ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES
QuarterWatch
Monitoring FDA MedWatch Reports

December 4, 2019 — New data from 2019 Q2

SCOPE OF INJURY FROM THERAPEUTIC DRUGS

- Major drop in patients exposed to prescription opioids
- Adult use of amphetamine-like stimulants grows rapidly
- Methotrexate: growing use and medication errors that are fatal
- Underreporting of serious and fatal adverse events

Executive Summary

In this issue we examine opposite trends in the medical use of two classes of drugs with the highest risk of dependence, addiction, and abuse: therapeutic opioids with a sharp decline in use, and prescribed amphetamine-like stimulants with a rapid increase in adults and more modest growth in use in children. In addition, we examine the continuing problem of methotrexate medication errors with harmful and fatal outcomes. We also investigate the extent of underreporting of serious adverse drug events to the U.S. Food and Drug Administration (FDA).

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP). Our primary data are computer excerpts from the U.S. Food and Drug Administration 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.

During 2019 Q2 the FDA received 338,324 new adverse event reports about 1,592 primary suspect drugs. Over the full 12 months ending June 30, 2019, the FDA received 1.8 million adverse event reports, including 439,044 cases of serious or fatal injury occurring in the U.S. The remainder were non-serious injuries or were reported from foreign countries, or both.

Overview: Dependence, Addiction, and Abuse Risks

The control of therapeutic drugs with risks of dependence and addiction are the responsibility of the Drug Enforcement Administration (DEA) rather than the FDA. The risks and required controls are classified on a scale from I to V. Schedule I describes psychoactive drugs without an accepted medical use. Examples include heroin and LSD. Schedule II includes drugs with "high abuse potential" and lists the two classes of drugs in this report: most opioids and various amphetamine formulations including methylphenidate. Schedule III identifies drugs with moderate-to-low risk of abuse such as ketamine and steroids. Schedule IV (low risk of abuse and dependence) includes benzodiazepines, sleep medications such as zolpidem, and the opioid tramadol. In addition, Schedule V identifies drugs with still lower but some risks. Controlled substance regulations require various restrictions on prescribing, refills, and precautions to prevent theft and diversion.

Prescription Opioid Exposure Declines, 2013-2017

Hidden in reports about the continuing increase in opioid overdose deaths is another notable and mostly favorable trend: Since 2013, the therapeutic use of prescription opioids has declined steadily with reductions ranging from the most potent opioids such as fentanyl to the lower-risk products such as tramadol. Here are highlights, measured in changes in reported prescriptions from 2013 to 2017 calculated from the federal Medical Expenditure Panel Survey:

- **The Trend.** Overall reported use of prescription opioids declined 25% over four years, from 49 million persons in 2013 to 37 million persons in 2017. Nevertheless, more than 1 in 10 Americans reported taking opioids in 2017.

- **Fentanyl**. Despite an increasing overdose death toll from illicit fentanyl added to street drugs, reported use of the prescription products declined by 55%. This synthetic opioid, 80 times more potent than morphine, provides a high risk of harm even with adherence to treatment guidelines.

- **Acetaminophen-Hydrocodone**. The most widely used opioid for many decades, this combination declined 40% in four years, a reduction of 8 million persons. However, a new abuse-deterrent formulation of hydrocodone acquired 2.6 million users.

- **Oxycodone.** This opioid–frequently cited in overdose deaths–was an exception to the downward trend in use. Overall, 4.2 million persons reported using oxycodone products in 2017, largely unchanged from 2013.

These data capture self-reported and then validated prescriptions and do not include illicit use. Even though therapeutic use declined 25%, reported overdose deaths associated with therapeutic or illicit use of prescription opioids increased by 18% over the four years. In 2017 the Centers for Disease Control and Prevention reported 17,029 deaths attributed to prescription opioids and 30,751 deaths from Schedule I opioids such as heroin.

Amphetamines Use Expands

While Schedule II opioid use declined from 2013-2017, we observed a substantial increase in the other major Schedule II drugs – the amphetamines and methylphenidate. Overall, reported use of prescribed amphetamine-like stimulants increased 37%, with the largest increase seen in amphetamine-dextroamphetamine (Adderall XR, others), which grew 53% in just four years. The changes are shown in Table 1.

Table 1. U.S. population exposure to amphetamine products, 2013-2017

	Frequent	2013	2017	Percent
Drug names	brand name*	Patients (in thousands)		change
Totals		5,660	7,762	37%
Amphetamine-Dextroamphetamine	Adderall XR	2,169	3,308	53%
Lisdexamfetamine	Vyvanse	1,017	1,438	41%
Methylphenidate	Concerta	1,944	2,513	29%
Dexmethylphenidate	Focalin XR	530	503	-5%

Source: Calculated from the Medical Expenditure Panel Survey.

* Many generics available for amphetamine-dexamphetamine and methyphenidate.

In this report we also examine the reasons for this substantial increase in use. The major factor was a 66% growth in amphetamine use among adults – rather than in children under 18 years of age, where use increased 14%, mainly for Attention Deficit Hyperactivity Disorder (ADHD). The reasons may include pharmaceutical promotion of the brand name drugs for adult indications, off-label use in patients seeking cognitive enhancement, and continued use in adults initially prescribed amphetamines as children.

Preventable Methotrexate Medication Errors

Methotrexate is a high-alert medication that inhibits cell division. It was first approved in 1953 to treat advanced cancers. However, its use has grown rapidly as increasing numbers of patients are prescribed methotrexate, primarily as a treatment rheumatoid arthritis and psoriasis. We estimate 1 million persons were exposed to methotrexate in 2017.

For non-oncologic uses, it is essential that methotrexate be taken only on a weekly basis rather than daily. The consequences of a daily-instead-of-weekly administration are dire. Even one week of daily administration can result in multiple painful and severe adverse events and death.

We analyzed 14 reported cases of mistaken daily consumption of methotrexate in the 18 months ending June 30, 2019. All occurred among patients age 65 or older. In 5 cases the patient died; the other 9 patients required hospitalization, often in intensive care. In addition, the breakdowns occurred at each phase of the process: the practitioner writing the prescription; the pharmacy staff who check, label, and dispense the drug, and the patient who receives the medication.

A medication with such a narrow therapeutic index that a week of daily administration can be fatal requires special precautions, including calendar packaging to facilitate weekly dosing, and clear, prominent written instructions, especially for older patients likely taking multiple medications. The FDA has not required these safety measures. Notably, the warning against daily administration is buried in the second page of the Patient Information Leaflet for methotrexate and does not communicate the potentially fatal consequences of non-adherence to weekly administration.

A drug with different dose regimens for indications as varied as lung cancer and skin problems needs special procedures in drug-ordering and dispensing systems to prevent a mistake. ISMP has long recommended defaulting to a weekly dosage regimen when entering electronic orders or prescriptions for all oral methotrexate, requiring an appropriate oncologic indication for all daily methotrexate orders, and provision of patient and family education. While these have been an ISMP Best-Practices recommendation for years, compliance is voluntary and partial.

While we examined 14 reported cases of erroneous daily consumption of methotrexate in this report, these data do not provide any estimate of how many cases of preventable patient harm and death might be occurring among a population numbering 1 million. Hundreds more reports indicate severe toxicity typical of an overdose but lack information about how it occurred. As explained below, the adverse event reporting rates for many older generic drugs are likely less than 1%. This means that not only do we not have adequate precautions in place, the post-market surveillance is so poor that we cannot measure the extent of this risk or assess whether we are making progress combatting this long-known medication error or losing ground because of its rapidly expanding use.

FDA Adverse Event Reporting System

Extent of Underreporting Examined

Here are the hard questions: Given that reporting an adverse drug event to the FDA is voluntary for consumers and medical professionals, do the reports at least approximate the number of serious injuries and deaths that actually occur from therapeutic use of drugs? Do they accurately measure the types of injuries occurring most frequently, and reliably point to the highest-risk drugs? Are there better data sources to guide

the important task of reducing injuries from drug treatment? Unfortunately, the answer to all these questions is: No

In this report we take on the challenging task of estimating the national incidence and FAERS reporting rates for five of the best-documented adverse drug events. We were limited to five case studies in part because of severe limitations in the underlying research about most adverse drug events. Key results are shown in Table 2. We focus on data from 2017 because it is the most recent available survey of overall patient exposure to therapeutic drugs.

Based on this sample of the best-documented adverse drug events, we estimate that approximately 1% of the serious injuries occurring are reported to FAERS. But the variability was large, ranging from fewer than 1 per thousand for some serious but frequent adverse events to a reporting rate of 7.6% for a rare but serious adverse effect of a newer drug receiving more intensive post-market surveillance from the drug manufacturer.

Table 2. Estimated annual adverse events and FAERS reports in 2017

Adverse event	Primary suspect drug	Frequent brand name	Estimated events	FAERS reports	Reporting rates
Total			276,062	2,550	0.92%
Severe gastrointestinal	Meloxicam	**Mobic**	45,336	31	0.07%
Severe gastrointestinal	Celecoxib	**Celebrex**	19,027	65	0.34%
Movement disorder	Risperidone	**Risperdal**	33,269	265	0.80%
Any bleeds	Apixaban	**Eliquis**	177,815	2,142	1.20%
Tuberculosis	Adalimumab	**Humira**	615	47	7.64%

FAERS = FDA Adverse Event Reporting System.

The example of meloxicam in Table 2 above illustrates how we calculated the reporting rates to FAERS. The FDA has estimated that at least 2% of those taking meloxicam for a year could experience a severe gastrointestinal event. Using an estimate of the whole U.S. population taking meloxicam in 2017, we calculated that 45,336 GI adverse events likely occurred. However, among 45,336 severe GI events, only 31 (0.07%) were reported to FAERS in 2017. The report includes full documentation of our methods.

The results in Table 2 also show that our cases involve a large number of events (n = 276,062) but focus on only five drugs. The examples selected have well-documented but mostly very high incidence rates over one full year of exposure: The FDA estimates that 2% of those treated with the analgesics meloxicam or celecoxib will experience severe gastrointestinal events; studies show 9% of those treated with risperidone will develop movement disorders, and 18% of those treated with the anticoagulant apixaban will develop bleeds. Tuberculosis in patients taking adalimumab occurred much more rarely, in 2 per thousand patients.

These five well-documented cases don't provide enough data to support an estimate of the overall number of persons who experience serious drug-induced injuries in one year's time. But with more than 400,000 serious and fatal adverse events in the U.S. reported to FAERS annually, it is clear that the extent of injury and death from the therapeutic use of drugs must be measured in millions.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a reporting system that does not acquire 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. While reporting rates vary among drugs, only a small fraction of the adverse events occurring are reported. 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

Three common themes run through our analysis of the safety risks of more than 20 therapeutic drugs: 1) Improving safety ought to be a primary public health concern because of the very large patient populations exposed to these risks. Almost all the drugs that are the focus of this report are taken regularly by many millions of people. 2) The assessment of most risks of therapeutic drugs is so weak that incidence rates can be estimated reliably for only few of the best-known and frequently occurring adverse drug events. 3) Post-market surveillance is especially weak in an era when 90% of dispensed drugs are generic rather than brand name products. 4) Many substantial risks of harm have been known but neglected for years.

The 25% reduction in opioid utilization shows clear results of the multiple public health campaigns to reduce deaths from opioid overdoses through guidelines and other measures to reduce prescribing. A steady stream of media publicity has likely reduced public willingness to take opioids for short-term pain relief. However, the reported death rates from prescription opioids have continued to increase slowly rather than declining, in contrast to illicit opioid deaths, which grew rapidly. This suggests the need for more research into the pathways that lead to dependence and addiction to identify the most effective point for intervention. For example, short-term dispensing limited to a few days' supply might provide needed pain relief without substantial risks.

The substantial growth in use of amphetamine stimulants has gone largely unnoticed and reverses safety campaigns of earlier decades to control the numbers of persons exposed to these drugs with their high risk of dependence, addiction, and abuse. While the overdose risks of the amphetamines are somewhat lower than for the opioids, this class of drugs has a long history of misuse. In particular, the FDA and the public health community need to monitor and evaluate the rapidly increasing use in the adult population, which increased 66% in just four years. The FDA should investigate the extent to which increased use is a product of promotion by the manufacturers for amphetamine products after the agency granted indications for adult use.

The harmful and fatal medication errors for oral methotrexate have been known for decades. ISMP published a comprehensive assessment of these errors in 2004. ISMP's biweekly newsletter, *ISMP Medication Safety Alert!* has alerted health professionals to this risk on more than 60 occasions. FDA actions are long overdue and include required calendar packaging to discourage daily use, simplified dosing schedules, and a new Medication Guide for patients. Our Best Practices recommendations for oral methotrexate should become mandatory guidelines.

We used five case studies to estimate that only around 1% or fewer serious adverse drug events likely occurring are reported to FAERS. There are exceptions, and we observed a 7.6% reporting rate for an expensive brand name biological product with a large patient assistance program. Advertising for new cases in some pharmaceutical litigation could increase the reporting rate still further. This mostly very low reporting rate should not be surprising, given a system that is voluntary for consumers and health professionals, and that has evolved with few regulatory changes over 50 years.

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Contents

Methods Summary

QuarterWatch monitors the safety of therapeutic drugs and biological products through analysis of adverse drug events reported to the FDA by consumers and health professionals, 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 website. (https://www.ismp.org/quarterwatch/methods)

The severity of the reported adverse event is classified as serious under FDA regulations 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.[2] Cases without these outcomes are classified as non-serious. Only cases reported for the first time in the reporting period were included in this analysis.

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 standardize adverse event reporting in clinical studies and post-market surveillance.[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 combine several related but more specific medical terms. Also, High Level Group Terms (HLGTs) combine several related HLTs, and System Organ Classes combine all the terms into 27 categories. The QuarterWatch database was updated in December 2018 to MedDRA version 21.1.

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the most recent version of the case report. Product names are standardized to drug ingredient names based on the National Library of Medicine's RxNorm terminology.[5] When cited in the text, tables, or charts, the brand name used for a drug 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 or other formulations. Reports are submitted to the FDA via two basic routes: directly to the FDA through its online portal (6% of reports) and through drug manufacturers (94% of reports), which are required to investigate and report adverse events that they hear about from consumers and health professionals. In QuarterWatch we describe as the *initial reporter* the type of individual (e.g., consumer, physician, pharmacist, nurse) who was the primary information source for events reported either directly or through a drug manufacturer.

We evaluated the exposure of patients to therapeutic drugs in this report with an analysis of the Medical Expenditure Panel Survey (MEPS), a representative survey of medical care received by persons in the U.S. [6] These survey results data are published annually for health policy research use by the federal Agency for Healthcare Research and Quality. Our analysis relies on population estimates of exposure to therapeutic drugs primarily calculated from the Prescribed Medicines data files for 2013 and 2017, which takes survey respondents' reports of what medications they took, and then validates the information with doctors' offices and pharmacies.

Results

Reports Overview

In 2019 Q2, the FDA received 338,324 new adverse event reports from domestic (69%) and foreign (31%) sources. The reports described suspected drug-related injuries that were serious or fatal (58%) or non-serious (42%). In recent years the quarterly report totals have varied between 300,000 and 400,000 new cases each quarter without a discernable pattern or trend. Over the longer term we have seen increases in non-serious domestic reports that are largely caused by growing numbers of drug manufacturers' patient assistance programs. These programs involve direct help getting insurance coverage, 24-hour nurse help lines, education for injectables, coupons, and reminder services for drugs that require periodic administration. While reporting is voluntary for consumers and health professionals, manufacturers must report any adverse event of which they are informed, and these patient assistance programs provide more settings in which a manufacturer might hear about a possible adverse event.

Trends in Drugs with Highest Dependency/Addiction Risk

We studied prescribed opioids and amphetamine-like stimulants to assess both the population at risk and the trends in use of these two major drug classes with the highest risks of abuse and dependence. Using the largest publicly available survey of therapeutic drug use,[6] we assessed the estimated number of individuals reporting use and the number of days' supply. We defined short-term use as a 30-day supply or less, with the remainder considered longer-term use.

While the drugs studied were mostly classified as Schedule II controlled substances (the highest-risk classification for dependency, addiction, and abuse for a therapeutic drug) [7] we identified major differences between the opioids indicated for pain and the amphetamine-like stimulants, which are primarily approved for Attention Deficit Hyperactivity Disorder (ADHD).

The prescription opioids were much more widely used—with 37 million people reporting use in 2017–but a large majority was for short-term use and overall use declined from 2013 to 2017.

The opposite pattern was seen in 2017 among the 7.8 million people reporting use of prescription stimulants such as amphetamine-dextroamphetamine, methylphenidate, and lisdexamfetamine. In the same four-year period, reported use of these stimulants increased rapidly, and most use was longer-term.

Prescription Opioid Use Declines

A rising toll of overdose deaths from opioids triggered one of the largest and most intense public health campaigns in recent years. At the federal level alone, major efforts were launched by the FDA, the Centers for Disease Control and Prevention (CDC), the Substance Abuse and Mental Health Services Administration (SAMHSA), the Drug Enforcement Administration (DEA), and the National Institute on Drug Abuse (NIDA). Among the initiatives have been stricter guidelines for prescribers, increased documentation requirements for prescribing some opioids, abuse resistant formulations, and outreach programs for disposal of unused opioids. Furthermore, hundreds of lawsuits have been filed against pharmaceutical companies alleging illegal opioid promotion.

Put simply, these initiatives have had a major effect. Measured as a change in exposure, the opioid campaigns have contributed to a sharp and sustained decline in reported therapeutic use of prescription opioids. From 2013 to 2017 the reported use of prescription opioids declined 25%. The difference in number of persons exposed was large: Over the 4-year period use declined from 52 million to 37 million persons. The changes are shown in Table 3.

Table 3. U.S. persons exposed to opioid drugs, 2013-2017			
	Persons (thousands)		Percent
	2013	2017	change
Total	49,000	36,508	-25%
Higher potency (Schedule II)			
Hydromorphone	**406**	**554**	**36%**
Fentanyl	592	269	-55%
Mid potency (Schedule II)			
Acetaminophen- Hydrocodone	20,174	12,008	-40%
Acetaminophen-Oycodone	6,899	4,324	-37%
Acetominophen-Codeine	4,938	3,262	-34%
Hydrocodone	**328**	**2,549**	**677%**
Morphine	896	721	-20%
Oxycodone	4,254	4,203	-1%
Lower potency			
Codeine (Schedule II,III)	461	277	-40%
Tramadol (Schedule IV)	7,102	5,728	-19%
Lowest potency (Schedule V)			
Codeine-Guaifenesin	2,027	2,022	0%
Codeine-Promethazine	923	592	-36%
Source: Calculated from the Medical Expenditure Panel Survey.			
Bold face identifies increases.			

The data reveal some notable trends:

- Fentanyl products–80 times more potent than morphine–declined by 55%, from 592,000 persons in 2013 to 269,000 persons in 2017. CDC reports about rising overdose deaths attributed to fentanyl focused on illicit fentanyl that was added to street drugs.[8] Fentanyl is one of the most dangerous therapeutic drugs available for outpatient use, with potentially fatal risks from prescription error, accidental exposure, leaking patches, and overuse in a 24-hour period.

- For decades, the acetaminophen-hydrocodone combination (Vicodin, others) was the most widely prescribed drug of any kind in the U.S. But over four years, reported use declined 40%–from 20 million persons in 2013 to 12 million persons in 2017. However, in 2017 it was still the 10th most frequently used prescription drug.

- Oxycodone (Oxycontin)–frequently implicated in diversion, illicit use, and overdose deaths–remained widely used and was virtually unchanged with approximately 4 million persons exposed in both 2013 and 2017.

- Lower potency opioid use also declined substantially. Tramadol (Ultram) use declined by 19% and codeine products by 40%.

- One opioid increased rapidly in use. In 2014, the FDA approved a new abuse deterrent, extended release formulation of hydrocodone (ER, Purdue) that did not include another analgesic such as acetaminophen or ibuprofen. It replaced Purdue's hydrocodone-ibuprofen combination (reported used by 328,000 persons in 2013) and grew to 2.6 million in 2017.

- Short-term exposures were also reduced. Opioids are frequently prescribed with only a few days' supply following a tooth extraction or surgery. We defined short-term exposure as prescriptions dispensed for less than a 30-day supply. In 2017, 78.6% of acetaminophen-hydrocodone use was short-term. Also, an overwhelming share (87.2%) of the reduction in patients exposed to this product resulted from less short-term use rather than from extended use.

- The use of the codeine cough medicines in Schedule V was overwhelmingly for short-term use, with 98% reporting short-term use of guaifenesin combination and 89.4% for the promethazine combination. Use may further decline in response to the FDA restricting their use in children in 2017. [9]

Discussion

Despite these favorable trends in exposure to prescription opioids, the CDC reports that opioid overdose deaths continued to increase, rising from 42,249 in 2016 to 47,600 in 2017, an increase of 12.7% in just a single year.[10] However all of this one-year increase occurred in non-prescription opioids, with notable increases in illicit fentanyl added to various street drugs. Overdose deaths related to prescription opioids were unchanged in the one-year period and have increased approximately 18% since 2013.[11] Note that the CDC overdose statistics for prescription opioids include intentional and unintentional overdoses and therapeutic and illicit use.

Nevertheless, these data show a sea change in the use of prescription opioids, reinforced in part by DEA up-classification of acetaminophen-hydrocodone to Schedule II and tramadol to Schedule IV. The largest effects, in numbers of patients exposed, are in reduced short-term use with prescriptions providing only a few days' supply.

Amphetamine Use Grows Rapidly

Amphetamines, a group of drugs with a decades-long history of dependence, addiction and misuse,[12] are making a comeback. We estimate that in four years' time exposure to amphetamine products increased by 37%. While the primary current approved use is in children with ADHD, the fastest growth occurred in adults.

The Drugs

Today amphetamines and amphetamine-like products are available in a wide variety of formulations and brand names. The most widely used are combinations of amphetamines, available both as generics and brand names Adderall and Adderall XR. Rapid growth is also occurring in lisdexamfetamine (Vyvanse), a pro-drug that the body quickly converts to amphetamines. Methylphenidate is a structurally related derivative of amphetamine[13] and is available in many generics and under the brand name Concerta. Dexmethylphenidate (Focalin, Focalin XR) is one iso-form of the same molecule. All are potent stimulants of the central nervous system (CNS) and increase the release of multiple neurotransmitters, including dopamine and norepinephrine.

The Problem

Like opioids, amphetamines have been widely used and abused for many decades. Like opioids, the DEA classifies them as Schedule II Controlled Substances–among the drugs ranked as dangerous with "high potential for abuse and potentially leading to severe psychological or physical dependence."[7] The

substances ranked as more dangerous (Schedule I) are not only illicit drugs such as heroin, methamphetamine, and LSD, but also marijuana, now legal for medical or recreational use in a growing number of states.

The Uses Evolve

Amphetamines first appeared in the late 1930s–long before strict drug regulation–and were promoted as a treatment for depression.[12] By the second world war, this stimulant's ability to increase alertness led to widespread use in the military. (One survey showed 15% of pilots regularly used amphetamines in combat.) After the war, amphetamines became used as a weight-loss drug because they are a potent appetite suppressant. By the 1970s the next target population was school-age children with ADHD. Many children with developing brains crave more stimulation than available in a typical grade-school classroom. Giving a chemical stimulant to overactive children has the effect of causing them to sit more calmly in class and focus on assigned tasks. The narrowing of focus on detailed tasks was observed in other populations, and some deemed it a "neuroenhancer" and aid to memorizing large amounts of information.[14]

The Risks

Information also accumulated about the adverse effects of amphetamine. Its risks of tolerance, dependence, addiction, and abuse led to restrictions in its use as a Schedule II Controlled Substance and prominent warnings about its risk of abuse and dependence. Like the milder stimulant ephedrine, amphetamines can cause irregular heart rhythms and sudden death. It some patients it led to outright psychosis that was for years denied by some prescribing physicians as "unmasking pre-existing schizophrenia." In children, it caused various tics and abnormal movements, including the disfiguring Tourette's syndrome. Its potent ability to suppress appetite led to cases of anorexia in adults and retarded growth in children. Despite being well documented as a dangerous, potentially addictive drugs, an estimated 7.8 million persons reported taking amphetamine products in 2017, or about 2.4% of population. This is likely still smaller than in the 1970s, when some estimates said around 5% of the population used these drugs.

Growth in Amphetamine Use

Concerns about dependence and addiction, doubts about the value of short-term weight loss, and the rise of other drugs to treat depression led to amphetamines being used primarily in children with ADHD. However, since 2013, marked growth has occurred among adults. We estimate that in just four years reported adult use increased by 66%. By 2017, a total of 4.2 million adults reporting taking amphetamines, exceeding the use in children. The changes are shown in Table 4.

Table 4. Children and adults exposed to amphetamine-like stimulants, 2013-2017

	Children (thousands)			Adults (thousands)		
	2013	2017	Pct Change	2013	2017	Pct Change
Totals	3,138	3,584	14%	2,522	4,177	66%
Amphetamine-Dextroamphetamine	721	842	17%	1,448	2,466	70%
Lisdexamfetamine	633	737	16%	384	701	82%
Methylphenidate	1,285	1,579	23%	659	934	42%
Dexmethylphenidate	500	428	-14%	30	76	149%

Source: Calculated from the Medical Expenditure Panel Survey. Children are < age 18.

The factors driving this rapid increase in adult amphetamine use have not been adequately studied. However, these factors appear to have contributed:

- Shire and Janssen, manufacturers of the brand-name amphetamine products (Adderall XR, Vyvanase, Concerta) pursued and received expanded indications for ADHD in adults beginning in 2008. In 2015 Shire sought and received FDA approval for an indication for binge eating in adults for Vyvanse.

- College students and others used amphetamines off-label for "neuroenhancement."

- Those with years of exposure to amphetamines as children developed psychological or physical dependence and continued to use it as adults.

- Polypharmacy. Our exposure data show amphetamines were frequently included in drug cocktails in hopes of enhancing the benefits or countering the adverse effects of the amphetamines or other CNS drugs. For amphetamine-dextroamphetamine we found that in 2017 36% were taking another CNS drug, notably benzodiazepines, and 19% were taking a psychiatric drug, primarily antidepressants.

Discussion

The rapid increase in amphetamine use in adults can be attributed in part to the FDA's willingness to grant Shire and Janssen expanded adult indications for its brand name amphetamine products, Adderall XR, Vyvanase, and Concerta. The FDA also approved Vyvanase for binge eating in 2015. After decades of concern about inappropriate use of amphetamines for weight loss, it was surprising that the FDA granted a weight loss indication on evidence from short-term trials that simply used different measurement terminology (binge eating). Having FDA-approved indications for amphetamine use in adults empowers prescribers to order the drug within the restrictions for Schedule II Controlled Substances. This rapid growth in the use of amphetamines should be a major safety concern.

Fatal Methotrexate Medication Errors

In only a few instances can taking an oral drug obtained at a retail or mail-order pharmacy result in death if taken daily for just a week rather than weekly as prescribed or intended. One such drug is methotrexate, a potent immunosuppressant that blocks cell division.

Methotrexate is a very old and toxic drug with a rapidly expanding patient population and long-standing problems about its safe use. It was first FDA approved in 1953, years before clinical testing was required to demonstrate benefit.[12] It is prescribed for disorders that range in severity from lung cancer to psoriasis. In recent years its use has expanded rapidly: from 2013 to 2017 we estimate that the number of exposed patients has nearly doubled: from 561,000 patients to 1 million. An additional hazard is an exceptionally wide range of dose and duration of treatment.

Methotrexate ranks among the most toxic drugs in regular outpatient use because of its ability to inhibit normal cell division. It has a Boxed Warning about 11 different risks, all serious and many fatal.[15] When given to 434 patients with rheumatoid arthritis, 12%-38% had to discontinue treatment because of toxicity.[16] It has adverse effects on the liver, kidneys, and lungs. It also can suppress the production of new blood cells in the bone marrow. It causes damage to mucosal protection in the mouth and gastrointestinal system, hair loss, fever, and decreased resistance to infection. Adding folic acid to the treatment regimen reduced liver toxicity but had no observable effect on its other adverse effects.[16]

The Dose Frequency Problem

A critical safety issue with oral methotrexate revolves around how frequently it should be taken. Put simply, a medication error in frequency of taking a tablet can cause severe harm or death. For rheumatoid arthritis and psoriasis, it is taken once weekly. For some oncology indications, much larger doses are

administered daily for several days, often with treatment interruptions to allow recovery. The chances for error and confusion about dose frequency are increased because the “weekly” doses for psoriasis and rheumatoid arthritis are sometimes ordered as 3 smaller divided doses over 12 hours. And for one oncology indication, methotrexate is taken twice weekly.

There are few oral medication errors with more immediate and severe consequences than for those patients who are prescribed methotrexate weekly and then take it daily instead. In just a few days’ time this can result in painful and extensive erosive skin conditions, suppression of blood cells, liver damage, and death.

FAERS Medication Error Cases

In cases reported to FAERS for the 18 months ending June 30, 2019, confusion over weekly-versus-daily oral methotrexate doses resulted in 5 patient deaths and 9 patients requiring hospitalization. The damage occurred quickly. In some cases, death and injury were the result of daily methotrexate administration for one week or less. For the 10 cases for which age and gender were available, ages ranged from 65 to 96 years age, and 8/10 were female. In one additional case a patient confused methotrexate with another pill of similar size and shape with consequences that were not reported.

Why Overdoses Occurred

A key question is how the drug intended for weekly use became taken daily. In six cases the apparent error was made by the patient. Given an older population much more likely to be taking multiple medications–most on a daily or more frequent basis–it is not surprising some patients became confused. Patients in their 70s and 80s might also have trouble reading the instructions printed on the medication bottle. The FDA-approved Patient Information Leaflet fails to highlight prominently the importance of not taking methotrexate daily for its most common uses, rheumatoid arthritis and psoriasis. (It appears at the bottom of a more general paragraph about dosing that does not mention the consequences.)

In one case also reported directly to the ISMP Medication Errors Reporting Program, a 75-year-old female was provided with these instructions on the bottle of methotrexate tablets (2.5mg): “Take 3 tablets by mouth one day a week for 2 weeks then increase to 4 tablets by mouth 1 day thereafter.” According to the report, the patient received a “real” counseling session with the pharmacist. She was hospitalized in the ICU after taking methotrexate daily for 5 days in septic shock, pancytopenia, and hypotension.

In eight cases the drug was dispensed, labeled, or ordered incorrectly. In one case a 96-year-old female in a nursing home was administered methotrexate daily for 27 days for rheumatoid arthritis. She died after 16 days of hospital care. In another case, a community pharmacy dispensed a 3-month supply of methotrexate with instructions to take 6 tablets 2.5 mg daily instead of weekly. The error was discovered only when the patient requested a refill three weeks later. The patient survived after a long hospital stay. A third dispensing error illustrates how multiple players on the health care team can contribute to the error. An 80-year-old female was admitted to the hospital with renal failure with an appropriate existing prescription for weekly methotrexate. In continuing her home medications upon admission, the attending physician wrote an incorrect order for daily methotrexate administration. But the pharmacist corrected the error and the patient received methotrexate only once during a 5-day hospital stay. Nevertheless, on discharge the attending physician relied on the uncorrected copy of the medication order for daily administration entered on admission, which was then dispensed. The patient was hospitalized again after taking methotrexate daily for 8 or 9 days.

Unreported Cases

An FDA-sponsored study investigated the incidence of this dose-frequency medication error among Kaiser-Permanente patients in Northern California.[17] The investigators found 3 confirmed cases of dose frequency error requiring treatment among just 722 patients getting their first methotrexate prescription, a rate of 4 per thousand.(They found no confirmed errors in refills). This incidence rate suggested that the

number of methotrexate dose frequency errors could be far greater than the 14 cases we investigated that were reported to the FDA over 18 months.

Other FAERS Data

Other kinds of serious adverse event reports citing methotrexate received in the 12 months ending June 30 provided supporting evidence of its toxicity at apparently normal doses. Among 1,810 domestic reports of injury were numerous examples of events also consistent with some form of overdose, notably suppression of bone marrow (n = 117), mucosal inflammation (n = 54), lung fibrosis and other damage (n = 130), and infections (n = 267). Because of the narrow therapeutic index of this drug, these events can also occur at therapeutic doses, especially in older patients.

Decades of Inaction

Harmful and fatal medication errors with oral methotrexate are not new. In 2004, ISMP published a scientific report[18] about 106 reported cases, including 25 deaths. They were linked to all phases of the medication use process–prescribing, dispensing, administering (by healthcare providers and patients). Since 1996, methotrexate medication errors have been examined in more than 60 issues of ISMP's newsletter *ISMP Medication Safety Alert!*. [19] ISMP has classified methotrexate as a high-alert medication[20] and additional precautions are included among our 14 Targeted Medication Safety Best Practices for Hospitals.[21]

In a modern protected society, we should not provide medications that can cause potentially fatal errors affecting up to 1 million people without adequate safety precautions in place. Further, we estimate the methotrexate error risk is getting worse rather than better. As noted, patient use nearly doubled in just four years, exposing many more patients to the risk. In 2017, we found 40% of those taking methotrexate were 65 years of age or older, and likely to be taking multiple medications. In addition, the only methotrexate product available in a calendar pack to prevent accidental daily administration–Rheumatrex–has been discontinued.

Actions Needed

Here are basic safety measures needed to reduce the risks of oral methotrexate:

- It should be dispensed in a calendar pack (as with oral contraceptives) to clarify weekly dosing.
- The methotrexate packaging and labeling should prominently state "For once weekly use."
- A new patient Medication Guide should be tailored to the weekly users (rheumatoid arthritis and psoriasis) and prominently state the importance of the weekly dose regimen and the consequences of non-adherence.
- Methotrexate for psoriasis and rheumatoid arthritis should be limited to dosages that can be taken just once a week rather than in a sequence of several divided doses 12 hours apart.
- Mail-order and community pharmacies should not dispense more than a 30-day supply or else they should include special packaging to prevent daily use.
- Counseling at the pharmacy, doctors' offices, and the hospital should include an extra step to assure understanding by asking the patient to repeat back the instructions for use.
- Electronic prescribing systems should default to a weekly dosing regimen, and an appropriate oncologic indication required to be entered to dispense methotrexate for daily dosing.

FDA Adverse Event Reporting System

The Extent of Underreporting

A central but unanswered question in the safety of therapeutic drugs is the number and type of injuries that result from medical treatment, and the drugs most often implicated. Neither the CDC nor the FDA has programs to research and publish comprehensive statistics. Hundreds of therapeutic drugs contain FDA-mandated restrictions, mandatory patient guides, or prominent warnings about specific adverse effects. But they rarely provide reliable information about how frequently these adverse events might occur.

The primary system to monitor adverse drug events suspected to have been caused by a therapeutic drug is, of course, FAERS–the system that collects voluntary reports of cases where a health professional or consumer believes taking a drug has caused a health problem. This has been the central data source for QuarterWatch for over a decade and the most frequent source of new FDA warnings about approved drugs.[22,23] But what does this large collection of case reports tell us about the extent of death, injury, and other harms that result from more than 3 billion dispensed prescriptions a year?

On an annual basis the FDA receives more than 400,000 domestic reports of serious injury and death. If only 1 in 10 of these injuries resulted in a voluntary report, that would imply that as many as 4 million people experienced a serious or fatal injury that was suspected of being connected with their drug treatment. Could this conceivably be true? To dig deeper into this question, we conducted five in-depth studies of specific drugs with higher rates of adverse effects and higher-quality scientific evidence about incidence. We found that overall, only about 1% of the serious adverse events we studied had been reported, but with wide variation ranging 7.6% of cases of one serious infection to less than 1 in 1,000 for severe gastrointestinal harms from drug taken by 5.7 million people. This is how we calculated our estimates:

Our Data Sources

One reason so few estimates of drug harms exist is the limited availability of adequately researched source data. The adverse events we selected to study required credible peer-reviewed or FDA data about how often they occur. Many randomized clinical trials underestimate adverse effects because investigators do not ask patients specifically about the adverse effect and rely on those volunteered without prompting. In addition, many clinical trials are conducted among carefully selected patients. However, for a few drugs, we found reliable incidence rates in some clinical trials specially designed to capture certain adverse events. In other cases, the FDA has authorized estimates from pooled trials in the official prescribing information.

Having collected risk estimates, the next step was estimating the number of patients exposed to that risk. We used the most recently released 2017 Medical Expenditure Panel Survey[6] to estimate the number of patient-years of exposure for each drug and adverse event. Finally, for the same year, 2017, we collected all domestic adverse events for the study drug reported to FAERS and flagged those events that described the same specific adverse effect. While this is the highest-quality method we could devise, the reader will also want to review the limitations discussed below. Our cases are summarized in Table 2, reprinted from the Executive Summary, with complete details below.

Table 2. Estimated annual adverse events and FAERS reports in 2017					
Adverse event	Primary suspect drug	Frequent brand name	Estimated events	FAERS reports	Reporting rates
Total			276,062	2,550	0.92%
Severe gastrointestinal	Meloxicam	**Mobic**	45,336	31	0.07%
Severe gastrointestinal	Celecoxib	**Celebrex**	19,027	65	0.34%
Movement disorder	Risperidone	**Risperdal**	33,269	265	0.80%
Any bleeds	Apixaban	**Eliquis**	177,815	2,142	1.20%
Tuberculosis	Adalimumab	**Humira**	615	47	7.64%
FAERS = FDA Adverse Event Reporting System.					

Cases 1-2: Severe GI side effects from 2 NSAIDS for arthritis/chronic pain

The Drugs

Approximately 30 million older Americans have osteoarthritis[24] and millions more have other forms of chronic pain that compromise their quality of life. For decades the primary treatment has been non-steroidal anti-inflammatory drugs (NSAIDS) such as naproxen, ibuprofen, meloxicam, and celecoxib. The benefit of NSAIDs is often substantial effects on osteoarthritis but they require long-term therapy. One primary drawback is that the same mechanism of action that reduces inflammation also blocks production of the protective coating of the stomach than limits the harms of digestive acids.

The Risks

One set of primary risks for NSAIDS are stomach ulcerations, perforations, and bleeds--severe gastrointestinal adverse effects also described as NSAID gastropathy. Beginning around 2000 a new group of NSAIDS called COX-2 inhibitors entered the market with an early claim that they provided the same pain relief in osteoarthritis but reduced risks of severe gastrointestinal (GI) adverse effects. This claim was tested, debated, and litigated at length. One authoritative summary appears in the FDA-approved prescribing information for two COX-2 inhibitors, meloxicam and celecoxib.[25,26] It states “Upper GI ulcers, gross bleeding or perforation caused by NSAIDS occurred in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year.” To allow for the possibility that the COX-2 inhibitors might have lower risks than other NSAIDs, we used the lower of the two long-term estimates, 2% risk per person-year.

The Drug Exposure

The two COX-2 inhibitors in this assessment are widely used: We estimate that 5.7 million patients took meloxicam in 2017, and 1.7 million took celecoxib. Because our MEPS source data provides the number of prescriptions and days’ supply, we could also calculate the number of patient-years of exposure to match the FDA’s risk estimate calculations.

The FAERS Reports

For the year 2017 we could identify only 261 domestic adverse event reports of all types for meloxicam and 1,218 for celecoxib. Here, even though the two drugs are similar, celecoxib was the suspect drug overall in more than 10 times the total number of reports as meloxicam. The difference largely persisted for the study event, GI ulcers, perforations, and bleeds.

The Results

The complete results are shown in Table 2. We estimate that use of meloxicam likely resulted in 45,336 cases of GI ulcers, perforation, and bleeds of which only 31 were reported as FAERS adverse events, a reporting rate of less than 1 per thousand (0.07%) The reporting rate was higher for the celecoxib products (0.34%) but still less than 1 percent. Among the19,027 severe gastrointestinal adverse events that likely occurred among celecoxib users, only 65 were reported to FAERS in 2017.

Discussion

Severe gastrointestinal harms from NSAIDS are one of the most prevalent and best-known risks of therapeutic drugs and have been studied for decades. Despite similar GI side effects for the drugs, we note the estimated reporting rate was higher for celecoxib but the overall rate for both was substantially less than 1%. This is also a notable illustration that the number of adverse events reported to FAERS for older drugs does not provide reliable information about how frequently they may be occurring among the population using the drug.

Case 3: Apixaban and Bleeding

The Drug

Apixaban (Eliquis) is an oral anticoagulant drug approved in 2012 as a treatment to reduce the risk of strokes in patients with atrial fibrillation, an abnormal heart rhythm that disrupts the function of the two upper pumping chambers of the heart.[27] They work as primer pumps for the main working chambers, the ventricles. Blood clots are more likely to form in the fluttering atria and cause strokes if the clots then travel to the brain, or pulmonary embolism if they lodge in the lungs.

The Risk

The risks of apixaban are closely related to its benefits–inhibiting the formation of blood clots. While an unwanted blood clot in the brain can have devastating consequences, the formation of blood clots is essential to plug leaks that may form elsewhere in the vascular system. The GI system and the brain are among the most vulnerable sites where clots are needed to repair damage. Inhibiting the body's ability to form blood clots leads to bleeding, often severe and sometimes life-threatening or fatal. The pivotal trial for approval of apixaban provided one of the most precise and complete estimates of a drug adverse effect to be found in the scientific literature. The trial was large (18,201 patients) and long (monitored for almost 2 years). Importantly, bleeding was monitored systematically in every patient and reported in depth in a peer-reviewed study.[28] The study reported that 18.1% of the treated patients experienced a bleeding event per year, including 4% classified as major or clinically relevant. The definition of "major" described a severe bleed requiring the transfusion of 2 units of blood or more or death. While 18.1% annual incidence is a high rate of harms in an older population, the apixaban results were better than warfarin, the previous standard treatment, and the same or better than three other similar drugs.

The Drug Exposure

In 2017 apixaban was reported taken by 1.8 million adults. Considering duration of treatment, it accounted for a total of 987,000 patient-years of treatment and an estimated 177,815 bleeding events, of which 39,500 were major or clinically relevant. Because the definition of the more severe subset of bleeding could not be matched to FAERS reporting, the broader and more general definition of any form of bleeding was used to calculate a reporting rate.

The FAERS Data

Apixaban was primary suspect drug in 7,126 domestic adverse event reports in 2017, including 2,142 (30%) that indicated any form of bleeding. The events described in the FAERS report ranged in severity from cerebral hemorrhages (n = 116) to feces blackened from likely GI bleeds (n = 19). Bleeding sites included the skin, gums, eyes, vagina, spleen, kidneys, heart, bladder, and various GI sites such as stomach, small intestine, large intestine, and rectum. Overall, we estimated that 1.2% of the bleeding events that likely occurred were reported to FAERS, with data shown in Table 2.

Discussion

The 1.2% reporting rate for apixaban was more than 10 times higher than for meloxicam, the generic, still but nearly 4 times higher than celecoxib. These data also indicate that, in part, apixaban is also more toxic. It also supports the proposition that brand name drugs have higher reporting rates than do generic drugs. This is because the manufacturers of brand name drugs usually have many more interactions with consumers and health professionals because of promotion of the brand name as well as marketing and educational activities and therefore learn of more adverse events–which they are required to report to the FDA. Reporting is voluntary for consumers and health professionals. But if they inform the manufacturer, the company must investigate the case and report it to the FDA.

Case 4: Adalimumab and Tuberculosis

Adalimumab (Humira) is an injectable biological product that is approved to treat numerous autoimmune disorders, notably rheumatoid arthritis, Crohn's disease, and plaque psoriasis. It is an immunosuppressant drug that achieves its effect through inhibiting tumor necrosis factor, a key component of the immune system. It is also notable for its high cost. With invoice revenue of $16.3 billion in 2017, it was ranked #1 in the United States.[29] It costs an estimated $44,000 per patient per year according to the federal pricing schedule.[30]

The Risks

The product is by intention an immunosuppressant, an intervention in cases where the immune system attacks some part of the person's own body. Its risks are primarily those expected of a potent immunosuppressant that inhibits a key actor: various kinds of infections and types of cancer. Notably, new and reactivated tuberculosis (TB) was detected in clinical studies and a Boxed Warning urges treating physicians to test for latent TB prior to treatment and to monitor all patients during and after treatment. While TB is by no means the only risk of adalimumab, it was monitored in 52 clinical trials and the company reported that 0.2 patients per 100 patient years developed active tuberculosis.[31]

Patient Exposure

Despite the fact that adalimumab brings in more revenue than any other therapeutic drug, exposure to the drug was modest in 2017 compared to the other case examples. We identified 612,00 patients who reported taking it at least once, and 307,457 patient-years after accounting for duration of treatment. However, because the incidence rate was low, we estimate adalimumab treatment for one year would result in 615 domestic cases of active TB.

The FAERS Data

Adalimumab has been notable for many years in the exceptionally large numbers of adverse event reports that are submitted each year. In 2017, it accounted for 18,435 domestic adverse event reports—which is 56 times more than for meloxicam, a drug taken by 9 times as many patients. Of this large total, 29% of the cases were coded as not serious, including injection site pain (n = 596), fatigue (n = 237), and headache (n =149). But the reports included serious infections such as pneumonia, intestinal obstructions, and cancer. There were 775 patient deaths and 5,484 cases that resulted in hospitalization. Among these

reports we found 46 case reports indicating any form of TB. We estimated that 7.6% of the TB cases that likely occurred in 2017 were reported to FAERS.

Discussion

We suspect that one reason for the large volume of adalimumab reports is the extensive interactions between AbbVie, the manufacturer, and patients. The adalimumab website (https://www.humira.com/) offers savings cards and prescription rebates, a way to check whether insurance would cover treatment, a nurse ambassador, a smart phone application, and other services. The nurse ambassador program alone could generate thousands of reports because, according to the sample transcripts, “She would ask me, “What’s going on? How’re you feeling?” If the patient responds that well, they have a bad cold, it could generate a report. Nurses could even make personal calls for face-to-face help with injections. Nevertheless, even in this setting of frequent contacts directly with patients, only 7.6% of the estimated cases were reported to FAERS.

Case 5: Risperidone and Movement Disorders

Risperidone (Risperdal) is a psychiatric drug approved for long-term treatment of schizophrenia and bipolar mania. However, its effects were primarily measured in 4 to 8 week trials in patients hospitalized for psychosis–an acute condition in which the patient loses touch with reality and experiences hallucinations, hears voices, sees things, or imagines threats and dangers that do not exist.[32] Its primary effects are believed to be achieved primarily through blocking a subset of brain receptors, called dopamine receptors.[33]

The Risks

The major drawback to risperidone and several similar drugs for psychosis is that the D_2 receptors that are blocked have multiple functions in the human body in addition to an effect on mood and behavior. The blocked receptors are found in 10 different areas of the brain and play a role in the regulation of body functions outside the CNS.[34] Notably, these same receptors play a central role in the extrapyramidal motor system. Blocking them also impairs motor control, with the most serious and persistent adverse effect being a condition called tardive dyskinesia. It produces uncontrollable twitching and other involuntary movements of the fingers, lips, tongue, face, and even entire limbs. With continued treatment, the damage becomes irreversible. Estimating the incidence of tardive dyskinesia is challenging because the damage is cumulative and dose dependent—the longer and more completely the receptors are blocked, the greater the chance of these harms. Usually, the clinical trials for approval of the newer generation of antipsychotic drugs recruited patients with previous exposure to other drugs with this same adverse effect. As noted, the trials were also short. However, a rare chance to assess this risk occurred in a long-term trial of risperidone in newly diagnosed patients with little or no previous exposure to drugs that cause tardive dyskinesia.[35] In addition, movement disorders were systematically assessed with the same standard protocol. After a median of 208 days’ treatment, 9.4% of the treated patients had confirmed dyskinesia.

The Exposure

In 2017, an estimated 566,600 U.S. patients reported taking risperidone at least once. After adjusting for duration, we estimate exposure at 346,600 patient-years. In the exposure data the patients reported taking risperidone for a median of 219 days – similar duration to the clinical trial noted above. We estimate that treatment in 2017 likely resulted in 33,269 cases of tardive dyskinesia.

The FAERS Data

In 2017 the FDA received 8,977 domestic case reports about adverse events in which risperidone was the primary suspect drug. The case total was dominated by a different risperidone side effect that is also a target of litigation: gynecomastia or the development of breasts in males (n = 6,075). Although only 15 cases

overall were specifically identified as connected to litigation, advertising for clients and other litigation events may have increased the totals for gynecomastia. For this assessment, the FAERS reports included 265 cases indicating dyskinesias or other related movement disorders. From these results we estimate that 0.8% cases of dyskinesia that likely occurred were reported to FAERS in 2017.

Discussion

The estimates for tardive dyskinesia have greater potential variability than the other cases in this in-depth study. That is because our estimates for dyskinesia incidence were for newly exposed patients in long-term treatment, and the FAERS reports don't reveal how long the patients had been exposed to antipsychotic drugs–and could have been for longer or shorter periods than the 208 days in the clinical trial, or the mean of 219 days in the exposure data. In addition, the persistence of the dyskinesia (tardive) could not be evaluated in these data.

Overview of the 5 Case Studies

The first and most straightforward conclusion is that simply adding up the estimated serious side effects for just these 5 drugs revealed that a large number of estimated injuries occurred in just one year–more than 276,000 cases. However, only 2,549 cases were reported to FAERS, or just under 1%. This overall percentage is consistent with our previously published study in 2012 in which we reported a 1% reporting rate for hemorrhages associated with for the anticoagulant warfarin and 0.9% for hospitalizations for bleeding from two platelet inhibitors, clopidogrel and ticlopidine.[36] A 2008 FDA study concluded that from 5% to 15% of cases of rhabdomyolysis (a rare form of severe liver damage) had been reported for brand name cholesterol lowering drugs.[37] This is consistent with our maximum estimated rate of 7.4% for another rare and distinctive adverse event reported for a brand name drug.

This reporting rate assessment has numerous limitations. We have estimated drug exposure from a large national survey with its own limitations. The incidence rates came from authoritative sources, but each had its own limitations. We needed to match the adverse event described briefly in a published study or FDA-approved prescribing information with a much larger and more complex adverse event vocabulary, MedDRA.[3] While we focused on widely used drugs, the rates of adverse events were calculated for persons who took them continuously for a year. For millions of people either these same or other drugs are taken only short term, with much lower risks. Many other drugs with large patient populations are better tolerated and have lower rates of adverse effects by many measures.

Conclusions

These results from five in-depth case studies describe a useful range of estimates of both the number of injuries and the fraction reported to FAERS. They further support a conclusion repeated frequently in QuarterWatch reports: because of variability in reporting rate, the number of adverse event reports in this system does not provide reliable information to estimate the incidence of adverse events—but it helps establish the strength of the association. Even viewed as an order of magnitude estimate of serious injuries attributable to therapeutic drugs, these data emphasize the need for better surveillance of the risk of injury from the therapeutic use of drugs, and more aggressive interventions to reduce risk and assure safe use.

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QuarterWatch Team and Funding Sources

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Thomas J. Moore serves as a part-time project director for QuarterWatch. He has developed and maintains the master adverse event database that serves as the primary data source for the publication and conducts the primary analysis for each issue. Mr. Moore receives an honorarium from ISMP for each issue, with the remaining work being on a volunteer basis. He is also a professorial lecturer in the Department of Epidemiology in The George Washington University Milken Institute School of Public Health. Mr. Moore conducts and publishes other independent studies in the peer-reviewed scientific literature and works as a consultant on drug safety issues, doing business under the name Drug Safety Research. He also collaborates on a research project at the Johns Hopkins Bloomberg School of Public Health that studies the costs of clinical trials and is supported by the Laura and John Arnold Foundation. He was a consulting expert to the Attorney General of the State of Texas in a Medicaid fraud lawsuit against Johnson & Johnson regarding the antipsychotic drug Risperdal (risperidone). In addition, he conducts confidential assessments for attorneys inquiring about the emerging safety profiles of drugs.

Curt D. Furberg, MD, PhD is a Professor Emeritus of Public Health Sciences at Wake Forest University School of Medicine and serves as senior medical adviser to QuarterWatch. He receives no compensation for his work in assessing scientific evidence, defining safety issues, shaping the written report, and communicating with the FDA and others about QuarterWatch findings. He continues to have a research role at Wake Forest and has published more than 450 peer-reviewed scientific articles. An expert on clinical trials of drug treatments, Dr. Furberg is author of a major textbook on that subject and has worked for the National Institutes of Health and the pharmaceutical industry as an investigator in clinical drug research. In the past 4 years, he has given expert testimony or depositions in cases involving Pradaxa (dabigatran), incretin-based medications, Xarelto (rivaroxaban), and testosterone replacement products.

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Michael R. Cohen, RPh, MS, ScD (hon), DPS (hon) is founder and President of ISMP and guides the overall policies and content of QuarterWatch. He also edits the other ISMP newsletters and is author of the textbook *Medication Errors*. He has served as an advisor and consultant to the FDA, and for his work in medication safety was recognized as a MacArthur Fellow by the John D. and Catherine T. MacArthur Foundation. Dr. Cohen receives a regular salary as president of ISMP and does not engage in outside consulting or legal testimony.