ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES QuarterWatch
Monitoring FDA MedWatch Reports

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ANNUAL REPORT ISSUE: FOUR FEARED ADVERSE EVENTS

Rhabdomyolysis: Severe damage to skeletal muscle
Serotonin or Neuroleptic Malignant Syndrome: Key neurotransmitters disrupted
SJS/TEN: Autoimmune reaction destroys large areas of skin
PML: A deadly viral infection of the brain

Executive Summary

In this issue, we survey the full year of new adverse drug event reports received by the U.S. Food and Drug Administration (FDA) during 2017 to identify drugs most frequently named as suspects in four distinctive and severe adverse drug events. While these adverse events are apparently uncommon, all four are life-threatening medical emergencies; with some, the damage is irreversible. The drugs implicated in these events include many different classes, including antidepressants, antibiotics, and drugs for pain, multiple sclerosis, epilepsy, and psychosis. Rapid diagnosis, identification, and cessation of suspect drugs are central to the treatment of all four disorders.

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.

For the full year of 2017, the FDA received 1,211,683 new adverse drug event reports, a 2.2% increase from the previous year and an increase of 83.1% from five years earlier. The reports identified 1,731 primary suspect drugs, but the number for reports for each drug ranged from as few as 1 case (122 drugs) to more than 10,000 cases (17 drugs). Factors that influence the number of adverse event reports include the toxicity profile of the drug, the number of patients exposed, and the educational and marketing activities of drug manufacturers, which may cause them to learn of more adverse drug events they are required to report. The 2017 total includes 309,641 (25.5%) foreign cases submitted by manufacturers who also market the U.S.-approved drugs abroad.

Overview of Critical Adverse Drug Events

These are the four adverse events examined in this issue of QuarterWatch:

- **Rhabdomyolysis**. This disorder occurs when drugs directly or indirectly damage or destroy skeletal muscle cells, which then release such large quantities of cellular proteins that they overwhelm the kidney's filtering capacity to remove them. Notably, this is the most extreme subset of the spectrum of muscle damage induced by therapeutic drugs.

- **Serotonin or Neuroleptic Malignant Syndrome**. In serotonin syndrome, an overdose or combination of drugs that increase the levels of this neurotransmitter produces a rapid onset of

abnormal behavior and thought, muscle spasms, and compromises of the autonomic nervous system. Neuroleptic malignant syndrome is largely similar except that drugs blocking dopamine receptors trigger the syndrome, and the abnormal muscle contractions are described as lead pipe rigidity.

- **Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN).** In this disorder, the body's immune system attacks and destroys the skin, producing a condition similar to severe burns. The difference between SJS and TEN is the extent of body surface area affected, with SJS limited to less severe cases where less than 10% of body surface is compromised.

- **Progressive Multifocal Leukoencephalopathy (PML).** This is an often-fatal viral infection of the brain that occurs when immunosuppressive drugs compromise the body's ability to hold a widely prevalent virus in check. Antibody studies indicate that the virus–John Cunningham virus or JCV–can be found in 50%-70% of the adult population. But both the initial infection and later latency are without symptoms until immune compromise allows the virus to attack and destroy the white matter of the brain.

Common Features

While common adverse drug events–for example, nausea–have many causes, in all conditions of interest, drugs are by far the most prominent cause. Unlike many adverse events, these conditions are rarely confounded by signs and symptoms of the underlying medical problem being treated. Some overlap occurs between these disorders. The uncontrolled muscle contractions of neuroleptic malignant syndrome can cause damage so severe that rhabdomyolysis also ensues. Some psychiatric drugs affect both serotonin and dopamine neurotransmitters and can contribute to both syndromes or make them difficult to distinguish.

Incidence Is Unknown

These severe adverse events share with many other harms of therapeutic drugs the limitation that their true rate of occurrence is unknown, and thus the 4,631 reported cases in 2017 do not provide reliable insights into how frequently they may occur in exposed patients. The QuarterWatch case count for 2017 is shown in Table 1. Although the number of unreported cases is unknown, these events are relatively uncommon, at least in these severe forms.

Table 1. Cases reported to the FDA of four severe drug adverse events, 2017

Adverse drug event	Number of cases	FAERS mortality rate	Number of suspect drugs*	Most frequent reported suspect
Rhabdomyolysis	1,549	12%	25	Atorvastatin
Serotonin or Neuroleptic Malignant Syndrome	1,485	11%	30	Sertraline
Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis	1,178	18%	20	Lamotrigine
Progressive Multifocal Leukoencephalopathy	419	29%	4	Natalizumab

* ≥ 10 cases reported in 2017. One drug or one case could be in multiple categories.

Drug Risks of Note

The drugs that we describe as providing the strongest signals were identified in 10 or more cases reported in 2017, and with only a few exceptions were also cited in previously published case reports. This report also contains more detailed tables for the drugs identified for each of the four adverse drug events. However, these drugs of note emerged from our evaluation of the entire group of reports:

- **Lamotrigine and SJS/TEN**. This drug for epilepsy and bipolar disorder led all others in reported cases in 2017 (n = 128). Lamotrigine is also linked to other hypersensitivity reactions, including angioedema, other serious skin rashes, and multiorgan hypersensitivity. The prescribing information also includes warnings for sudden unexplained deaths, suicidal behavior and ideation, and blood disorders.

- **Statins and Rhabdomyolysis. T**hree of the five most frequently implicated drugs were atorvastatin (n = 114), simvastatin (n = 97), and rosuvastatin (n = 53). Rhabdomyolysis captures only the most severe cases of muscle pain and damage, a documented but still poorly managed adverse effect of this class of drugs**.**

- **Aripiprazole and Four Adverse Effects.** This antipsychotic drug is notable for the breadth of its evident toxicity. It not only ranked No. 1 in neuroleptic malignant syndrome (n = 189), but also was a leading suspect in rhabdomyolysis (n = 83), serotonin syndrome (n = 37), and SJS/TEN (n = 16). In addition, we have linked it to reports of pathological gambling and hypersexuality.

- **Tramadol and Serotonin Syndrome**. This opioid pain reliever was suspect in 37 cases of serotonin syndrome—which often occurs rapidly, especially when another drug affecting serotonin is added to those already being taken. Physicians are often unaware that tramadol is also a serotonin reuptake inhibitor, sharing this mechanism of action with many antidepressant drugs.

The Adverse Event Reporting System

Reports for these four adverse events reveal both strengths and weaknesses in the FDA regulations for manufacturer reporting of adverse drug events. The strength is the requirement for manufacturers to survey the medical literature regularly and forward published case reports. Published cases are typically of higher quality and completeness than spontaneous reports from other sources and frequently include formal causality assessments. For these adverse drug events, an unusually large fraction of cases was derived from the medical literature.

The weaknesses result from the lack of adequate guidance to ensure consistent reporting of the medical literature. In reviewing the published reports, we found cases where the drug had been administered but was not a suspect, but the manufacturer reported it anyway to be cautious. For generic drugs, one literature case can result in as many as five duplicate reports. FDA reporting guidances also do not specify a uniform format for literature citations.

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 FDA Adverse Event Reporting System continues to be a vital and important tool for postmarket surveillance. Overall 5 of 21 FDA Drug Safety Communications in 2017 relied entirely or in part on FAERS data. But the system desperately needs an update. As of September 2018, the FDA indicates it is still working on a revision of its crucial guidance for reporting adverse drug events, a document last updated in 2001. No drafts for discussion have been released. As we have previously reported at length, the system has not been modernized to capture the changing information environment in the era of social media and other digital interactions.

This issue surveys four distinctive and severe adverse drug events. The positive news is that the FDA has devoted substantial scrutiny to these potentially lethal risks and insisted that most suspect drugs include clear warnings in the prescribing information for physicians. Also, warnings are often included in consumer Medication Guides. The negative perspective is that the FDA provides no information and has no published method for assessing how frequently these adverse events occur, and which drugs are most often the suspects. Because these events are distinctive, severe, and mostly drug-related, they are excellent candidates for study in the agency's Sentinel System or another electronic health records data system.

This report identifies four specific drug risks of note. For lamotrigine, risks of several forms of hypersensitivity are so great that physicians should consider safer alternatives to this widely used treatment. The findings for statins and rhabdomyolysis are linked to damage and destruction of skeletal muscles, and both consumers and physicians should be alert to symptoms, including more numerous but milder cases of muscle pain and damage. Aripiprazole was a strong suspect in four different severe adverse effects in addition to the toxicity it shares with other antipsychotic drugs. Finally, physicians should be aware that tramadol has substantial effects on serotonin reuptake and be alert to the possibility that concomitant use with most antidepressants could result in life-threatening episodes of serotonin syndrome.

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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 web site. (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 not serious, Only cases reported for the first time in 2017 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 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 2017 to MedDRA version 20.1.

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the most recent version of the case report. The drug 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 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 formulations.

The tables of reported adverse event terms in this report provide counts of standardized adverse event Preferred Terms (PTs). However, each case report can contain one or more terms, including near synonyms (e.g., p*ain, abdominal pain*). The percentage for each term in the tables is the fraction of cases in which the term was found.

We report the number of prescriptions and patients prescribed selected drugs from our own analysis of published data from the Medical Expenditure Panel Survey.[6] It is the largest publicly available survey of prescription drug use with raw data made available annually by the Agency for Healthcare Research and Quality. The latest available data are for 2015.

During analysis of the four distinctive and severe adverse drug events that are the focus of this issue, we found that unusual numbers of adverse event reports were extracted from the published literature by drug manufacturers. This ranged from 20% for rhabdomyolysis cases to 37% for progressive multifocal leukoencephalopathy. To prevent an overcount we screened the literature reports and excluded cases where more than one manufacturer of a generic drug cited the same literature report for the same drug. In some instances, we found as many as four adverse event reports citing the same published case.

Results

Report Trends

In 2017, the FDA received 1,211,683 new adverse drug event reports into its FDA Adverse Event Reporting System (FAERS), a 2.2% increase from the previous year and an 83.1% increase from five years earlier. This total can be divided into these categories: Serious, disabling and fatal events from the U.S. (27.0%), similar serious events from other countries (25.5%), and non-serious events (47.5%). The increase in reports can be attributed to these factors: (1) Because of the steady stream of new approvals, an increasing number of drugs are under postmarket surveillance; (2) In the internet era, there are more manufacturer channels of communication with patients and healthcare professionals, causing them to learn of more adverse drug events; (3) The FDA has approved more drugs with restricted distribution schemes, increasing contact with patients and revealing more adverse events; (4) An increasing share of foreign reports because of globalization of the pharmaceutical industry and consolidation into fewer and larger companies.

Among the most notable changes in the 2017 data were exceptional growth in reports made directly to the FDA rather than through drug manufacturers. The 2017 total was 61,296 direct reports, reflecting an increase of 21.7% over the prior year. Also, the steady growth of serious foreign reports meant that the share of reports from foreign countries (25.5%) nearly equaled domestic serious reports (27.0%).

Four Severe Adverse Drug Events

We surveyed a full year of new adverse drug event reports received by the FAERS during 2017 to identify the most frequently named suspect drugs in four distinctive and severe adverse drug events:

- Rhabdomyolysis
- Serotonin syndrome and neuroleptic malignant syndrome (NMS)
- Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)
- Progressive multifocal leukoencephalopathy (PML)

Overall, we identified 4,631 adverse event reports of these life-threatening medical emergencies and found the strongest signals for 79 drugs.* The list of suspects is intended to highlight the highest risk drugs but is not comprehensive. More than 100 drugs have been linked to SJS/TEN alone,[7] and as many or more have effects on the serotonin neurotransmitters and might contribute to serotonin syndrome.[8]

Characteristics of the patients and reports, shown in Table 2, provide two insights into the common features of all four severe adverse drug events. The patient characteristics reveal little if anything about a vulnerable subpopulation; instead, they show that for the at-risk drugs these idiosyncratic reactions can occur across the entire patient population. Note that 60% of cases of serotonin syndrome occurred in females, likely reflecting higher utilization of antidepressant drugs. But the reverse was true for antipsychotic drugs, where use in schizophrenia is more common in males. While consumers typically account for half or more of all adverse event reports, they account for only 14%-25% of these cases. Likely the higher proportion of cases from health professionals reflects the challenging nature of treatment of these medical emergencies and interest in unusual cases. But it also implies substantial under-reporting, since few consumers could be unaware these events had occurred.

* A drug was counted twice if it had events in two categories.

While this may be the first comprehensive survey of these important adverse drug events, there are also limitations in our primary data source, the 2017 adverse drug event reports. Overall, we found that the report quality for these distinctive adverse events was higher than average. In particular, case reports in the published literature rank among the highest quality assessments of specific drug harms to be found in any form of reporting. However, we also observed problems in the extraction of these literature reports into FAERS electronic submissions. First, we found some drugs used for treatment of these events listed as suspects in the manufacturer reports because they were listed among the drugs identified as being administered to the patient at some point. Also, for generic drugs, more than one manufacturer may have submitted the same published case. While we screened the literature reports for duplicate citations, some inconsistently described duplicate cases may have been overlooked. Finally, given that tens of millions of consumers were exposed to the leading suspect drugs, and adverse event reports numbered in a few thousand, these data provide some assurance that these severe reactions are relatively rare. However, there are insufficient data to attempt to estimate under-reporting.

Table 2. Patient and report characteristics, key severe adverse drug events, 2017

	Rhabdomyolysis	SJS/TEN	Serotonin syndr.	NMS	PML
Total cases	1,549	1,178	735	750	419
Patients					
Age, median, IQR**	58 (41-70)	50 (25-66)	50 (27-63)	47 (27-61)	51 (41-65)
Gender, % female	38	57	60	39	57
Source					
Consumer, %	14	20	25	24	10
Heath professional,%	95	88	86	76	90
From literature,%	20	24	31	21	37

* NMS = Neuroleptic malignant syndrome; PML = Progressive multifocal leukoencephalopathy

** Interquartile range (25th and 75th percentile)

Rhabdomyolysis

In 2017, we identified 1,549 adverse event reports for rhabdomyolysis—the extensive and potentially life-threatening breakdown of skeletal muscle cells. We found the strongest signals for 25 drugs, including 3 statins for cholesterol-lowering, 7 antipsychotic drugs, and 4 diverse drugs for pain (Table 3). While many of these drugs were known suspects, we also identified two novel and recently approved drugs, a checkpoint inhibitor to treat cancers, nivolumab, and a combination cardiovascular product for chronic heart failure, sacubitril-valsartan.

Table 3. Strong signals for rhabdomyolysis, 2017*

Suspect drug	Cases
Statins	**264**
ATORVASTATIN	114
SIMVASTATIN	97
ROSUVASTATIN	53
Antipsychotics	**184**
ARIPIPRAZOLE	83
QUETIAPINE	23
RISPERIDONE	19
OLANZAPINE	19
PALIPERIDONE	18
CLOZAPINE	12
HALOPERIDOL	10

The Event Defined

Many drugs have the unwanted capacity to damage and destroy skeletal muscle cells. The problem begins when drugs impair the function of the primary energy source of muscle cells, adenosine triphosphate (ATP).[9] If the interference with ATP is substantial, the muscle's ability to relax and contract is compromised. Ultimately the muscle cell disintegrates and releases its contents into the bloodstream. One signal that this process is occurring is high levels of the enzyme creatine kinase, which is released by skeletal muscle cells that are damaged or destroyed.[10] In addition, the disintegrating cells also release myoglobin, a distinctive protein that stores oxygen in muscle cells.

Rhabdomyolysis occurs when destruction of skeletal muscle cells is so extensive that it threatens to cause kidney failure because the organ cannot filter out the large quantities of myoglobin and other cellular proteins that have been released. The condition is often defined as the appearance of myoglobin in the urine and elevated levels of creatine kinase 5-10 times the upper limit of normal (ULN).[11] [12] Thus, rhabdomyolysis falls at the extreme end of a spectrum of muscle damage that can occur from multiple causes, including extreme exertion, traumatic injury, and substance abuse, notably opioids. Symptoms and signs may include muscle pain, dark urine (from myoglobin), fever, vomiting, and muscle cramping. The release of calcium, potassium, and sodium from disintegrating cells can trigger potentially life-threatening heart rhythm disorders.

Management includes identifying and discontinuing the cause of muscle damage, preventing kidney failure, restoring normal body fluid balance, and correcting any elevation of electrolytes sodium, potassium and calcium.

Table 3, continued	
Pain	**86**
METHADONE	**30**
ACETAMINOPHEN	24
PREGABALIN	17
GABAPENTIN	15
Epilepsy	**77**
LEVETIRACETAM	64
LAMOTRIGINE	13
Oncology	**40**
NIVOLUMAB	25
TRABECTEDIN	15
Antidepressants	**25**
SERTRALINE	13
VENLAFAXINE	12
Other	**68**
METFORMIN	20
DAPTOMYCIN	15
FUROSEMIDE	12
AMLODIPINE	11
SACUBITRIL; VALSARTAN	10
*≥ 10 reported cases in 2017	

Drugs Implicated

Rhabdomyolysis was notable for the large number of drugs implicated, and the large populations of patients exposed. The strongest suspect drugs are shown in Table 3. The cholesterol-lowering statins accounted for the largest proportion of cases, and atorvastatin accounted for the most reports of all drugs. All the major statins were implicated, except that pravastatin–with five cases in 2017–did not meet our strong signal criteria. In addition, cerivastatin was withdrawn in 2001 because of excess risk of death from rhabdomyolysis.

Also prominent were seven of the most widely prescribed antipsychotic drugs. Most of these 184 cases were secondary to another life-threatening adverse drug reaction, neuroleptic malignant syndrome, which is discussed later in this report.

Also notable were strong signals for two more recently approved drugs. Nivolumab is among a group of new cancer drugs called immune checkpoint inhibitors that open tumor and other cells to attack by T cells by blocking a key signaling protein. Growing evidence shows treatment can also result in T cell attacks on muscles and body organs.[13] Sacubitril-valsartan is a new combination product for heart failure and had clinical trial evidence of possible muscle harm.

While this report identifies the 25 leading suspects with the strongest signals, overall 179 different drugs accounted for 2 or more reports in 2017.

Serotonin or Neuroleptic Malignant Syndrome

Serotonin syndrome and neuroleptic malignant syndrome (NMS) share many similarities and some notable differences.[14] [15] Both involve important neurotransmitters that help mediate many body functions, notably mood, behavior, body temperature, heartbeat, digestion, blood pressure, and voluntary and involuntary muscle movements. Both syndromes involve life-threatening disruptions of the central nervous system. Both are caused by psychiatric or analgesic drugs that target serotonin receptors or, in the case of neuroleptic malignant syndrome, dopamine receptors.

The specific signs and symptoms that can be present in either syndrome may involve one or several different dysfunctions of the CNS. They may involve erratic or irregular heartbeats, drooling, irregular

breathing, loss of control over body temperature, mostly fever but sometimes hypothermia. The most common symptom is loss of normal muscle control, or clonus, causing painful spastic or continuous muscle contractions that can be so severe that muscle cells are damaged and leak their contents, causing rhabdomyolysis. As might be expected of neurotransmitter dysfunction, these syndromes can also involve altered mental status that can range from confusion to a coma.

The onset of both syndromes can be very rapid, with serotonin syndrome often occurring within hours of drug consumption, and NMS within a few days. The key components of management for both is to stabilize the abnormal and erratic behavior of the CNS, and then identify and remove the causal drug agents.

Serotonin Syndrome

As the name implies, serotonin syndrome is linked to drugs that alter serum levels of serotonin. The most widely used suspects are antidepressants, most of which interfere with the normal reuptake of serotonin, which is normally present for milliseconds in the synaptic cleft between neurons before being reabsorbed.[16] But other drugs also affect serotonin. Tramadol, one of the most widely used opioids, also impedes serotonin reuptake.[17] Also involved is the over-the-counter cough medicine dextromethorphan, and anti-nausea medications that block serotonin receptors, notably ondansetron and granisetron.[18] The extensive use of drugs with an effect on serotonin means that the population exposed numbers tens of millions.

Serotonin syndrome appears to be uncommonly identified as being caused by a single serotonergic drug at therapeutic doses. The most commonly reported causes are interactions between multiple serotonergic drugs, or accidental or intentional drug overdoses. The syndrome varies widely in severity and can range from mild hypertension or disruption of the normal heartbeat (which might not be obviously linked to the suspect drugs) to agitation, hallucinations, fever, vomiting, diarrhea, and spastic muscle contractions. The psychiatric symptoms can sometimes be mistaken for a worsening of the mental disorder being treated.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome or NMS occurs among drugs that block dopamine receptors as one of their mechanisms of action, primarily antipsychotic drugs.[19] This adverse event is a life-threatening medical emergency that occurs at normal therapeutic doses, usually within a few days of starting treatment or switching between antipsychotic drugs.[20] It can also occur on abrupt withdrawal of the drugs, and with other drugs that affect normal dopamine neurotransmission.

The hallmark symptoms are disturbed mental functioning, lead pipe muscle rigidity, and loss of control over body temperature, usually fever. It shares with serotonin syndrome a compromise of the autonomic nervous system with effects on heartbeat, breathing, blood pressure, and other body functions. Treatment includes immediate cessation of the dopamine-blocking agent and urgent management of the disrupted body functions such as heartbeat and blood pressure.

Table 4. Strong signals for serotonin and neuroleptic malignant syndromes, 2017

Suspect drugs	Cases
Serotonin Syndrome	
Antidepressants	284
SERTRALINE	63
VENLAFAXINE	50
FLUOXETINE	35
ESCITALOPRAM	29
DULOXETINE	26
CITALOPRAM	22
VORTIOXETINE	21
PAROXETINE	20
BUPROPION	18
Antipsychotics	82
ARIPIPRAZOLE	37
QUETIAPINE	31
OLANZAPINE	14
Opioids	47
TRAMADOL	37
TAPENTADOL	10
Other	61
LINEZOLID	17
METHYLPHENIDATE	12
ONDANSETRON	11
LITHIUM	11
SODIUM OXYBATE	10
Neuroleptic Malignant Syndrome*	
Antipsychotics	497
ARIPIPRAZOLE	189
OLANZAPINE	95
QUETIAPINE	77
RISPERIDONE	50
HALOPERIDOL	34
CLOZAPINE	31
PALIPERIDONE	21
*Antipsychotic drugs only	

In the literature, the crude estimates of mortality from neuroleptic malignant syndrome are approximately 10%.[21] In the FEARS adverse event data for 2017, 16% of reported cases resulted in patient death.

Confusion and Crossover Between Syndromes

The similarity in symptoms between the two syndromes, according to reviews, leads to confusion in diagnosing the correct one.[14] The cases are also confounded by polypharmacy, among consumers simultaneously taking antidepressant, antipsychotic, and possibly other drugs. Still another layer of complication arises because some antipsychotic drugs have effects on both dopamine and serotonin receptors, notably aripiprazole. Furthermore, the muscle contractions of NMS are so severe that seven antipsychotics also were listed among the strongest signals for rhabdomyolysis.

The FAERS Data

The 19 drugs identified as having the strongest signals for serotonin syndrome and the 7 antipsychotics that are strong suspects for NMS are shown in Table 4. While our case definition for NMS was limited to drugs that block dopamine receptors, we also identified cases for valproic acid (n = 15), lithium (n = 14), and 3 antidepressants, sertraline (n = 13), mirtazapine (n = 12), and paroxetine (n = 11). Even the FDA warnings for antidepressant drugs such as paroxetine express uncertainty as to which of the two syndromes may occur.[22]

Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) is likely the oldest known severe skin disorder caused primarily by drugs, with the first two cases described in 1922 by two New York City physicians, A.M. Stevens and F.C. Johnson.[23] The symptoms were then--and are now--severe, disfiguring, and painful. This autoimmune disorder develops when dermal cells are attacked and killed by T cells and natural killer (NK) cells.[24] Blister-like skin lesions develop (Stevens and Johnson described it as resembling scalding) on the face, eyes, and genitals, and may extend to skin on large areas of the body. The outer skin layers slough off when even slightly rubbed, a finding known as Nikolsy's sign. SJS is now defined as the subset of the least severe cases in which less than 10% of the body surface area (BSA) is affected. If more than 30% of BSA is affected, the same disorder is defined as Toxic Epidermal Necrolysis (TEN), with the remaining percentages called SJS/TEN overlap. The disorder develops over a mean of 8 days, beginning with a rash and ending with the maximum detachment of skin. Recent cohort studies suggest the mortality rate ranges from 12% for the least severe cases to 49% for TEN cases with large BSA effects.[25]

Drugs are the primary but not exclusive cause of SJS/TEN, with more than 100 drugs implicated in published studies. Incidence is very rare, measured in a few cases per million patient-years in populations without adjustment for exposure, but up to 0.04% of patients exposed to lamotrigine in clinical trials.[26] Some of the newer and potent oncology drugs (see below)–many targeting the immune system–may have much higher event rates.

Table 5. Strong signals for Stevens-Johnson syndrome/toxic epidermal necrolysis, 2017

Suspect drug	Cases
LAMOTRIGINE	128
SULFAMETHOXAZOLE; TRIMETHOPRIM	50
ALLOPURINOL	43
IBUPROFEN	39
ACETAMINOPHEN	39
CARBAMAZEPINE	34
NIVOLUMAB	23
PHENYTOIN	22
PEMBROLIZUMAB	20
VANCOMYCIN	18
LENALIDOMIDE	17
OMEPRAZOLE	16
ARIPIPRAZOLE	16
CIPROFLOXACIN	15
VALPROIC ACID	13
LEVETIRACETAM	13
DICLOFENAC	13
FLUCONAZOLE	12
COBIMETINIB	12
CLINDAMYCIN	10

Signals From 2017 FAERS Data

In the 2017 adverse drug event data we identified 20 drugs with the strongest signals meeting our criteria. The strong suspects are shown in Table 5. These and other reports highlight the high risk of lamotrigine. We noted also that cases were reported for some of the most widely used of all therapeutic drugs: ibuprofen, acetaminophen, and omeprazole. Our 2017 list also includes three recently approved oncology drugs with much smaller patient populations: nivolumab, pembrolizumab, and cobimetinib. While our strongest signals were linked to 20 drugs, the 2017 FAERS data identified 134 additional drugs with 2 to 9 reported cases. Notable among these possible suspects were 4 of the most widely used antibiotics, amoxicillin (n = 9), levofloxacin (n = 8), clarithromycin (n = 8), and azithromycin (n = 7).

Progressive Multifocal Leukoencephalopathy (PML)

Lurking harmlessly in the bodies of 50%-70% of the population is a small DNA virus called the John Cunningham virus (JCV).[27] [28] First infection usually occurs in childhood, producing no clinical symptoms. The virus remains latent throughout life, but detectable through assays that reveal the presence of antibodies, evidence that the immune system has detected and acted against it. However, some specific immunosuppressant drugs–mostly monoclonal antibodies–disable the body's viral defense to JCV in some patients. The latent virus is activated and spreads, notably to the brain. The consequences are a potentially fatal brain infection called progressive multifocal leukoencephalopathy or PML.

The symptoms and signs of PML are changes in behavior, confused thinking, problems speaking, impaired gait, and visual disturbances. They are the result of extensive viral lesions in the white matter of the brain. The primary damage is to the myelin-producing cells. The diagnosis is confirmed through repeated magnetic resonance imaging of the brain to identify the spreading lesions, and the presence of JCV. While there are no documented antiviral treatments, survival is improved through reactivating the immune system. In the 1980s PML was seen frequently in the most severely immunocompromised HIV patients, and a primary cause of 1%-5% of HIV deaths.[29] Published studies report incidence figures based on extremely limited samples of identified cases, but range from about 1 per 1,000 patients taking natalizumab for multiple sclerosis, to 1 per 32,000 for rituximab, an oncology drug.

The FAERS Reports

In 2017 we identified 419 reported cases of PML with a case fatality rate of 29%, the highest for any of the four severe adverse events in this study. A large fraction (34.2%) were extracted from the international medical literature and overall, 74% were foreign. The strongest signals were seen in these drugs:

- **Natalizumab (n = 154).** This monoclonal antibody treatment for multiple sclerosis (MS) and Crohn's disease became one of the best studied and best-known causes of PML. It was withdrawn in 2005 after 3 patients died of PML in clinical trials, and then reintroduced in 2006 with some of the most prominent and dire warnings among all drugs. It was also one of the early drugs with a restricted distribution program, which required enrollment of both patients and prescribers. Because of this and other patient support programs, it is likely that a greater proportion of cases occurring are reported to the FDA.

- **Rituximab (n = 59).** This monoclonal antibody treatment is approved for non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis. It has boxed warnings for PML, death after the first infusion, SJS/TEN, and reactivation of hepatitis B. In 2017 it had also 9 reported cases of SJS/TEN and 34 cases of agranulocytosis.

- **Fingolimod (n = 20).** This immunosuppressant treatment for MS is available with none of the highly prominent warnings or restrictions of natalizumab. It includes PML as 1 of 11 warnings about severe adverse effects, which also include other viral infections, heart block, skin cancer, macular edema, respiratory effects, and liver injury.

- **Mycophenolate (n = 10)**. This immunosuppressant drug is used to prevent rejection of organ transplants. It is associated with reactivation of several viral infections, including JCV, cytomegalovirus, and hepatis B and C.

Other Treatments for Multiple Sclerosis

We identified smaller numbers of reports for two other treatments for MS, dimethyl fumarate (n = 5), and alemtuzumab (n = 4). Alemtuzumab has a restricted distribution program similar to natalizumab, but because of its risk of potentially life-threatening infusion reactions and cancer. Overall, 35 more drugs were possible suspects, each accounting for 2 to 9 case reports in 2017.

Conclusions

The suspect drugs identified in this report include some of the most widely used therapeutic medications, including ibuprofen, omeprazole, and metformin. While more research is needed to identify when certain patients are vulnerable to these life-threatening adverse reactions, the incidence is likely measured in cases per million patients for most drugs. On the other hand, the risks for certain other drugs appear so disproportionate that alternative treatments should be considered. These drugs include natalizumab for multiple sclerosis, lamotrigine for epilepsy and bipolar disorder, and aripiprazole for psychosis and treatment-resistant depression. In the case of rhabdomyolysis, the definition of the disorder captures only a relatively small fraction of cases where therapeutic drugs damage and destroy skeletal muscle cells, but not so extensively as to overwhelm the kidneys. Drug harm to muscle cells is an underestimated risk of therapeutic drugs because of limited monitoring and sparse research.

The most important unanswered questions in these data are how many cases are in fact occurring but are not reported, and the extent to which family practice and emergency department physicians are trained to be aware of the presenting symptoms. Given such distinctive adverse events that usually involve hospitalization, estimating the extent of diagnosed cases could be addressed with the FDA's Sentinel System, with its access to millions of patient health records. Better management of these devastating adverse events requires much better information about the number of injuries that are occurring, why some patients are vulnerable, and the most likely suspect drugs.

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