA. Official drug labels are wordy, lengthy, written in tiny font, and often discarded by the pharmacist before reaching consumers' hands. Their layout is confusing, and drug risks may be categorized either as "warnings," "cautions," and "adverse events." The FDA recently mandated a new "highlights" section for drug labels to increase readability and consolidation of safety warnings into a single section, but these rules currently apply only to newly approved drugs, and will not include drugs approved prior to 2001. As a result drug labels remain esoteric and largely ignored by patients, and not user-friendly to physicians.

### **Requirements for Drug Promotion**

The drug label also sets the legal parameters for advertising claims that may be made regarding a drug's indications and effects. Marketing claims made regarding medications are legally required to be based in sound clinical trials. Pharmaceutical companies are held to a higher standard than other industries in terms of requirements for marketing statements. This additional regulation is due to the fact that medication information is complex, and potential consequences may be severe and even life-threatening. Promotional materials must pertain to uses of a drug approved by the FDA; all other claims are "off-label promotion," and prohibited. Physicians may prescribe virtually any medication for any reason, but pharmaceutical companies may not market their products for off-label uses. Pharmaceutical companies have fought these regulations under as limiting their free speech or preventing truthful and necessary patient information, as have some patient groups often supported by the pharmaceutical manufacturers.

### **Off-label use**

Off-label use is prescription of medication for a condition for which no FDA approved indication exists. Off label use is common and in certain cases, including the treatment of pediatric populations or patients with rare diseases, it may reflect the standard of care. Use of drugs for indications not approved by FDA may represent a reasonable therapy, particularly for conditions for which no approved therapy exists, but may also expose patients to increased risk or poor efficacy and can increase health care costs. A recent nationwide study showed that 21% of the 725 million drug prescriptions written in the U.S. in the year 2001 were used without FDA approved indication, or off-label. Among medications used off-label, 73% lacked demonstrated clinical efficacy. Many studies of off-label efficacy are funded by the drug's manufacturer. Studies have shown that industry-funded studies favor publication of positive rather than negative or equivocal results, and often fail to criticize the safety or efficacy of the products involved. There is evidence that over 70% of off-label uses may have little scientific support.

Among SSRIs, only Prozac has clearly shown efficacy for treating depression in children, and therefore it is the only SSRI that is FDA approved to treat depression in

children and adolescents. The largest placebo-controlled, randomized clinical trial of SSRIs in children, the TADS study (Treatment for Adolescents with Depression), found a significant decrease in symptoms of depression with Prozac vs. placebo. As measured by the Childhood Depression Scale Revised, use of placebo was associated with a decrease of 19.4 points on a scale of 113, whereas use of Prozac was associated with a decrease of 22.6 points ( $P=0.003$ ). However, a meta-analysis of 15 published and unpublished studies published in the *Lancet* in 2004 found that when unpublished data was aggregated with published data, the risks of use of SSRIs (except for Prozac) outweighed the benefits. This study cautioned against the non-reporting of negative clinical trials and called for greater transparency by the pharmaceutical industry regarding reporting of negative clinical trials.

### **Suicide and Children**

In the United States in the last 40 years, suicide rates have doubled in the 15- to 19-year age group and tripled in the 10- to 14-year age group. Suicide is the 3<sup>rd</sup> leading cause of death among children age 10-19. This patient has clearly shown suicidal ideation, or “suicidality.” However, the patient does not appear to have a plan, access to violent means, or evidence of chronic thoughts of suicide, lowering her risk of completing the suicidal act. Risk factors for suicidal behavior in children and adolescents include: psychiatric disorders, previous suicide attempt, family history of mood disorder or suicidal behavior, history of physical or sexual abuse, exposure to violence, access to violent weapons, alcohol and drug use, exposure to suicide, social stress and isolation, and emotional and cognitive factors.

### **Concerns regarding SSRI use in children**

Much concern surrounds the use of SSRIs in children, because of a potential increase in suicidality, which has been found during initiation of treatment and following changes in dosing. No direct link between SSRIs and increased rate of completed suicide has been published. However, suicide incidence has been difficult to assess since children with suicidal ideation are often excluded from the large clinical trials of safety and efficacy of the antidepressants.

An FDA analysis of 24 placebo-controlled randomized trials of SSRIs in more than 4400 children treated for major depressive disorder found that 78 (2%) patients experienced adverse events involving suicidal ideation or behavior. Among those events reported, patients on antidepressants had an increased risk of suicidality during the first few months of treatment compared with those on placebo (4% vs. 2%), and the rate of suicidality among children assigned to antidepressants was twice that of the placebo group (RR 2.19; 95%CI 1.5-3.19). There has been concern over the adequacy of the methods used, as the number of events was small and the studies were not designed to measure suicidality as an outcome.

The TADS study excluded children at high risk for suicide (such as those with clear intent or a plan) but 30% of participants did have some evidence of suicidality at entry. There was no statistically significant change in suicidality after 12 weeks of treatment with Prozac.

Although the only SSRI FDA-approved for treatment of depression in children is Prozac, 30-40% of children and adolescents with depression do not respond to the initial antidepressant chosen. Therefore, use of non-approved medications may be necessary, including sertraline, citalopram, and paroxetine. Sertraline and Fluvoxamine are approved for treatment of obsessive-compulsive disorder in children.

### **Monitoring for Children on SSRIs**

In terms of monitoring, the diagnosis of Major Depressive Disorder should be confirmed before initiation of therapy. A full history, physical, and EKG should be obtained as well as a pregnancy test in girls. The FDA recommends that monitoring be conducted of all pediatric patients started on antidepressant therapy. Symptoms are expected to improve within 2-4 weeks after the target dose is achieved, and a trial of 4-6 weeks is considered adequate; if after this time there is no improvement in symptoms, change to another medication is indicated. The physician and family should then monitor for worsening depression and suicidality, as well as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, or mania. Monitoring should take place weekly for the first four weeks of treatment, biweekly for the next four weeks, at 12 weeks, and as clinically indicated beyond 12 weeks.

Sudden discontinuation of SSRIs can precipitate SSRI withdrawal syndrome, which may consist of symptoms of worsened depression, dizziness, paresthesia, myalgias, loose stools, visual disturbances, irritability, mood worsening, headache, and insomnia. The question of how to treat the pediatric patient on SSRIs with suicidality is therefore not easy.

The case highlights the issue that the vast majority of clinical studies are completed in middle-aged adults. Only 25% of approved drugs have enough clinical data in children to support FDA approval in this population. In 1997, Congress passed Section 505a of the FDA Modernization Act, known as the Pediatric Exclusivity Provision, which provided companies with an extra 6 months of patent protection for drugs for which studies were conducted in children as per FDA specifications. The Best Pharmaceuticals for Children Act, passed in 2002, extended the economic benefits extended for such research. These studies do not have to be published. As a result, a pharmaceutical manufacturer can spend a few million dollars organizing a small study and receive a market exclusivity extension that can be worth billions of dollars for blockbuster drugs (Li, 2007). This has encouraged studies in pediatric populations, but whether rigorous, well-controlled studies are produced that can lead to evidence-based pediatric prescribing is another question.

### **Side Effects, Allergies, and Adverse Drug Reactions (ADRs)**

An adverse drug reaction is a toxic reaction to a medical therapy.

An allergy is a hypersensitivity to a particular antigen (allergen) resulting in harmful immunologic reactions on subsequent exposures.

A side effect is a consequence other than the one for which an agent is used, which includes but is not limited to adverse events. For instance, a desired side effect of minoxidil is hair regrowth.

### **Physician Reporting of ADRs**

It is the responsibility of the physician to inform the patient of potential side effects to new medications. However, over 90 million Americans do not have adequate health literacy to enable them to safely navigate the healthcare system. Therefore, physicians cannot assume that patients will read and understand the side effect profiles listed on new medications, nor can it be assumed that patients will report side effects to physicians. It is therefore imperative that physicians explain possible side effects of medications, what patients may notice, and what to do if these side effects are noted.

### **Improving Physician Reporting Rates**

Although physicians are asked to report adverse events, the majority go unreported. There are several reasons physicians might not warn patients of potential adverse events, including not wanting to alarm patients regarding rare yet severe toxicities, lack of time during the office visit to mention these effects, concern over malpractice litigation, or lack of awareness on the part of the physician as to adverse events of a prescription drug. Other potential reasons for non-reporting include the belief that adequate studies of drugs are made prior to approval, belief that it is difficult to determine whether a particular reaction is definitively responsible for a reaction, or belief that one report would not change the overall course of medication use. In one study of doctor's attitudes underlying non-reporting in Germany, the main factors stated for non-reporting included: the ADR already being well-known (75%), too trivial to report (71%), causality uncertain (66%). In this study, 20% of physicians claimed to not know of the spontaneous reporting system, and 30% did not know how to report an ADR (Hasford, 2002).

Potential remedies for this underreporting might be to create incentives for asking about adverse reactions at follow up visits, facilitating this asking via electronic medical record prompts, standardized forms, or hospital-wide programs, rewarding those who report events each year, or penalizing those who never report such events. Any of these initiatives, of course, places additional burden on the already limited time allocated to the patient-doctor relationship. In the German study, 54% of physicians claimed that they would be more likely to report an ADR if provided education on the subject. An educational intervention for physicians in Portugal was successful at increasing the rate of reporting of ADRs (Figueiras, 2006).

### **Pharmaceutical Company Reporting of ADRs**

Pharmaceutical importers, manufacturers, and distributors are mandated to report adverse events to the FDA Center for Drug Evaluation and Research (CDER) via MedWatch, the reporting arm of the Adverse Event Reporting System. Healthcare professionals, consumers, and patients report adverse events on a voluntary basis to MedWatch. These events are categorized as death, life-threatening illness, hospitalization, birth defects, disability, or adverse events requiring interventions to prevent permanent damage. However, the timing differs based on the way that the reaction is classified -- more serious reactions must be reported by a manufacturer immediately, while less serious reactions can be aggregated and reported quarterly. Adverse event reporting by pharmaceutical regulatory authorities overseas is not analyzed by the FDA.

AERS reports are evaluated by clinical reviewers at CDER and the Center for Biologics Evaluation and Research (CBER). Further epidemiological studies may be requested when appropriate. Ultimately, the FDA may take regulatory actions towards public health, such as requesting that the manufacturer update a product's labeling information, sending a "Dear Health Care Professional" letter, or re-evaluating an approval decision. On some occasions, many years have elapsed between an FDA request to change a product's label, and the actual change, due to negotiations about the wording between the FDA and the manufacturer.

### **Reasons Underlying Underdiagnosis of ADRs**

As we see in the hospital, any recognized adverse event, whether immunologic or not is often labeled as an allergy. An additional problem is that physicians and other health professionals may not recognize a medication reaction or interaction as a cause of a patient's

symptoms such as nausea and vomiting, particularly when the patient is on multiple medications. This may be due to failure to ask about recent medication changes or how a patient is taking the medication, lack of awareness of the potential side effects of medications or their interactions, or a desire not to feel that the physician herself has caused the problem.

Case 2-3 (2 weeks later)

### **The Current Post-Approval Surveillance System for Medications**

Currently, the FDA requires a three-part series of trials for medication approval. “Phase IV” is the term used to refer to post-marketing studies, though it is not a formally designated stage of drug evaluation at all. In principle, an increased burden of proof for approval can decrease the number of beneficial medications available, yet lax criteria for approval can increase the number of potentially hazardous medications on the market. A balance must therefore be struck to maximize both safety and efficacy. After a drug is approved, there is no organized post-marketing surveillance currently in place in the American drug regulatory system, and the FDA’s regulatory authority decreases significantly. Though the FDA can suggest post-marketing follow-up analysis that needs to be done by a drug manufacturer, it has little authority to require drug manufacturers to complete these studies (Kesselheim, 2006).

The case of the medication rofecoxib (Vioxx) highlights this point. Rofecoxib, a selective cyclooxygenase inhibitor, was approved by the FDA in 1999 and widely used thereafter to treat arthritis and other forms of chronic pain. COX-2 inhibitors were promoted for decreasing the risk of GI bleeding compared to other NSAIDs. In 2003, rofecoxib generated \$2.5 billion in revenue for Merck. In 2004, the company voluntarily withdrew rofecoxib from the market because of evidence of a near-doubling of the rate of heart attack or stroke. Early randomized clinical studies of rofecoxib showed increased cardiovascular risk over traditional NSAIDs, but the manufacturer did not pursue investigation of that side effect after the drug’s approval; the drug was removed from the market only when the side effects surfaced again in other, unrelated trials.

When drugs are approved, drug manufacturers often make “commitments” to the FDA that they will pursue unresolved questions about drug safety through routine clinical trials. However, an FDA report in 2005 found that in its active file of such commitments, over 70% of such studies had not even been initiated. Despite preliminary reservations by members of the FDA advisory committee about its safety, insufficient post-marketing surveillance was conducted to follow up these concerns. Expanding the FDA’s regulatory authority to require post-marketing studies as a condition of marketing authorization and then to require the manufacturer to engage in a reapproval process based on these data would help ensure that the proper studies are conducted (Kesselheim, 2006).

The Prescription Drug User Fee Act was enacted in 1992 to expedite processing of new medications by requiring a fee paid by the pharmaceutical company for reviewing any new medication for approval. These fees are used to pay the salaries of FDA reviewers assessing new drug applications. The Act was seen by the pharmaceutical industry as a way to improve the FDA’s capacity to review new drugs, and came at a time when HIV activists were condemning the FDA’s slowness in approving potentially life-saving AIDS therapies. The act did reduce drug review time. On the other hand, critics have argued that PDUFA ties the FDA closely to the interests of the drug industry. For example, the law mandated deadlines for approval decisions, decreasing the availability of FDA scientists for other regulatory functions, and PDUFA in its original incarnation included no financing of post-marketing surveillance. No other federal regulatory body derives such a large proportion of its operating budget from the industry it oversees. Most worrisome is the notion that the “the organization (FDA) is accountable to the industry it regulates,” with all of the questionable ethics that arrive from that proposition (Avorn, 2007).

One important part of post-marketing safety in this country is that there is no existing active post-approval surveillance system. Adverse effects information relies heavily on spontaneous reporting of adverse events by health professionals, drug manufacturers, consumers, and others. These events are reported electronically to the Center for Drug Evaluation and Research, a branch of the FDA. The Adverse Event Reporting System is an important means of detecting trends in adverse outcomes, but an estimated 90% of adverse events go unreported each year. Several potential factors may account for this laxity in reporting, including lack of awareness of the importance of reporting adverse events, lack of recognition of adverse events, lack of time to report adverse events, lack of incentive to report or repercussions to non-reporting. This has led to the fear that dangerous drugs remain on the market. A recent report published in JAMA revealed that of the nearly 500 drugs approved between 1975 and 2000, 10.2% either acquired a new black box warning or were withdrawn from the market. Using these statistics, the author calculated a 25% risk of serious adverse drug reaction being discovered between the time a drug is approved and 25 years later.

Another problem with the current approach to post-market surveillance is that important adverse events may go unrecognized, including severe yet rare events, events occurring months or years after starting the drug, or events noted during off-label use. One system that has been proposed to address this issue is a national database encompassing demographics, hospitalizations and mortality, and all medications used to determine drug interactions as well as adverse events. This system is employed by the Finnish and resulted in findings that among over 15,000 patients hospitalized for a suicide attempt, those who had ever taken antidepressants were more likely to attempt suicide again but were less likely to complete the suicidal act, and had lower mortality rates overall (Klein, 2007).

### **FDA Warnings Regarding Drug Safety**

The FDA has a variety of mechanisms to warn the public and health care providers as to adverse drug events that carry the risk of death or significant injury. It is not generally able to demand additional studies be done on a particular product, or the aegis to restrict use of the product except in very rare circumstances. While it may remove an indication of the drug, off-label use may persist. Less serious warnings include “Dear Health Care Professional” letters and case reports in the medical literature and through public health warnings. Warnings may be required on the drug label, including bolded warnings without boxes, and the “black box warning”, which is the strongest warning the FDA requires before it may remove an indication of the drug or take it off the market completely. Deliberations between the FDA and the pharmaceutical companies over the content and wording of these warnings may be intense, and may delay placement of the warning for months or years.

In the case of SSRIs in children, in October 2003 the FDA issued a public health advisory regarding several reports of children and adolescents taking SSRIs who considered or attempted suicide. Later that year, the Medicines and Healthcare Products Regulatory Agency in the UK and the European Medicines Agency issued letters to doctors advising against the use of antidepressants in children and adolescents. In January 2004, the FDA directed manufacturers of antidepressants including SSRIs, TCAs, and MAOIs to include a boxed warning (“black box warning”) regarding the risk of suicidality (see warning below). Unfortunately, “suicidality” is an unclear term and may be easily misconstrued as indicating increased risk of completed suicide, which has not been shown to result from SSRI use.

*Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert established name] is not approved for use in pediatric patients.*

### **Pharmaceutical Companies and Overuse of Unsafe Drugs**

The recent experience with rofecoxib (Vioxx) has raised public awareness of the fact that the risk of adverse events may be suppressed by the pharmaceutical industry despite FDA guidelines and vigilance. In the case of antidepressant use in children, a famous case was brought against GlaxoSmithKline in 2004 by then-Attorney General of New York, Eliot Spitzer. The suit alleged that GSK withheld negative studies on the lack of effectiveness of Paxil in children and its potential risk of suicidality, and charged that an internal 1999 GSK document showed that the company intended to “manage the dissemination of data in order to minimize any potential negative commercial impact.” The suit stated that GSK conducted five clinical trials of Paxil in adolescents and children, yet published only one study that had mixed results. The results of one non-disclosed study were then publicized by an informant in 1999 and all of the studies were submitted to the FDA in 2002 for approval of Paxil for additional uses.

This suit raised the question of whether pharmaceutical companies should be required to disclose all studies conducted on a particular product, particularly as there is no “Journal of Negative Studies.” GSK, in turn, alleged that as Paxil was not approved for use in adolescents, it could not be expected to communicate the findings of these studies to physicians. A FDA health warning followed that cautioned health professionals to “carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality” and reinforced that only Prozac was approved to treat major depressive disorder in children.

### **Public Awareness of Drug Safety Risks**

Often, patients hear about medication risks through the Internet and the media, which may yield imperfect data. While it is important to warn patients of major drug reactions, mentioning every possible drug interaction and rare side effect is impractical; therefore, adequate surveillance coupled with mention of major, common side effects strikes a healthy balance of caution and protection.

## **Case 2-4 (5 days later)**

### **Drug Safety Concerns and Underuse of Medications**

Between 1998 and 2003 there was a 91% increase in prescriptions for SSRIs to children and adolescents in the U.S., and a 33% decrease in suicide rate. In response to widespread concern regarding the safety of antidepressants in children, there was a decrease in prescription of SSRIs from 2003-2004 of 22%, and an increase in the child and adolescent suicide rate of 14% during this time period, the largest change in suicide rate seen since 1979. The only other increases in suicide rate since 1998 were a 1% increase in 1998 and a 3% increase in 2000. While this change is correlative, not causal, these statistics reinforce the fact that antidepressants increase suicidality not suicide rate, and that there is a fine balance between medicating the severely depressed and monitoring for adverse effects.

### **Pharmacovigilance and Drug Safety**

Pharmacovigilance is the science of detection, assessment, and prevention of adverse effects of medications. It includes the spontaneous reporting system and mechanisms for systematic surveillance of patients taking drugs with potential serious adverse drug reactions.

One of the well-defined surveillance systems relates to use of isotretinoin (Accutane) for acne. Isotretinoin can cause fetal abnormalities, and any female patient must have a negative pregnancy test 2 weeks prior to starting isotretinoin, and must avoid pregnancy while on the medication and for one month following use, with 2 forms of birth control. Because 2000 women using isotretinoin became pregnant between 1988-2003, providers and patients are now required to enroll in the iPLEDGE program to prevent pregnancy.

The serotonergic antagonist alosetron (Lotronex), introduced by GlaxoSmithKline for treatment of tenesmus and urgency associated with irritable bowel syndrome in women highlights the struggle within the current system to attain adequate pharmacovigilance. Alosetron was approved for women with diarrhea-predominant IBS in 2000. Within 4 months, the FDA received seven reports of serious complications of constipation, in which six patients were hospitalized and three required surgery, including one total colectomy for obstruction. During the same period, 8 reports of ischemic colitis were received, requiring 4 patients to be hospitalized and 4 to require colonoscopy. In response, the FDA added a safety labeling warning of risk of complications and stipulating that only women with chronic IBS should be prescribed the drug, that women should not use the drug while constipated, and that any woman with a history of severe constipation or ischemic colitis should not use the drug. The labeling also included a brochure for patients describing warning symptoms and appropriate response. Following continued reports of adverse effects, including death, alosetron was withdrawn from the market later that year. In 2002, the FDA reapproved alosetron for limited marketing, narrowing the indication to use only in patients with severe diarrhea-predominant IBS, which includes diarrhea and one or more of: abdominal pain, urgency or incontinence, or impact on daily functioning due to IBS. Potential patients must have IBS for greater than 6 months, have ruled out acute gastrointestinal or surgical conditions, and have failed other forms of medical management. In addition, physicians must enroll in a voluntary risk management program offered by GSK in order to qualify to prescribe alosetron.

### **Physician-physician communication**

There are many different ways a patient's care is communicated to primary care physicians: through electronic medical records and letters from specialists and the emergency department. However, such communication may not be sent, and given lack of universal electronic medical records and interfaces between different health care systems, information is easily lost, with resultant errors in treatment, medication, and potential duplication in diagnostics. In a recent Kaiser survey, 34% of people say that they or a family member had experienced a medical error at some point in their life, and of frequent health care consumers – those with chronic illness – 50% say that they have experienced a medical error in their own care or that of a family member. Consumers were more likely to cite problems with physician workload, inadequate staffing, and poor communication among healthcare providers as causes of medical errors than any other cause.

## Day 5 (Six months later)

### **Regulation and oversight of post-approval monitoring and new directions**

The FDA sets the standards for medication approval and post-approval monitoring in this country, but pharmaceutical policy activists and watchdog groups also monitor the process and offer academic and nonacademic criticisms of the current process as well as specific violations. Via spontaneous reporting, it is the job of the healthcare professional and healthcare consumers to report adverse events and medication interactions. It is the role of the FDA to alert the public to dangerous drugs via labeling and other measures cited above. It is the role of the pharmaceutical companies to cite potential side effects of medications in all advertising, and the role of the media to report grievances and controversies involving specific medications to the public.

Following the rofecoxib episode and the controversy surrounding SSRIs in children, the FDA asked for a review of its safety surveillance system by the Institute of Medicine (IOM), a subsidiary of the National Academy of Sciences which provides objective evidence-based advice to policymakers, health professionals, the private sector, and the public. The IOM report, “The Future of Drug Safety: Protecting and Promoting the Health of the Public” (2007), and described in an article in the *New England Journal of Medicine* by Mark McClellan, former head of the Centers for Medicare and Medicaid Services (CMS), details four major areas needing improvement in the current medication FDA-driven post-approval monitoring scheme. The first is resource allocation for the FDA. The report concluded that the FDA is “severely underfunded” by Congress and as a result dependent on user fees, resulting in the conflicts noted above. The report recommended increasing the CDER budget by nearly \$30 million.

Second, the proposal encouraged new regulatory capabilities of the FDA, which would require medication guides for patients, limit direct-to-consumer advertising, require certain post-marketing studies, restrict which physicians can prescribe a drug, require documentation of appropriate laboratory testing for specific drugs with significant risk for ADRs, such as isotretinoin, as described above. Critics argued that the measure would complicate drug prescribing, burden physicians and patients and encroach upon the already limited time for office visits, lead to substitution for other, less indicated medications, and thereby lead to medication errors.

Third, the report called for strengthened post-marketing surveillance, by mandating development of a national electronically-driven risk information database based on patient experience with each new drug. Such a database could detect trends toward ADRs more quickly and direct follow-up studies and warnings where necessary.

Finally, the report recommended changes in management and oversight of CDER, including increased presence of experts in pharmacology and epidemiology throughout the pre-and post-marketing review process. The report pointed out, for example, that oversight of CDER has changed hands 10 times over the past several years, which severely compromises continuity and moving forward as an institution.

The same year, the Government Accounting Office (GAO) also issued a report in light of the concerns surrounding FDA assurance of drug safety. It also highlighted FDA organizational structure and decision making, the effectiveness of the current process, and the steps the FDA was taking to improve its decision making process. The GAO recommended, as did the IOM, that Congress expand the FDA’s authority to require pharmaceutical companies to conduct post-marketing studies when needed, and that the

FDA track post-market drug safety issues in a more systematic way, revise its policy regarding post-marketing decision-making, and clarify the way decisions are made and organizational roles.

The FDA responded with the creation of a Drug Safety Oversight Board, and a draft of new policy on post-marketing decision making. In 2007, Congress reauthorized the Prescription Drug User Fee in a law known as the FDAAA (FDA Amendments Act), which partially implemented some of these recommendations. It preserved the user fee mechanism, which on the one hand increased funding to an organization which might otherwise be stymied by increased regulatory demands in the face of recent scandals, but also put 40% of the funding of the CDER in the hands of the industry it regulates.

Another potential source of change given the continuing issue over selective reporting of negative studies is the medical journals themselves. In 2004, the International Committee of Medical Journal Editors, which includes publications such as NEJM and JAMA, began requiring as a condition for publication registration in a public trials registry at the stage of patient enrollment in the study. Since 2005, the Clinical Trials Registry has been maintained by the federal government to provide transparency of medical trials, particularly as they pertain to safety testing in pharmaceuticals.

### **Patient and physician input in the process of medication surveillance**

Patients can inform themselves of potential drug side effects by asking their doctor, reading the drug label, and investigating on the internet. They can then report side effects to their doctor, or report ADRs directly via MedWatch. In addition, patients can publicize ADRs and safety checks they feel are lacking, and lobby Congress to increase funding for CDER and the FDA. Doctors can selectively prescribe medications they deem safe and effective after familiarizing themselves with the clinical trials and post-marketing data, and aim to prescribe within FDA approval guidelines when available. They can remain cognizant that their patient population may not resemble the clinical trial population, and amend their prescribing as such. They can also push for more diversity in clinical trial populations. They can mention potential side effects to patients, and implement adequate surveillance systems to monitor their patients starting on new medications. They can ask patients specifically about side effects at surveillance appointments and in routine follow-up, and can remember to report ADRs to MedWatch as well as to remain abreast of post-marketing data regarding medications they prescribe. They can lobby Congress to reduce FDA dependence on user fees by increasing appropriations to FDA and CDER in particular, and can also publicize the inadequacies in the current system as they see pertaining to their patients.

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