ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES
QuarterWatch
Monitoring FDA MedWatch Reports

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ANNUAL REPORT ISSUE

Oral anticoagulants the nation's top risk of acute injury from drugs
Millions at risk from withdrawal symptoms
FAERS: A key monitoring system suffering from continued neglect

Executive Summary

This year's annual report issue focuses on drugs and specific adverse reactions that affect large patient populations and involve substantial numbers of serious injuries. In the absence of any official or unofficial systematic assessments of overall harms attributable to the therapeutic use of drugs, we examine notable signals of significant drug risks as reflected in 1.2 million adverse drug event reports received by the U.S. Food and Drug Administration (FDA) in 2016. Key findings are described below.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP). We analyze computer excerpts from the FDA Adverse Event Reporting System (FAERS). These reports (best known as MedWatch reports) are a cornerstone of the nation's system for monitoring the safety of prescription drugs after FDA marketing approval.

In calendar 2016 the FDA received 1,165,073 new reports of adverse events from the therapeutic use of prescription and over-the-counter drugs, a 1.9% decline from the previous year. This marks the first annual decline since the year 2000. Event reporting is voluntary for consumers and health professionals, who can report suspected events either directly to the FDA (n = 50,878 reports) or to drug manufacturers (n = 1.1 million reports). Manufacturers are required to report all adverse events they learn of in the normal course of business, from either consumers or health professionals, or through marketing and educational activities. A few drugs have special restrictions and reporting requirements that generate much larger numbers of reports than for drugs prescribed and distributed through normal pharmacy channels.

One indicator of the drug risks to the U.S. public is the subtotal of new adverse event reports that are domestic in origin and are fatal, disabling, or serious enough to result in hospitalization or have other severe medical consequences. In 2016, the FDA received 311,790 reports in this category, a decline of 8.4% from the previous year. The annual toll included 45,255 (14.5%) patient deaths, and 110,179 cases (35.3%) requiring hospitalization. For 8.1% of the 2016 cases, a medication error was shown as contributing to the injury reported. These annual totals include the new data released for 2016 Q4, which are summarized in this report. The FAERS report totals greatly underestimate the extent of drug-related injuries actually occurring, with wide variation among drugs and events. Published estimates show that between 1% and 34% of all serious events are reported, including approximately 8%-10% for brand name drugs.

The types of injuries reported affected every body system and include severe damage to the kidneys and liver, fatal cardiac events, cancer, potentially life-threatening allergic reactions, as well neuropsychiatric effects such as depression, suicidal thoughts, and aggressive and violent acts. Although these largely voluntary reports capture only a fraction of the severe injuries that occur, the therapeutic use of drugs constitutes a major public health risk of the same order of magnitude as illicit use of drugs or violent crime. Two notable drug risks are examined in these 2016 data.

Exposure of the U.S. population to therapeutic drugs is extensive. In 2016, a total of 4.5 billion outpatient prescriptions were dispensed, a 1.9% increase over 2015, according to QuintilesIMS. Of that total, 89.5% were for generic drugs, the remainder for brand name drugs.

Oral Anticoagulant Drugs

The unacceptably high risks of oral anticoagulant drugs are illustrated in new results from two data sources: the FAERS adverse event reports for 2016, and a new systematic study by the Centers for Disease Control and Prevention (CDC).

Anticoagulant drugs–led by rivaroxaban (XARELTO)–accounted for 21,996 reports of severe injuries in the U.S., including 3,018 reported deaths, according to our analysis of 2016 FDA adverse event data. Practically all these injuries (n = 17,218) were from hemorrhages, making bleeding one of the most frequently reported serious adverse drug effects of all types. This class of drugs also includes warfarin (COUMADIN), apixaban (ELIQUIS), dabigatran (PRADAXA), and edoxaban (SAVAYSA).

A separate CDC study released in late 2016 showed that anticoagulant drugs accounted for more emergency department (ED) visits for outpatient adverse effects than any other class of drugs in therapeutic use, including opioids (non-abuse visits), antibiotics, and diabetes drugs. The anticoagulant events were mostly severe, with 48.8% requiring a hospital stay. Further, using these data, QuarterWatch estimates 6.3% of patients exposed to an anticoagulant for one year will need to visit the emergency room. Over the 10-year history of the CDC adverse event study, emergency department visits for anticoagulant adverse drug effects increased more than 2-fold. The CDC data also illustrate that FAERS voluntary reporting substantially underestimates the drug-related injuries actually occurring. While not strictly comparable, the CDC's systematic study shows an estimated 228,600 ED annual visits for anticoagulants, or more than 10 times the FAERS total of voluntary reports.

In this report we outline five positive steps that can be taken to improve the safety of this high-risk class of drugs. It examines how and why industry promotion of a new generation of oral anticoagulants for ease of use rather than improved safety has led to tens of thousands of emergency room visits and hospitalizations.

Drugs with Withdrawal Effects

Nausea. Dizziness. Electric shock-like sensations. Insomnia. Anxiety. These are the leading symptoms reported by patients who stop taking a wide variety of psychoactive drugs, including antidepressants, sedatives/hypnotics, and opioids. While issues involving opioid withdrawal are well known, the safety issue extends to drugs with even larger patient populations, most notably antidepressants and a large group of pain and anti-anxiety drugs. For many of these drug classes, the severity, duration, and likelihood of withdrawal effects is underestimated in prescribing information for physicians and Medication Guides for patients. In other cases, withdrawal effects were too poorly studied to support adequate estimates of injury rates.

We analyzed 4,016 reports of drug withdrawal effects in 2016 and identified 42 drugs with clear signals for withdrawal effects. Basic neuroscience reveals that the chemical intrusion of psychoactive drugs into complex, interacting signaling circuits changes how they function. When the drugs are withdrawn, especially abruptly, a wide array of symptoms occur as these circuits seek to readjust. The population at risk is very large. Members of the QuarterWatch team published a scientific study showing that about 1 in 6 adults were

taking a psychiatric drug, 84.3% long-term where withdrawal effects are more likely. Millions more take nerve pain or opioid medications on a long-term basis. The four neurotransmitters or receptors associated with withdrawal effects and reported drugs were:

Serotonin. Although they have multiple effects, most antidepressants inhibit the reuptake of serotonin. The largest number of withdrawal reports in 2016 (n = 888) was for duloxetine (CYMBALTA) which is active on serotonin, norepinephrine, and dopamine receptors. Clinical discontinuation studies of antidepressants with shorter half-lives showed 46%-78% of patients experienced two or more symptoms. We also saw signals for venlafaxine (EFFEXOR), desvenlafaxine (PRISTIQ), sertraline (ZOLOFT), and paroxetine (PAXIL).

Gamma-aminobutyric acid (GABA). In most settings, drugs that enhance the function of GABA receptors and increase the effects of this neurotransmitter have sedative, hypnotic, or anti-anxiety effects. The most widely used GABA-related drugs are benzodiazepine tranquilizers, notably alprazolam (XANAX), clonazepam (KLONOPIN), and lorazepam (ATIVAN). Another widely used sleep medication, zolpidem (AMBIEN), also targets GABA receptors, and also had a signal. A third family of drugs provide a synthetic form of GABA and can affect perceptions of pain. Withdrawal symptom signals were also identified for two drugs in this group, pregabalin (LYRICA) and gabapentin (NEURONTIN).

Opioid. This class of drugs is the best known for withdrawal effects, and 13 different opioids made the 2016 list. It included the most potent opioid, fentanyl, the most widely used opioid, acetaminophen-hydrocodone, as well as drugs to treat opioid addiction and overdose, buprenorphine, methadone, and naltrexone.

Dopamine. Antipsychotic drugs block normal signaling from dopamine D_2 receptors, but affect other neuroreceptors as well. We identified signals for the two widely used antipsychotics, quetiapine (SEROQUEL) and olanzapine (ZYPREXA). A signal was also seen for methylphenidate (RITALIN), which has an indirect effect on dopamine neurotransmission.

Widespread adult exposure to these drugs with these withdrawal symptoms is compounded by two other problems: Clinical testing for withdrawal effects ranges from limited to non-existent, and standard information for physicians and patients is inadequate for many drugs, and, in some cases, frankly misleading.

Adverse Event Reporting System

FAERS is the nation's primary system for monitoring the risks of therapeutic drugs after approval. It is the source data for a large majority of FDA withdrawals, warnings, and restrictions. One goal of QuarterWatch is to monitor independently how well the system is working. For our 2016 annual assessment, we were unable to identify any substantial improvements in this aging monitoring system, which continues to suffer from FDA management neglect and failure to update its reporting requirements for the digital era.

The simplest measure of system performance is the extent of reasonably complete reports. When an event is reported, substantial detail is needed to evaluate whether the suspect drug was a credible suspect for the medical disorder described. Details are needed to understand the medical characteristics of the adverse event reported. To examine report quality, our analysis was limited to cases with a serious outcome such as death or hospitalization.

When consumers and health professionals took the initiative to report a suspected serious adverse drug event directly to the FDA, report completeness and quality were reasonably good. In 2016, 85% were judged reasonably complete, meaning the cases included minimal standards of age, gender, an event date, and at least one valid medical term to describe what happened. The limitation is that for 2016, only 4.4% of the serious adverse event reports were submitted directly to the FDA. The remaining cases came from drug manufacturers.

For drug manufacturers, only 42.5% of reports were scored as reasonably complete, with the most notable shortcoming being a failure to provide patient age, which occurred in 36.8% of manufacturer reports. Large manufacturer performance in reporting age and gender in the appropriate fields ranged from 96.9% for Actelion, a specialty drug subsidiary of Johnson & Johnson, to 0.3% for Cipla, a generic drug manufacturer based in India.

We also examined whether postmarket safety reporting for newly approved drugs might be more complete than for older drugs with better known safety profiles. Among 36 drugs approved in 2015, we identified 17,133 reports, with only 44% scored as reasonably complete, about the same results as for brand name drugs on the market for longer periods.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a reporting system that does not collect data systematically. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. While the sheer numbers of case reports have scientific weight, because of variation in reporting rates, they reveal little about how frequently the events occur in the broader patient population. More complete disclaimers and descriptions of our criteria are included in the Methods Summary section of this report. A disclosure statement expands our description of this project and its staff.

Conclusions

The 1.2 million reports of deaths and injury from approved therapeutic drugs in 2016 underline the need for the FDA to balance demands to approve new drugs more quickly with increased emphasis on drug safety and the systems that monitor drug safety.

The starting place is better data about the number and severity of injuries, the drugs most frequently implicated, and the kinds of injuries most likely to occur. We could identify one modest program at CDC monitoring the prevalence of acute adverse drug events seen in the emergency room; although valuable, it could not capture many kinds of adverse drug events.

We recommend that the CDC and FDA convene an expert panel to design how to expand the existing CDC program to capture the full scope of adverse drug reactions and suspect drugs, including in-hospital events, and publish these data annually to guide policy. We know how many buildings burn; the government counts elevator accidents, workplace injuries, auto collisions, aircraft near misses, and petroleum spills. An accurate and comprehensive assessment of the risks of therapeutic drugs is an essential foundation for progress in drug safety.

The FDA also needs to update FAERS, which has suffered from more than a decade of regulatory neglect. The agency's technology has improved, and the FDA now receives more than a million reports a year through nearly all-digital systems. But the completeness and quality of manufacturer reports are poor, and the regulations and guidances that set reporting requirements are obsolete and date to before the digital era. There is little point, for example, in requiring manufacturers to report deaths of patients with largely fatal illnesses without determining whether the drug itself contributed to the death. The agency has invested more than $200 million in its Sentinel system for postmarket surveillance using electronic health data. While the system provides valuable perspectives on patient risks, because of reliability problems in the underlying data it has not been the primary source for a single drug withdrawal, boxed warning, contraindication, or warning since inception in 2009. The agency has indicated that it expects to revise its 2001 draft Guidance for Industry on postmarket safety reporting, but details about the scope and depth of this review were unknown.

This annual QuarterWatch report also outlines two major drug safety issues where better focus on drug risks can substantially reduce the extent of injury. Few outpatient drug treatments cause injuries to 6% or more of the patients treated for a year. However, those risk levels are seen for anticoagulant drugs, and a CDC study shows injuries have increased. Drug withdrawal effects are well known for the opioids, but not for antidepressants and certain other drugs. In systematic studies, several antidepressants caused withdrawal effects in more than 44%-78% of patients attempting to discontinue the drug, and these problems were reflected in thousands of adverse drug event reports. As we discuss in this full report, withdrawal effects are not systematically assessed, and the information for patients and doctors about how to discontinue many drugs is incomplete or inaccurate. Finally, our previous finding that 84.3% of adult users of psychiatric drugs are taking these drugs long-term raises the question of how many tried to stop use and misinterpreted withdrawal symptoms as sign their symptoms were recurring.

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Methods Summary

QuarterWatch monitors the safety of prescription drugs through analysis of adverse drug events reported to FDA by consumers and health professional, either directly to the agency or through drug manufacturers. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source.[1] A full description of our methodology is available on the QuarterWatch pages of the ISMP web site. (http://www.ismp.org/QuarterWatch/detailedMethods.aspx)

The severity of the adverse event was classified as serious under FDA regulation[2] if the case report specified an outcome of death, disability, hospitalization, required intervention to prevent harm, was life threatening, or had other medically serious consequences. Cases without these outcomes were classified as not serious, and all new cases were included in this analysis unless indicated otherwise. Earlier QuarterWatch issues have focused primarily on a subset of adverse events, those that are domestic and coded with serious outcomes. We continue to monitor domestic, serious reports as an important subset of the newly released case reports.

In these data, the adverse events reported are described by medical terms selected from the Medical Dictionary for Regulatory Activities (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and postmarketing reports.[3] The MedDRA terminology also defines broader categories of adverse events that can include any of a list of more specific and related medical terms. We use these categories, called Standardized MedDRA Queries (SMQs), to identify possible cases of some adverse events.[4] We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that also combine several related but more specific medical terms. High Level Group Terms (HLGTs) combine several related HLTs, and System Organ Classes combine the terms into 27 categories. The QuarterWatch database was updated in November 2016 to MedDRA version 19.1.

To identify signals for reports of drug withdrawal symptoms, we utilized the disproportionality method of Evans.[5] For example, a signal for insomnia is identified when a drug has twice as many insomnia cases as expected for that drug, were the events randomly distributed. This is known as the Proportional Reporting Ratio (PRR). We limited the study population to evaluable drugs (those with at least 50 cases of all types in the preceding 12 months). To rule out a chance effect, a candidate drug had to include 5 or more insomnia cases, a Yates X^2 of at least 4, and probability that the event occurred by chance of ≤ 0.05.

To provide a broader perspective on the adverse events reported, we assess the patient exposure to drugs on the basis of dispensed outpatient prescription data provided by QuintilesIMS Inc. The data we rely on are an estimate of total non-governmental prescriptions dispensed through retail and mail channels. Our agreement with QuintilesIMS includes the following disclaimer:

"The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from an QuintilesIMS Inc. information service called the National Prescription Audit™ for 2016 (All Rights Reserved). Such statements, findings, conclusions, views, and opinions are not necessarily those of QuintilesIMS Inc. or any of its affiliated or subsidiary entities."

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the case report. The drug names are standardized to drug ingredient names based on the National Library of Medicine's RxNorm terminology. When cited in the text, tables, or charts, the brand name of drugs used is normally the one most frequently indicated on the case reports but may account for a small or large share of the actual reports identified. Unless specified, QuarterWatch does not distinguish dose, route of administration, or extended release and other preparations.

Results

Report Trends

Short-Term Annual Trends

In 2016 the FDA received 1.2 million adverse event reports from all sources for injuries of all severity, a 1.9% decline from the previous year. This is the first year-to-year decline since 2000, and only the second decline since the current reporting system was established in 1998. Declines were seen in numerous categories, including U.S. domestic reports of fatal and serious injuries (-8.4%) and reports originating from consumers (-10.4%). The only notable exception was an increase in reports for serious events occurring outside the U.S., which totaled 282,149 cases, an increase of 8.8%.

To calculate the annual trends we included the newly released data for 2016 Q4. In this quarter the FDA received 255,469 new reports, a 7.9% decline from the previous quarter, and a 13.2% decline from 2015 Q4. The trend was similar for the key subset of domestic, serious and fatal adverse drug event reports. In 2016 Q4 the FDA received 67,041 reports in this category, a decline of 13% from the previous quarter and 15.2% from the same quarter one year earlier. This is the third quarter in a row to post a decline in domestic, serious and fatal adverse drug events.

Long-Term Annual Trends

Viewed from the perspective of a decade, there has been a very large increase in reports submitted to FAERS. In 2007, the FDA received only 273,100 case reports in the entire year, compared to the 1.2 million in 2016. Some of these changes do not reflect increased risks to the U.S. public; the two biggest effects are from changes in digital technology and the globalization of the pharmaceutical industry. Since 2006, the number of foreign reports has grown more than 3-fold, from 74,935 to 282,149. Because foreign reports are generally limited to health professionals (rather than consumers) and are limited to events with a serious outcome, this additional volume of reports helps support studies associating various kinds of adverse events with suspect drugs. The second long-term trend is greatly increased numbers of events that are not serious, but occurred in the U.S. Since 2007 these non-serious events have increased more than 6-fold from 81,882 in 2007 to 526,795 reports in 2016. A change to all-electronic submission for drug manufacturers was the largest factor expanding the flow of non-serious reports into the FAERS system. Previously, many of these reports were received but regarded as low-priority for entry into the computer system for analysis. A third category has been the growth of restricted distribution drugs, where much more extensive surveillance of the patient population occurs, in some cases including every patient.

A portion of this long-term increase, however, reflects the increased use of drugs with substantial toxicity. Previous issues of QuarterWatch have also reported on new drugs.[6–8] Notable are three classes of biological products and small molecule drugs that suppress the immune system: 1) The anti-TNF biological products for rheumatoid arthritis and Crohn's disease; 2) Drugs and biological products for psoriasis; 3) Immunosuppressants for multiple sclerosis. The newer anticoagulants, also discussed in this issue, cause injury in more than 6% of patients per year. Two new classes of Type 2 diabetes medications have also increased reports of new kinds of adverse events.[9,10] A large number of new cancer treatments (with 14 new drugs approved since January 2015) also increases totals and reflects the substantial risk of these new agents.

Oral Anticoagulant Drugs

Harms from oral anticoagulant drugs earn rank as the highest priority drug safety problem in 2016 by several measures. In clinical trials these drugs have a high rate of injury, causing bleeding in 8%-19% of patient treated for a year.[11–13] It has a large and growing patient population, notably among the elderly,

with an estimated 3.8 million patient-years exposure by the end of 2016, according to dispensed outpatient prescription data from QuintilesIMS. Reports of serious injury and death also featured prominently in the 2016 FAERS data. We identified 21,996 reports of severe injury in the U.S. implicating 5 oral anticoagulants, including 3,018 patient deaths. The primary suspect drugs were rivaroxaban (XARELTO), warfarin (COUMADIN), dabigatran (PRADAXA), apixaban (ELIQUIS), and edoxaban (SAVAYSA). As will be shown below, these totals likely reflect less than 10% of events actually occurring.

A systematic study of emergency department (ED) visits for adverse drug events confirms and extends these findings.[14] This Centers for Disease Control and Prevention (CDC) study showed that the oral anticoagulant drugs caused more emergency department visits than any other class of drugs, and 2.4 times more than opioids in therapeutic use. Furthermore, the CDC data, from 2013-2014, showed a problem getting steadily worse.

The Wrong Turn

Warfarin, a close chemical cousin of rat poison, has been a standard but hazardous treatment for preventing unwanted blood clots since 1954. The largest patient population are those with atrial fibrillation, a heart rhythm disorder of the two upper pumping chambers of the heart that creates a setting where blood clots may form and then be pumped into the brain, creating ischemic strokes. Starting in 2010, the pharmaceutical industry began marketing modern replacements that more directly block formation of the thrombin threads that bind together platelets that aggregate to form a blood clot. But in a decision that would cause tens of thousands of hemorrhages, industry opted to develop new oral anticoagulants that were easier to use rather than safer than warfarin. While warfarin requires biweekly monitoring and individual dose adjustment, the new generation of oral anticoagulants was tested and approved at only one or two therapeutic doses, no monitoring required, recommended, or in most cases possible. Two of the four new agents proved to be poorly suited to greatly simplified dose schemes. Soon after approval of the first agent, dabigatran (PRADAXA), QuarterWatch raised questions about whether its single therapeutic dose was causing excess bleeding in the elderly.[15] A second new agent, rivaroxaban (XARELTO), was marketed for easier once-a-day dosing (instead of twice) despite having a shorter half-life than the others. Another QuarterWatch report[7] noted that this pharmacodynamic limitation resulted in higher than optimal anticoagulation early in the 24-hour cycle, and potentially suboptimal effects later after the body cleared much the active drug.[16] With two doses better adapted to patient characteristics, only apixaban (ELIQUIS) had a credible claim to a modest improvement in safety over warfarin.[11] The initial opportunity to markedly improve the safety of this high-risk treatment was lost.

The FAERS Data

Nearly seven years after approval of the first of the new oral anticoagulants, the drugs continue to account for large numbers of reported serious injuries and deaths in the U.S. The overwhelming risk of harm seen in these data was hemorrhage. Among the 21,996 domestic reports, 17,218 cases (78.3%) involved hemorrhages in some form. Gastrointestinal hemorrhages were most numerous (n = 8,495), but we also identified 1,019 cerebral hemorrhages, and another 790 possible cases of cerebral hemorrhage. In other cases, the site of bleeding was not identified. From the earlier testing of anticoagulants for stroke prevention it was known that lowering the risk of ischemic strokes from blood clots increased the risk of hemorrhagic strokes.[17] The only other notable adverse effects of the anticoagulants were renal failure and impairment (n = 835).

Because of higher reporting rates for brand name vs generic drugs, the results for suspect drugs skewed toward the new brand name products. Rivaroxaban alone accounted for 15,043 cases (68.4%), apixaban for 3,148 (14.3%), dabigatran for 1,944 (8.8%), and edoxaban with 108 cases (0.5%). The generic warfarin accounted for 1,753 cases (8%). The totals for rivaroxaban were also increased by large numbers of reports with event dates in prior years but first reported to the FDA in 2016.

The CDC Study of Emergency Department Visits

When systemically measured at the door of emergency departments (EDs), the results for anticoagulant drugs illustrate both the high incidence and the severity of the risks associated with this class of drugs. The new CDC study published in late 2016 but using 2013-2014 data [14] showed:

- Anticoagulants alone accounted for 17.6% (95% CI 14.1-21.0) of all ED visits for drug adverse events, more than any other class of drugs, even those taken by much larger patient populations.

- The events were severe, with hospitalization required for 63.8% (95% CI 49.8-77.8) of patients taking direct thrombin inhibitors (dabigatran), 50.4% (95% CI 43.0-57.8) for those taking Factor Xa inhibitors (rivaroxaban), and 48.5% (95% CI 41.8-55.1) for warfarin. (For comparison, visits linked to therapeutic use of opioids resulted in 24.6% hospitalized, antibiotic reactions, 7.1%.)

- When adjusted to count only patients exposed to the oral anticoagulants, QuarterWatch estimated that 6.3% of patients exposed for 12 months will need to visit the emergency department, with 3.1% requiring hospitalization.

- Anticoagulant drug injuries increased over the 10-year history of the CDC survey. From 2005-2006 to 2013-2014, the anticoagulant-related visits increased more than 2-fold, reflecting a combination of factors that include increased use, different drugs that may have increased risk, and better event identification in the survey. In the two years since the cutoff date for the CDC study, the overall use of anticoagulants continued to increase, with the newer agents replacing some warfarin use.

Strengths and Limitations of CDC Study

The CDC results were extracted from the only systematic U.S. government study of adverse drug events using an explicit methodology that can produce reliable estimates of drug-related injury. It has been conducted since 2004 by the CDC and the Consumer Products Safety Commission, in cooperation with the FDA. Officially called the National Electronic Injury Surveillance System-Cooperative Adverse Drug Events Surveillance System, it monitors all ED visits to identify adverse drug events in a representative sample of 58-64 hospital emergency departments.[14]

The estimates above also have several limitations. The CDC study only identified acute events requiring a visit to the ED, and thus did not capture some kinds of important outpatient adverse drug events, including many psychiatric symptoms, several forms of digestive and breathing problems, movement disorders, and those that resulted in drug discontinuation or a physician's office visit. The ED study also did not include in-hospital events, out-of-hospital deaths, and direct hospital admissions. It also would not capture injuries that were not recognized as drug-related in the emergency department.

In the specific case of anticoagulant drug-related injuries, the CDC study methodology would not capture events that were direct hospital admissions, were treated in doctors' offices, or resulted in out-of-hospital death. On the other hand, the reported CDC events included a substantial number of cases where a monitoring test showed dangerously elevated levels of warfarin and the patient was immediately sent to the ED to assess overdose risk, but without an acute injury.

Progress on Dabigatran

By the end of 2016 two safety concerns about dabigatran had been addressed, at least part. It became the first of the newer agents with an FDA-approved antidote for dabigatran hemorrhage. Unlike warfarin, the new agents lack an antidote to reverse the anticoagulant effect when the drugs cause bleeding. The agency approved idarucizumab (PRAXBIND) in late 2015 using three different expedited pathways to speed approval: a "breakthrough" drug designation, a priority review, and accelerated approval.[18] It also received orphan drug status. The monoclonal antibody binds to dabigatran, rendering it ineffective. By one measure it was notably effective. Two measures of blood clotting function returned to normal within 10-30 minutes of

starting the drug in 88%-100% of the 123 bleeding patients tested.[19] While the anticoagulant drug effect was quickly neutralized, bleeding continued in many cases. The median time to halting bleeding was 9.8 hours, and one patient bled for 62 days. Of the 123 patients in which the antidote was tested, 26 died despite the antidote, including 12 patients in 2 days or less. These results emphasize the importance of preventing bleeds rather than treating them.

A second dabigatran safety issue resolved was the unavailability in the U.S. of a reduced therapeutic dose for older patients or those with moderately impaired kidney function. The FDA was the only regulator among the advanced countries that limited the drug to a single 150 mg therapeutic dose (twice daily), and an untested 75 mg dose for patients with severe kidney impairment.[20] In late 2015 the FDA joined the rest of the world in authorizing an intermediate 110 mg dose.[21] The prescribing information still did not recommend its use in atrial fibrillation, but physicians were free to follow the European Medicines Agency (EMA) recommendation to use the reduced dose in patients age 75 or older and/or with one or more risk factors for bleeding.[22] However, by the 4th quarter of 2016, little use in this country was being made of the 110 mg dose, which accounted for less than 1% of dabigatran prescriptions, according to dispensed outpatient prescription data from QuintilesIMS.

The unresolved safety issue for dabigatran relates to its 5-fold variability in anticoagulant effect in patients receiving the same dose.[23] This results in at least 40% of dabigatran patients receiving a suboptimal dose, according to simulation studies.

Rivaroxaban/Apixaban Antidote Not Approved

While the FDA approved an antidote for dabigatran, it declined to approve a similar antidote for rivaroxaban and apixaban, developed by Portola Pharmaceuticals. Despite a published study showing similar results to those for the dabigatran antidote,[24] the company said the FDA had declined to approve the drug in June 2016, citing manufacturing issues.[25]

Changes in Exposure

Overall, exposure to oral anticoagulants increased 2.6% from the 4th quarter of 2015 to the 4th quarter of 2016. We estimate current exposure at 3.8 million person-years. Much larger changes in specific agents were observed, with apixaban use increasing rapidly and warfarin use declining. Changes are shown in Table 1.

Table 1. Changes in exposure to oral anticoagulants, 2015 Q4 to 2016 Q4*

	Dispensed Rx		Percent	Market
Drug name	**2015 Q4**	**2016 Q4**	**change**	**share****
Apixaban	1,315,213	2,183,821	66.0%	19.2%
Dabigatran Etexilate	487,527	486,176	-0.3%	4.3%
Edoxaban	23,563	23,886	1.4%	0.2%
Rivaroxaban	1,948,201	2,209,216	13.4%	19.4%
Warfarin	7,332,251	6,488,962	-11.5%	57.0%
Total oral anticoagulants	11,106,755	11,392,061	2.6%	

* Dispensed outpatient prescriptions, QuintilesIMS

** In 2016 Q4

Actions Not Taken

From the outset, long-term use of oral anticoagulants was a dangerous balance between a clearly demonstrated benefit in preventing ischemic strokes against a high risk of bleeding, including a smaller but still substantially increased risk of hemorrhagic strokes.[26] Many health professionals were willing to risk causing more hemorrhages that could be treated in the interests of preventing disabling, life-changing

ischemic strokes. But the need is great to reduce the risks of this class of drugs. Among the practical steps needed:

1. Insure wide availability of antidotes for bleeding caused by the newer agents. The CDC study shows that anticoagulant bleeds are to be expected in practically every emergency department.

2. Establish guidelines for combined therapy with anti-platelet agents (aspirin, clopidogrel, prasugrel) and oral anticoagulants, especially in older patients. Combining two forms of blood clot inhibition at least doubles the bleeding risk, but little information is available to guide decisions about when this therapy provides benefits that outweigh the increased risks.

3. Re-evaluate the suitability of rivaroxaban's once-a-day dosing scheme compared to similar agents with a dosing scheme better matched to the drug half-life. While rivaroxaban clinical trial results suggested risks and benefits roughly similar to those of warfarin,[12] safety gains are likely with the twice-daily dosing scheme used by the other agents.[27]

4. Provide therapeutic ranges for dabigatran to identify patients with suboptimal and excess anticoagulant effects. A drug with a 5-fold variability in anticoagulant effect at the same dose needs blood level testing to identify those with a dose outside the therapeutic range.[20]

5. Take steps to ensure that the ease-of-use of the newer agents does not lead to overuse of these drugs, especially in atrial fibrillation patients at lower risk of ischemic stroke and in older patients with the highest bleeding risks.

Drug Withdrawal Symptoms

Some of the most frequent side effects of psychoactive drugs appear when patients try to stop them. Our survey of 2016 reports identified clear signals for withdrawal effects for 42 therapeutic drugs, including 13 different opioids, 10 antidepressant drugs, and 10 drugs with effects on gamma aminobutyric acid (GABA) neurotransmission, and 3 with effects on dopamine. While few would be surprised at evidence for oxycodone and other opioids, others might underestimate the risk of withdrawal effects when stopping antidepressants and anti-anxiety and sleep medications.

Method

To identify cases we selected every 2016 report with an event term in the "Drug withdrawal" Standardized MedDRA Query. It contains preferred terms (PTs) specifically indicating some form of withdrawal. Suspect drugs had to meet these additional requirements: 1) It had to be primary suspect in at least 10 reported cases, 2) It had to have twice as many cases as expected, given the number of total adverse event reports for the drug; 3) There had to be at least a 95% probability that the number of withdrawal cases could not have occurred by chance. This method identified 4,016 cases overall identifying 240 possible drugs, but just 42 met our definition of a clear and credible signal of drug risk in these one-year data. It was not feasible to assess either the severity or duration of the withdrawal effects. The overall results are shown in Table 2. The column titled PRR reflects how unexpected the finding was, e.g. a PRR = 4 means that the number of withdrawal syndrome reports was 4 times the number expected, given the total number of reports for that drug.

Neurotransmitters and Receptors

The data in Table 2 show that withdrawal effects are (with only a few exceptions) linked to the major neurotransmitters or receptors that are primary targets for psychoactive drugs. These data illustrate the pharmacological fact that when drugs alter the functioning of these neurotransmission circuits in the brain, the central nervous system (CNS) makes counter adjustments in signal transmission, reuptake, or receptors.

Cellular receptor changes made in response to the intrusion of psychoactive drugs include receptor upregulation (neurons express more receptors) or downregulation (receptors disappear), and sensitization (are more easily triggered), or desensitization (become less responsive). The extent of this neural remodeling varies greatly with the individual patient, drug half-life, dose, and duration of treatment. Some individuals discontinue psychoactive drugs easily, or with minor symptoms, or after a short taper period. For others, the effects are more severe, more prolonged, and in a few cases do not resolve.

Table 2. Drugs with signals for withdrawal symptoms, 2016			
Drug name	**Class**	**Cases**	**PRR**
Effects on serotonin			
Duloxetine	Antidepressant	888	135.6
Paroxetine	Antidepressant	275	55.3
Venlafaxine	Antidepressant	119	15.4
Desvenlafaxine	Antidepressant	59	19.5
Sertraline	Antidepressant	55	5.0
Mirtazapine	Antidepressant	37	10.8
Citalopram	Antidepressant	34	5.3
Bupropion	Antidepressant	21	3.8
Escitalopram	Antidepressant	15	3.7
Fluoxetine	Antidepressant	13	3.2
Effects on GABA			
Pregabalin	Nerve Pain	198	6.8
Vigabatrin	Anti-epileptic	59	12.6
Gabapentin	Nerve Pain	45	2.9
Clonazepam	Benzodiazepine	36	9.5
Alprazolam	Benzodiazepine	34	5.6
Clobazam	Benzodiazepine	34	17.2
Zolpidem	Sedative	20	5.1
Lorazepam	Benzodiazepine	18	7.2
Dexmedetomidine	Sedative	18	26.8
Diazepam	Benzodiazepine	16	4.5
Continued on next page			

Table 2. Drugs with signals for withdrawal symptoms, 2016*			
Drug name	**Class**	**Cases**	**PRR**
Effects on opioid receptors			
Buprenorphine; Naloxone	Addiction treatment	195	38.7
Oxycodone	Analgesic	159	18.2
Fentanyl	Analgesic	154	10.1
Buprenorphine	Addiction treatment	130	13.7
Naltrexone	Addiction treatment	84	16.3
Naloxegol	Opioid constipation	54	28.5
Morphine	Analgesic	47	6.5
Tramadol	Analgesic	33	6.3
Hydrocodone	Analgesic	19	5.8
Acetaminophen; Hydrocodone	Analgesic	18	5.8
Naloxone	Overdose treatment	17	38.7
Morphine; Naltrexone	Addiction treatment	14	19.5
Methadone	Addiction treatment	13	8.3
Effects on dopamine			
Quetiapine	Anti-psychotic	26	3.1
Olanzapine	Anti-psychotic	19	2.9
Methylphenidate	ADHD	17	2.0
Other mechanisms			
Baclofen	Muscle relaxant	315	37.7
Cetirizine	Antihistamine	41	4.1
Ziconotide	Analgesic	22	18.4
Omeprazole	Proton pump inhibitor	17	2.0
Pramipexole	Anti-Parkinsons	13	12.2
Clonidine	ADHD, blood pressure	12	7.6
Continued from preceeding page			

Defining Drug Withdrawal

Withdrawal symptoms in these data are defined as a constellation of symptoms that appear when a drug is stopped, and remit if the drug is resumed. This overlaps with but is not a synonym for the medical term *addiction,* which typically refers to "an individual pathologically pursuing reward and/or relief by substance use and other behaviors."[28] Drugs with withdrawal symptoms also vary in the risk of *tolerance*, meaning that increasing doses are required to achieve the same effect, such as euphoria or pain relief. The overdose risk of opioids is closely linked to tolerance; antidepressants usually do not carry these same risks. The third related property is *intoxication,* meaning clinically significant behavioral or psychological changes while on the drug.[29] The best test of whether a symptom is related to withdrawal is that it lessens or disappears shortly after the drug is restarted.

Withdrawal Symptoms

Our sample of one year of adverse drug event reports provides a reasonable cross section of the specific symptoms of withdrawal that occur most frequently. The symptoms reported in ≥ 1% of cases are shown in Table 3.

Table 3. Most frequent withdrawal symptoms, 2016*			
Rank	Preferred term	Number**, percent	
1	Nausea	955	2.8
2	Dizziness	939	2.8
3	Paraesthesia***	935	2.8
4	Insomnia	831	2.5
5	Anxiety	812	2.4
6	Suicidal Ideation	719	2.1
7	Headache	713	2.1
8	Agitation	694	2.0
9	Fatigue	686	2.0
10	Irritability	682	2.0
11	Hyperhidrosis	651	1.9
12	Vertigo	547	1.6
13	Confusional State	483	1.4
14	Tremor	470	1.4
15	Vomiting	448	1.3
16	Nightmare	414	1.2
17	Mood Swings	408	1.2
18	Diarrhoea	406	1.2
19	Sleep Disorder	379	1.1
20	Pain	337	1.0
* Identified in ? 1% of cases.			
** One case could mention multiple symptoms			
***Mostly electric shock-like sensations			

A more systematic study of antidepressant withdrawal symptoms identified 43 possible symptoms,[30] and included all of the symptoms listed in Table 3. In these data and others, individuals typically have more than one symptom and often several. When discontinuation symptoms appear depends in part on how quickly the discontinued drug is eliminated from the body. For antidepressant drugs symptoms usually appear within a few days of stopping; for opioids they can begin within hours for short-acting opioids and about 30 hours for longer-acting.[31]

Population Exposure

Population exposure to therapeutic drugs with risk of withdrawal symptoms is extensive. Members of the QuarterWatch team used a major federal government medical survey to report that 1 in 6 adults were taking psychiatric drugs, or an estimated 40 million persons, and 84.3% were longer-term users who might be at risk for withdrawal symptoms.[32] These same data show other large populations at risk for withdrawal symptoms, including 9.6 million adults taking opioids for 31 days or more, and another 9.4 million taking synthetic GABA drugs. It is hard to identify a risk of therapeutic drugs that potentially affects a larger fraction of the adult population.

Warnings and Controls

For some classes of drugs, elaborate controls, stark warnings, and other measures are in effect to manage the risks of long-term use and of the physiological problems that may occur when a person seeks to stop taking the drug. In modestly varying degree these measures apply to opioid narcotics, benzodiazepine tranquilizers for anxiety, and many other sedatives. On the other hand, the warnings and patient information for antidepressants with the highest likelihood of withdrawal symptoms are inadequate.

Antidepressant Evidence

Only a few controlled studies have examined the likelihood of withdrawal symptoms after abrupt discontinuation of antidepressants. An analysis of 6 trials of duloxetine (ranked #1 in our tabulation) showed that 44.4% of patients experienced one or more withdrawal symptoms.[33] Another comparison showed that 66% of paroxetine patients and 60% of sertraline patients had withdrawal symptoms.[30] In a study of venlafaxine (ranked #3 above), 78% of patients reported withdrawal symptoms.[34] In addition, some studies were conducted after short-term rather than long-term exposure. Two books examining withdrawal symptoms for antidepressant drugs and providing practical advice on discontinuation[35,36] concluded that the symptoms are most frequent and severe for drugs with a half-life of 12 hours or less, and least frequent for drugs that remain in circulation for days, notably fluoxetine. Table 2 confirms the weaker signal for some antidepressants with longer half-lives. These books also note that initial withdrawal symptoms often mimic the original problem (depression, insomnia), misleading patients into believing their problems are recurring.

Both the FDA-approved warnings for physicians and information for patients give no hint of the extent of withdrawal symptoms that a majority of patients taking antidepressants will experience. We surveyed the FDA-approved prescribing information for the three antidepressants with the strongest signals in 2016. The warnings are summarized in Appendix A. For example, venlafaxine prescribing information vaguely states that discontinuation "has been found to be associated with the appearance of new symptoms." The prescribing information for duloxetine lists 11 symptoms (all included in Table 3) but says each occurred "at a 1% or greater rate." In fact, the first listed duloxetine symptom–dizziness–was reported to occur in 19% of patients after long-term treatment.[33] It was true that dizziness occurred at a rate of more than 1%, but this statement is misleading about the true likelihood. The same was true of nausea (9.9%) and anxiety (9.8%). For paroxetine, the symptoms are described as equaling or exceeding 2%. Further, neither physician or patient information provides specific information about how long or how slowly antidepressant drugs may need to be tapered. The time to resolve antidepressant withdrawal reactions varies but can take weeks to months in many cases.

Patient Medication Guides

The Medication Guide information for patients (also shown in Appendix A) is presented as an argument to continue taking the drug: "Never stop an antidepressant medication without first talking to a healthcare provider." However, healthcare providers who relied on the physicians' prescribing information would have little effective guidance about how best to manage a medication halt.

Where Data Are Lacking

Little clinical study information about withdrawal effects could be found for two groups of drugs, the synthetic GABA agents and antipsychotic drugs. The only discussion in the prescribing information for pregabalin and gabapentin was a brief mention that anti-epileptic drugs should not be discontinued abruptly because of increased risk of seizures.[37,38] And no discussion of discontinuation could be identified in the package inserts for olanzapine and quetiapine.[39,40] Further complicating analysis is the fact that the synthetic GABA agents and antipsychotics are frequently combined with other psychoactive agents, notably benzodiazepines and antidepressants.

Limitations

Neither our list of common withdrawal symptoms nor table of suspect drugs is comprehensive. For example, other information sources or warnings associate abrupt discontinuation of benzodiazepines with seizures, and beta-blockers with rebound exacerbation of coronary artery disease. Also, other drugs with mechanisms of action similar to those identified may share withdrawal effects, but didn't have enough reports in 2016 to meet our study criteria.

Conclusions

The 2016 data from FAERS show that drug withdrawal effects remain a primary hazard of the therapeutic use of drugs. While the withdrawal effects of the opioids and benzodiazepines are a major policy focus today, and the drug information includes clear warnings, the information about antidepressant withdrawal is currently inadequate. In addition, withdrawal effects for psychoactive drugs are not systematically studied at the time of approval, and the disclosure of the withdrawal studies that are conducted is limited. Finally, just telling patients not to stop a medication without consulting a healthcare professional is not an adequate warning about likely effects of stopping these drugs.

Adverse Event Reporting System

In 2016 a majority of serious adverse event reports collected and submitted by drug manufacturers were incomplete. Among 575,912 reports of serious injury submitted by the pharmaceutical industry, 57.5% did not meet four basic standards for completeness: 1) Patient age; 2) Sex; 3) Event date; and 4) At least one medical term to describe what happened. At the most elementary level, patient age was not reported in 36.8% of manufacturer case reports. Reports submitted directly to the FDA by health professionals and consumers were much better: 85% met all 4 basic standards, and 5.7% did not have the patient age.

The FAERS system remains the primary tool for identifying new adverse drug effects for drugs that have already won FDA approval. It can identify important (and sometimes fatal) side effects that were not understood, properly assessed, or simply not detected in pre-approval drug testing. With some drugs approved following clinical testing in 200 or fewer patients, better postmarket surveillance should be an important regulatory priority. Although the FDA has invested more than $200 million in its Sentinel System based on electronic health data from millions of patients, our published analysis showed that limitations in the underlying and diverse patient data and other problems have limited its value as a primary source for making regulatory decisions such as drug withdrawals, boxed warnings, or contraindications.[41] The performance of Sentinel was further explored in a recent on-line investigation.[42]

Differences Among Manufacturers

We detected major differences in report completeness among the 27 large drug manufacturers who submitted 5,000 or more adverse event reports in 2016. Using the elementary standard of whether the report included patient age and sex we found three manufacturers performed well: Actelion included age/gender in 96.9% of 6,037 reports; Gilead 88.7% of 14,215 reports, and Aurobindo, 86.5% of 5,957 reports. At the other extreme Cipla, an India-based generic manufacturer, coded age and gender on 0.3% of reports of serious injury, and Mylan on 1.1%. While generic drug manufacturers collect a much larger share of their reported cases from the medical literature (which might omit age or gender), we noted that generic manufacturer Ranbaxy obtained age from 69.9% of its 6,552 reported cases. It is also possible that Mylan and Cipla included age and gender information in the narrative section of some reports (information that is not publicly released), but did not code the fields intended for that purpose, indicating a software problem in its electronic submissions program.

We asked Cipla and Mylan for comment about the missing age and gender information. Mylan told us that the company collected age and gender data and complied with FDA regulations, but could not comment on the excerpts we reviewed.

The reporting burden on manufacturers did not appear to strongly predict report completeness. Overall, companies submitting more reports did somewhat better on completeness, suggesting that management and organization are the keys to better reports. (Pearson's R = 0.3 for report volume verse completeness)

Results for Newly Approved Drugs

Higher quality postmarket surveillance seemed most important for drugs just entering the market. Therefore, we evaluated the 2016 serious reports for 36 drugs first approved in 2015. Report completeness for the 17,133 cases for the newest drugs was similar to that for the older ones. More reports for newer drugs were missing age (39% vs. 37%), but a smaller share failed the 4 completeness standards (66% vs 68%). The newer drug reports, however, were revised more frequently to collect initially missing information (46% vs 31%). Because the FDA requires that new, serious adverse events be reported within 15 days, revisions are important to collect information that might be missing at initial report.

The Need to Update the FAERS System

Since the last time the FDA updated its guidance in 2001, reports into the FAERS system have increased almost 10-fold, from 143,000 to 1.2 million in 2016. The burden and costs for drug companies have likely increased by similar margins. While this large increase in report volume permits richer and more sophisticated analysis, its value is limited by poor report quality from drug manufacturers. As we have previously shown,[43] some kinds of reports have little or no value whatsoever, notably cases coded as a patient “death” or “hospitalization” without any information or indication that the drug was suspected of causing the event. A full-scale modernization of the FAERS reporting requirements is needed to build on the new possibilities for better postmarket surveillance created in the modern age of digital information.

Appendix A: Antidepressant Withdrawal Warnings

Prescribing Information for Duloxetine (CYMBALTA)

5.7 Discontinuation of Treatment with CYMBALTA [44]

Discontinuation symptoms have been systematically evaluated in patients taking CYMBALTA. Following abrupt or tapered discontinuation in adult placebo-controlled clinical trials, the following symptoms occurred at 1% or greater and at a significantly higher rate in CYMBALTA-treated patients compared to those discontinuing from placebo: dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with CYMBALTA. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate [see Dosage and Administration (2.7)].

Patient Counseling Information:

Discontinuation of Treatment — Instruct patients that discontinuation of CYMBALTA may be associated with symptoms such as dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue, and should be advised not to alter their dosing regimen, or stop taking CYMBALTA without consulting their physician [see Warnings and Precautions (5.7)].

Medication Guide for duloxetine (CYMBALTA)

What else do I need to know about antidepressant medicines?

- *Never stop an antidepressant medicine without first talking to a healthcare provider. Stopping an antidepressant medicine suddenly can cause other symptoms.*

Prescribing Information for Paroxetine (PAXIL)

Precautions:[45]

Discontinuation of Treatment With PAXIL:

Recent clinical trials supporting the various approved indications for PAXIL employed a taper phase regimen, rather than an abrupt discontinuation of treatment. The taper phase regimen used in GAD and PTSD clinical trials involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped.

With this regimen in those studies, the following adverse events were reported at an incidence of 2% or greater for PAXIL and were at least twice that reported for placebo: Abnormal dreams, paresthesia, and dizziness. In the majority of patients, these events were mild to moderate and were self-limiting and did not require medical intervention.

During marketing of PAXIL and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring upon the discontinuation of these drugs (particularly when abrupt), including the following: Dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations and tinnitus), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with PAXIL. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

See also PRECAUTIONS: Pediatric Use, for adverse events reported upon discontinuation of treatment with PAXIL in pediatric patients.

Patient Counseling Information:

Discontinuation of Treatment With PAXIL:

Symptoms associated with discontinuation of PAXIL have been reported (see PRECAUTIONS):

Discontinuation of Treatment With PAXIL. Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which PAXIL is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered.

Medication Guide for Paroxetine (PAXIL)

Do not stop PAXIL without first talking to your healthcare provider. Stopping PAXIL too quickly may cause serious symptoms including:

- *anxiety, irritability, high or low mood, feeling restless, or changes in sleep habits*
- *headache, sweating, nausea, dizziness*
- *electric shock-like sensations, shaking, confusion*

Prescribing Information for Venlafaxine (EFFEXOR XR)

5.7 Discontinuation Syndrome[46]

Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, including prospective analyses of clinical studies in GAD and retrospective surveys of studies in MDD and SAD. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been found to be associated with the appearance of new symptoms, the frequency of which increased with increased dose level and with longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, impaired coordination and balance, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, flu-like symptoms, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting.

During marketing of Effexor XR, other SNRIs, and SSRIs, there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Effexor XR. A gradual reduction in the dose, rather than abrupt cessation, is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate [see Dosage and Administration (2.8)].

Patient Counseling Information:

Discontinuation Symptoms

Advise patients not to stop taking Effexor XR without talking first with their healthcare professional. Patients should be aware that discontinuation effects may occur when stopping Effexor XR [see Warnings and Precautions (5.7) and Adverse Reactions (6.1)].

Medication Guide for Venlafaxine (EFFEXOR XR)

Do not stop EFFEXOR XR without first talking to your healthcare provider. Stopping EFFEXOR XR too quickly or changing from another antidepressant too quickly may cause serious symptoms including:

anxiety, irritability

feeling tired, restless or problems sleeping

headache, sweating, dizziness

electric shock-like sensations, shaking, confusion, nightmares

vomiting, nausea, diarrhea

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