ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES
QuarterWatch
Monitoring FDA MedWatch Reports

January 25, 2017 — New data from 2016 Q2

PERSPECTIVES FROM NEW ADVERSE EVENT REPORTS

Antidepressants, allergy drugs among 87 products with signals for insomnia
Liver failure and antiviral failure with hepatitis C direct-acting drugs
Harms of antipsychotic drugs reappraised

Executive Summary

In this issue we analyze two notably different adverse drug events. We identify drugs with signals for insomnia, one of the most common drug side effects that can both impair the quality of life and at times affect health. At the other extreme we examine the emerging risks of the new drugs for hepatitis C for triggering liver failure, a rare and catastrophic medical event that often ends in death or a liver transplant. We also summarize our recently published, peer-reviewed study of the harms of antipsychotic drugs.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP) that monitors all adverse drug event reports submitted to the U.S. Food and Drug Administration (FDA). 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. We also receive dispensed outpatient prescription data from QuintilesIMS, a health information company.

The FDA received 269,776 new reports about adverse drug events in the second quarter of 2016, a decline of 20.8% from the previous quarter, but an increase of 5.9% from the same period one year earlier. The reports identified 1,386 different primary suspect drugs, but only 675 drugs accounted for 25 or more reports, and only 385 drugs for 100 or more reports. Among the new reports 78,123 cases (29%) described domestic, drug-related injuries that were serious, disabling, or fatal.

The oral anticoagulant rivaroxaban (XARELTO) accounted for more reports than any other drug in several categories among regularly monitored drugs. It accounted for the most domestic reports of serious injury (n = 6,262), the largest number of U.S. patient deaths (n = 614), and the most cases in patients age 75 years and older (n = 669). The factors that account for the high rivaroxaban totals are summarized in this report, but include the fact that some of the serious injuries were reported on an annual rather than quarterly basis. This and other data reinforce the conclusion that oral anticoagulants are among the highest-risk outpatient drug treatments in medicine today.

87 Drugs with Signals for Insomnia

Having trouble falling asleep, staying asleep, or awaking too early is a problem that affects nearly half the adult population. However, depending on the severity, frequency, and any health consequences, the prevalence can be lower, with rates of persistent insomnia in the range of 10%-42%. Insomnia is also one of

the most frequently reported adverse drug events. In the most recent 12 months we identified 16,301 reported domestic cases. With a problem so widespread we expected that a great many drugs would have a few reported cases, and the link to the drug might be uncertain. In this report we outline the methods used to identify the most likely suspect drugs. The key criterion was that a drug had to have at least twice as many reports of insomnia as would be expected if they were occurring by chance. The results showed credible signals indicating a link to insomnia for 87 different drugs. In many instances, our suspects were confirmed by a plausible mechanism of action or had previous warnings. Some key findings:

- **Fluoroquinolone antibiotics**. We saw signals for the three most widely prescribed drugs in this class, ciprofloxacin (CIPRO), levofloxacin (LEVAQUIN), and moxifloxacin (AVELOX). No other antibiotics were implicated, and the result was consistent with the known neurological activity of the fluoroquinolones.

- **Antidepressants**. Most antidepressants, 13 in total, were associated with higher than expected reports of insomnia. While depression itself can result in insomnia, this effect is consistent with clinical trials data, mechanism of action, and existing warnings.

- **Stimulant effects**. It was not surprising to find many drugs with simulant effects implicated in insomnia. However, it notable that so many different kinds of drugs involved, many with large patient populations. The list included many allergy and cold medications containing pseudoephedrine, obesity drugs with phentermine as an ingredient, and all four of the widely used drugs for attention deficit hyperactivity disorder (ADHD). Even synthetic thyroid hormone, the No. 1 most prescribed drug in the most recent quarter, was implicated.

- **Antivirals.** We identified signals for 11 different antiviral drugs targeting a wide spectrum of viral disorders including influenza, hepatitis B and C, and human immunodeficiency virus (HIV). A link between these antivirals and insomnia has not been extensively studied, and we regarded the link as unexpected.

While we saw clear signals for the 87 drugs identified in this report, the degree of safety concern varied among drugs, their use, and patient populations. Concerns would be greater for the long-term use of ADHD drugs and antidepressants, compared to a few days' treatment with oseltamivir (TAMIFLU). In other cases, such as treating hepatitis C for 12 weeks, the insomnia might be regarded as a lesser side effect to be tolerated to achieve suppression or possible eradication of the virus. Finally, individuals who are experiencing insomnia might consider whether any of the drugs on this list might be causing or contributing to the problem.

New Safety Issues for Hepatitis C Antivirals

In October 2016 the FDA identified the first new major safety problem linked to the nine new direct-acting antiviral drugs for hepatitis C, including sofosbuvir (SOVALDI), ledipasvir-sofosbuvir (HARVONI), and simeprevir (OLYSIO). While the drugs appeared to suppress the hepatitis C virus to undetectable levels in most patients, treatment opened the door to reactivation of hepatitis B, with severe health consequences, including liver transplant and death. The FDA report described 24 cases of hepatitis B reactivation, including 3 cases of acute liver failure, a catastrophic drug adverse event involving damage to the liver so severe that continued survival is threatened. Searching beyond the FDA's cited cases to review the most recent 12 months' FAERS data, we identified 524 reported cases of liver failure associated with the drugs, and another 1,058 reports of severe liver injury. In a further 761 cases the adverse event was antiviral failure against the targeted virus. Our data show the need for further investigation into the negative consequences of these expensive and important new drugs.

The direct-acting antivirals for hepatitis C are notable new drugs in several respects. The chronic infection is widespread, affecting 2-3 million in the U.S. and millions more worldwide, but can persist for

decades without symptoms. It can also progress to cirrhosis of increasing severity and in some cases liver cancer. The direct-acting antivirals, the first approved in November 2013, represented a major advance: They often suppress the virus to undetectable levels more quickly than other antivirals (12 weeks instead of 26 weeks), are more effective, eliminating detectable virus in 89-100% of selected patients enrolled in clinical studies, and are better tolerated, cutting dropout rates nearly in half. They are also notable in their high cost: $55,000-$125,000 per patient, according to data from QuintilesIMS. Despite only an estimated 250,000 patients treated in 2015, the list-price spending for hepatitis treatments exceeded similar spending for cholesterol-lowering drugs, antibiotics, or blood pressure drugs, each with patient populations measured in tens of millions.

The 524 reported cases of liver failure included all the approved direct-acting antivirals as either primary or secondary suspect drugs, often in combination with each other or with ribavirin. Almost half the cases also included the hallmark symptom of liver failure, encephalopathy, which is a form of brain injury resulting in delirium, personality changes, suicidal behavior, sleep-wake reversal, and coma. Overall, 165 (31.5%) had died at the time of the report. While it was challenging to separate cases to which complications of hepatitis C might have contributed, 90% of the cases were submitted by healthcare professionals, who would be likely to understand the natural progression of the disease. The suspect drugs are shown in Table 1.

Table 1. Primary (PS), Secondary (SS) suspect drugs in liver cases

Drug name	Brand	PS	SS	Total	Percent*
Daclatasvir	Daklinza	74	25	99	18.9%
Elbasvir-Grazoprevir	Zepatier	1	0	1	0.2%
Ledipasvir-Sofosbuvir	Harvoni	116	5	121	23.1%
Paritaprevir combinations	Viekira Pak**	120	61	181	34.5%
Simeprevir	Olysio	16	21	37	7.1%
Sofosbuvir	Sovaldi	91	80	171	32.6%

*Percent of unique cases n = 524. **Includes Technivie, Viekira XR

The Harms of Antipsychotics Reappraised

Antipsychotic drugs often do not provide enough benefit to justify their toxic side effects, according to a new analysis of key scientific studies published in the medical journal *Drug Safety*. The authors are two members of the QuarterWatch project team, Thomas J. Moore, director; and Curt D. Furberg, senior medical advisor. This study differs from many regular QuarterWatch items in two ways: It originally appeared in a peer-reviewed scientific journal, and it was based on primary evidence from randomized clinical trials rather than on adverse drug event reports.

The study focused on the six most widely used antipsychotic drugs, accounting for nearly 54 million U.S. prescriptions in 2015. The drugs are used not only to treat psychosis (hearing voices, hallucinations, and paranoia) but also for treatment-resistant depression and some forms of bipolar disorder. They are also prescribed off-label for use in the elderly with dementia and to control problem behavior in children. The most widely prescribed antipsychotic drug in 2015 was quetiapine (SEROQUEL), followed by risperidone (RISPERDAL), and aripiprazole (ABILIFY). All are available as generic drugs, and a table with prescription volume appears in this report.

Treatment failure was the most common outcome of clinical trials of antipsychotic drugs in this analysis, even among patients selected as having the best chance of benefiting. Treatment failure occurred when the patients stopped the drug because of intolerable side effects, or because the physician or patient refused continued treatment for other reasons. Treatment failure occurred in a majority of patients treated for psychosis with quetiapine even though they were hospitalized for most of the six-week study. Overall patient improvement in that study was rated by treating physicians as “minimal” or less. Results were worse when antipsychotic drugs were used in hopes of preventing relapse. In a one-year clinical trial comparing haloperidol (HALDOL) to risperidone (RISPERDAL), relapse or treatment failure occurred in 93% of the

haloperidol patients and 69% of those treated with risperidone. In a study of the same two drugs in early schizophrenia patients treated for a year, 10% suffered irreversible damage to the motor system and more than 40% were taking medications for parkinsonism adverse effects.

The study was published online (http://link.springer.com/article/10.1007/s40264-016-0475-0) and is available on request from ISMP.

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

While direct-acting antivirals to treat hepatitis C should be ranked as a major medical advance, the large number of cases of liver failure and death as well as antiviral failure show the need for further investigation of the serious adverse effects of this expensive new class of drugs. The activation of hepatitis B cases highlighted by the FDA could not have been detected in clinical testing for approval because such patients were excluded. In addition, some safety data before approval for ledipasvir-sofosbuvir was uninterpretable because of lack of a control group of any kind, and a new reliance on historical data to characterize benefit. Beyond the most severe liver failure cases were hundreds of additional cases where liver function was impaired rather than improved by treatment. Policies to approve new treatments quickly exact a price in serious injuries and deaths that might have been avoided with a more complete safety profile and better understanding of the most vulnerable patients.

Our survey of drugs linked to insomnia leads to conclusions of two kinds. Clearly, these drugs are contributing to the high prevalence of insomnia. Of particular concern are those taken long-term (notably antidepressants) and those used to treat children (ADHD drugs). In addition, our findings illustrate the value of adverse event reporting to identify common and relatively mild side effects as well as those that are fortunately rare but also severe and life-threatening.

Finally, the findings on the oral anticoagulant rivaroxaban and the summary of our more extensive review of the harms of antipsychotics highlight two classes of drugs with some of the highest risks in all of outpatient medicine. When a course of long-term treatment with both antipsychotics and oral anticoagulants can lead to injury of 10% or more of patients in one year's time, these data alone should make reducing these risks a major priority in drug safety for 2017.

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Methods Summary

QuarterWatch monitors the safety of prescription drugs through analysis of adverse drug events reported to FDA by consumers and health 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. (http://www.ismp.org/QuarterWatch/detailedMethods.aspx)

The severity of the adverse event was classified as serious under FDA regulation[2] if the case report specified an outcome of death, disability, hospitalization, required intervention to prevent harm, was life threatening, or had other medically serious consequences. Cases without these outcomes were classified as not serious and all new cases were included in this analysis unless indicated otherwise. Earlier QuarterWatch issues have focused primarily on a subset of adverse events, those that are domestic and coded with serious outcomes. We continue to monitor domestic, serious reports as an important subset of the newly released case reports. Some of these domestic events are described as "regularly monitored drugs" because we exclude certain drugs with mandatory reporting requirements, or drugs such as estrogens or insulins, which we group together because of uncertain product identification.

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 combine several related but more specific medical terms. High Level Group Terms (HLGTs) combine several related HLTs, and System Organ Classes combine the terms into 27 categories. The QuarterWatch database was updated in November 2016 to MedDRA version 19.1.

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

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

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

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

Results

Report Trends

The total number of adverse drug event reports received into FDA Adverse Event Reporting System (FAERS) has been relatively stable since the beginning of 2015. At that time, changes in the FAERS electronic data system caused a large, sustained increase in non-serious reports that had been either not submitted or received elsewhere at the FDA but not entered into its FAERS monitoring system. Types of reports received are shown in Table 2.

In 2016 Q2 the FDA received 269,776 new case reports about drug-related injuries, a decline of 70,999 cases (20.8%) from the previous quarter, but an increase of 15,017 (5.9%) from the same quarter in 2015. The largest report total ever was 354,021 cases, recorded in 2015 Q3. We also monitor separately domestic cases with a fatal, disabling, or serious outcome. This total for 2016 Q2 was 78,123 such cases, a substantial decline from record of 94,665 new cases reported in 2015 Q1.

Table 2. Report totals for 2016 Q2

	Number	%
New case reports	269,776	
Report source		
Consumer	114,063	42.3%
Foreign	66,300	24.6%
Health professional	75,752	28.1%
Lawyer	2,165	0.8%
Not stated	11,492	4.3%
Outcome		
Death	20,739	7.7%
Disability	3,849	1.4%
Birth defect	598	0.2%
Life threatening	4,339	1.6%
Req intervention	278	0.1%
Hospitalization	44,229	16.4%
Medically Serious	72,510	26.9%
Not Serious	123,234	45.7%

Rivaroxaban (XARELTO) Cases

Measured in the subgroup of serious, domestic adverse event reports, rivaroxaban (XARELTO) was a notable drug in 2016 Q2. Among regularly monitored drugs, rivaroxaban accounted for the largest number of reported fatal, serious, and disabling injuries (n = 6,262); the most domestic patient deaths (n = 614); and the largest number of events in patients age 75 years and older (n = 669).

We identified these primary reasons why rivaroxaban accounted for so many serious injuries: Rivaroxaban is an oral anticoagulant, which because of risk of hemorrhage ranks among the highest-risk outpatient drug treatments by several measures.[6–8] In addition, QuarterWatch has previously reported special problems with rivaroxaban because its 5- to 9-hour half-life renders it poorly suited to once-a-day administration. [9] Finally, after a drug has been on the market for three years, the FDA allows drug manufacturers to report annually instead of quarterly, those serious injuries for which the manufacturer has already provided an appropriate warning in the prescribing information. Rivaroxaban's case totals indicate that some serious and many non-serious cases were reported on an annual rather than quarterly basis.

87 Drugs with Signals for Insomnia

We investigated the possible role of therapeutic drugs in causing insomnia through analysis of nearly 1 million adverse event reports submitted to the FDA in the 12 months ending June 30, 2016. Overall, we identified 87 drugs with clear signals of an association with three forms of insomnia, difficulty falling asleep, remaining asleep, or awakening too early. Other kinds of scientific information also supported the link between most of these suspect drugs and insomnia.

A Widespread Problem

By any measure the prevalence of insomnia is high, but how high depends heavily on the event definitions, which vary widely among epidemiological studies and other estimates. A medical textbook on

sleep disorders[10] illustrated the wide range: In a survey, 42% of the respondents reported difficulties staying asleep a few nights a week or more, and 26% said they had difficulty falling asleep. At the other extreme, a precisely defined and treated medical disorder using the International Classification of Diseases, Revision 10 (ICD-10) produced an estimate of around 4%. The Centers for Disease Control and Prevention (CDC) estimates that 10% of the population suffers from chronic sleep problems based on responses to sleep questions on four health surveys.[11] In addition, numerous factors contribute to sleep problems, including anxiety, depression, shift work, arthritis, chronic pain, narcolepsy, and breathing abnormalities.

Methods

To identify insomnia cases, we used the MedDRA standard HLT umbrella category of "Difficulties initiating and maintaining sleep." This excludes other kinds of sleep disorders such as abnormal dreams, sleep apnea, and shift work disorder. Potential candidate drugs were limited to 715 drugs that reported at least 50 cases of any kind of adverse event during the 12-month period. We also excluded foreign cases (because non-serious events are not reported). For the one-year period we identified 935,187 eligible case reports of all types, including 16,301 cases indicating insomnia. Finally, a signal was defined as a drug with least twice as many insomnia reports as expected (proportional reporting ratio (PRR ≥ 2), and a strong enough association to rule out a chance effect. We excluded results for anxiety/sedative/hypnotics and narcolepsy drugs, because an insomnia complaint could have indicated treatment failure rather than a likely adverse effect. Additional statistical detail is provided in the Methods Summary.

Results

Our analysis focused on 6,942 reported cases of insomnia directly associated with the 87 different therapeutic drugs with signals. The patient population was similar to those reporting other kinds of drug adverse events: 64% were female and the median age was 54 years (with 25% age 44 years or younger, and 25% age 62 years or older). However, as might be expected for a sleep problem, consumers rather than health professionals were the original source of 85% of the reports (instead of approximately half of the reports for other kinds of events). Overall, 94.5% of the cases were identified with the Preferred Term of "insomnia" without additional specification. The suspect drugs included many that were not surprising and a few that were.

The Suspect Drugs

Our criteria identified 87 drugs with signals for an adverse event of insomnia, and we show the data in Table 3. It was notable that the signals often were seen for whole classes of drugs, indicating a common mechanism of action. Some key examples:

Not surprisingly, many drugs with stimulant effects were linked to insomnia. Notable were the main drugs for ADHD, even those with different stimulant effects. The allergy and cold medications with pseudoephedrine had signals, along with obesity drugs with phentermine, another stimulant.

The dopamine neurotransmitter plays a key role in the complex process of sleeping. Drugs with an effect on dopamine signaling were linked to insomnia, notably the smoking cessation drug varenicline (CHANTIX) and the restless legs syndrome treatment ropinirole (REQUIP). In addition, Table 3 lists four antipsychotic drugs that also block normal dopamine signaling. Also implicated was metoclopramide (REGLAN), a drug for nausea that also works by blocking normal dopamine signaling.

Side effect profiles of many antidepressant drugs reveal they are notable for causing nervousness and insomnia in some patients, but somnolence and impaired concentration in others.[12,13] Given that sleep disturbances are also a symptom of depression, these adverse effects may contribute to the limited effectiveness of these drugs in depression.[14]

Table 3. Insomnia signals for year ending June, 2016				
Drug name/Medical use	Brand name**	Insomnia	All reports	PRR*
Attention deficit/hyperactivity disorder (ADHD)				
Atomoxetine	Strattera	201	3969	2.9
Lisdexamfetamine	Vyvanse	61	1353	2.6
Guanfacine	Intuniv	11	250	2.5
Amphetamines	Adderall	39	1056	2.1
Allergy, OTC				
Loratadine; Pseudoephedrine	Claritin D	44	213	11.9
Fexofenadine; Pseudoephedrine	Allegra-D	74	469	9.1
Doxylamine	Unisom	9	78	6.6
Fexofenadine	Allegra	108	2896	2.2
Antibiotics, fluoroquinolone				
Ciprofloxacin	Cipro	77	1252	3.5
Levofloxacin	Levaquin	102	1811	3.3
Moxifloxacin	Avelox	11	279	2.3
Antidepressants				
Trazodone	Desyrel	33	307	6.2
Vilazodone	Viibryd	28	264	6.1
Mirtazapine	Remeron	17	195	5.0
Fluoxetine	Prozac	108	1480	4.2
Duloxetine	Cymbalta	1081	15547	4.2
Amitriptyline	Elavil	8	133	3.5
Venlafaxine	Effexor	82	1411	3.4
Paroxetine	Paxil	38	686	3.2
Bupropion	Wellbutrin	73	1388	3.0
Desvenlafaxine	Pristiq	37	728	2.9
Escitalopram	Lexapro	15	296	2.9
Sertraline	Zoloft	58	1280	2.6
Vortioxetine	Brintellix	52	1166	2.6
Cold/cough OTC				
Ibuprofen; Pseudoephedrine	Multiple OTC	8	93	4.9
Pseudoephedrine	Sudafed	50	632	4.6
Dextromethorphan; Guaifenesin	Multiple OTC	26	554	2.7
Guaifenesin	Multiple OTC	69	1725	2.3
Dopamine related				
Selegiline	Zelapar	14	84	9.6
Pramipexole	Mirapex	11	170	3.7
Ropinirole	Requip	10	170	3.4
Varenicline	Chantix	90	1692	3.1
Rotigotine	Neupro	12	313	2.2
Hormones				
Thyroid	Thyroid	6	68	5.1
Corticotropin	Acthar	114	1735	3.8
Norditropin	Norditropin	6	117	2.9
Levothyroxine	Synthroid	73	2031	2.1
Obesity				
Phentermine; Topiramate	Qsymia	10	172	3.3
Phentermine	Adipex-P	5	96	3.0
* PRR = Proportional Reporting Ratio. ** Many drugs have multiple brand names not shown here.				

Table continues next page

Table 3. Insomnia signals for year ending June, 2016, continued				
Drug name/Medical use	Brand name**	Insomnia	All reports	PRR*
Antipsychotic				
Quetiapine	Seroquel	70	944	4.3
Ziprasidone	Geodon	12	266	2.6
Lurasidone	Latuda	14	329	2.4
Brexpiprazole	Rexulti	36	989	2.1
Antiviral				
Paritaprevir Combination	Viekira Pak	615	6032	6.0
Sofosbuvir	Sovaldi	104	1239	4.8
Abacavir; Dolutegravir; Lamivudine	Triumeq	32	400	4.6
Interferon Alfa	Pegasys	1267	17022	4.6
Ribavirin	Copegus	107	1476	4.2
Efavirenz; Emtricitabine; Tenofovir	Atripla	16	232	4.0
Emtricitabine; Tenofovir	Truvada	18	265	3.9
Dolutegravir	Tivicay	10	149	3.9
Daclatasvir	Daklinza	28	499	3.2
Ledipasvir; Sofosbuvir	Harvoni	196	3880	2.9
Oseltamivir	Tamiflu	39	890	2.5
Cancer treatment				
Anastrozole	Arimidex	14	312	2.6
Alemtuzumab	Campath	18	454	2.3
Cholesterol lowering				
Pitavastatin	Livalo	6	115	3.0
Pravastatin	Pravachol	11	257	2.5
Hypertension				
Propranolol	Inderal	17	280	3.5
Clonidine	Catapres	17	398	2.5
Opioid related				
Naltrexone	Revia	98	1406	4.0
Buprenorphine; Naloxone	Suboxone	85	1730	2.8
Acetaminophen; Codeine	Multiple	7	149	2.7
Tapentadol	Nucynta	21	485	2.5
Acetaminophen; Oxycodone	Percocet	14	390	2.1
Other medical uses				
Roflumilast	Daliresp	15	129	6.7
Montelukast	Singulair	30	329	5.2
Finasteride	Propecia	20	243	4.7
Silodosin	Rapaflo	8	114	4.0
Milnacipran	Savella	5	72	4.0
Metoclopramide	Reglan	7	111	3.6
Pregabalin	Lyrica	462	7532	3.6
Donepezil	Aricept	5	86	3.3
Tetrabenazine	Xenazine	71	1347	3.0
Tizanidine	Zanaflex	7	134	3.0
Dalfampridine	Ampyra	488	10301	2.8

* PRR = Proportional Reporting Ratio. ** Many drugs have multiple brand names not shown here.

Other Findings

Only one of the many classes of antibiotics were implicated–fluoroquinolones such as ciprofloxacin (CIPRO), levofloxacin (LEVAQUIN), and moxifloxacin (AVELOX). These antibiotics are also implicated in other neurological adverse effects. [12] It was interesting to identify 11 different antiviral drug products. Included were oseltamivir (TAMIFLU) and four of the new hepatitis C direct-acting antivirals that are examined separately in this report.

Largest Patient Populations

Dispensed outpatient prescription data show that drugs with insomnia signals rank high among the most widely used agents. Synthetic thyroid hormone (or levothyroxine) has a stimulant effect and an insomnia signal and was ranked as the single most widely dispensed outpatient drug in 2016 Q2, with 30.6 million prescriptions, according to data from QuintilesIMS. A signal was also seen for montelukast (SINGULAR), ranked No. 22 with 10.1 million prescriptions. Using federal health survey data, we recently reported that 12% of the adult population was taking antidepressant medications.[15] Comparable data for OTC cold and allergy medications were not available, but these medications also account for large patient populations.

Limitations

Our insomnia analysis has limitations, including those associated with all adverse event data. In addition, while we selected reports with event terms indicating insomnia, many of those reports included symptoms of other adverse effects as well. A typical adverse event report in the most recent 12 months of data contained 2-3 different event terms. Problems such as depression and anxiety also cause insomnia, and it is possible the drug was incorrectly made the suspect. While we examined almost 1 million reports, our data were extracted from a single 12-month period. Although all the listed drugs met our criteria, the relationship was borderline for a few drugs. We identified only two cholesterol lowering drugs, pravastatin (PRAVACHOL) and pitavastatin (LIVALO), with only 17 reported cases of insomnia. Further research is needed to explore possible insomnia in these agents, or in this entire class of widely prescribed drugs. We suspect the relationship between the opioids and insomnia is complex and could involve both underlying pain and nighttime withdrawal symptoms. Finally, we do not have information to assess the duration of the insomnia.

Conclusions

Insomnia is a problem with many causes. The drugs associated with insomnia are many, and widely used. Those struggling with insomnia may want to consider whether drugs we have identified could be contributing the problem. Many of the listed drugs, notably antibiotics, flu medications, and cold remedies, are used short term and their likely impact is transient and not serious. Others might provide benefits substantial enough to warrant tolerating the negative impact on sleep. We have greater concerns about the long-term effects on sleep of antidepressants and ADHD drugs. In addition, for classes of drugs where only a few are implicated, numerous alternatives are available.

New Safety Issues for Hepatitis C Antivirals

While the FDA has generously designated 46 different drugs in development as *breakthroughs* in the last year alone, [16] the newer direct-acting antiviral drugs for hepatitis C were a major advance that fully earned the term. Sofosbuvir (SOVALDI) and simeprevir (OLYSIO) were the first of the new agents, approved in late 2013. At present there are nine direct-acting antiviral products used in various combinations against the different genotypes of hepatitis C. Although these drugs are unmistakably an advance, we examine two safety issues that have emerged through postmarket surveillance. The most serious is liver failure, a catastrophic drug adverse event that often leads to death absent a liver transplant. And although these drugs have claims of eradicating the hepatitis C virus below the limits of detection in an estimated 9 of 10 treated,

we identified hundreds of cases where health professionals and patients reported antiviral failure of this expensive drug treatment. In addition, these emerging safety issues enrich a broader case study of what happens when modern drug development programs produce genuine breakthroughs.

An Unusual Disease

The human liver is vulnerable to viral infection, and at least five different families of virus have been identified and are designated hepatitis A through E.[17] Hepatitis infections can trigger acute attacks with nausea, fever, darkened urine, abdominal pain, and jaundice. Most such cases resolve spontaneously. Hepatitis C, however, rarely causes these acute, clinically detectable symptoms, but can become chronic. In a large majority of cases, hepatitis C is asymptomatic. Absent a virologic assay, many patients are unaware they even have the disease.[18] Over a period of 20 to 25 years, however, 5% to 20% will develop cirrhosis, which may steadily increase in severity. Among that fraction of hepatitis C patients who develop cirrhosis, 1% to 3% a year develop liver cancer. An estimated 2-3 million persons in the U.S. are currently infected. An RNA virus, hepatitis C is transmitted through blood and is often seen as a co-infection with HIV and among intravenous drug users.

Until the newest agents were approved, hepatitis C was usually treated with a cocktail of antivirals, including ribavirin and various forms of interferon alfa, for 24 to 48 weeks.[19] The treatments caused extensive adverse effects, including hemolytic anemia, vomiting, diarrhea, insomnia, psychosis, depression, and suicide. Even when the therapy accurately targeted the correct hepatitis C genotype, it eliminated detectable virus in only 50-75% of the patients. One result was that most hepatitis C patients were not treated or discontinued treatment.

A Costly Treatment Revolution

The development and FDA approval of advanced direct-acting antivirals transformed the treatment of the disease. The regimens took only 12 weeks in most cases, and achieved suppression of detectable virus in 89-100% of selected patients in controlled clinical trials.[20] Notably, the combinations that did not require ribavirin were better tolerated, cutting discontinuations by one-half or more.

While this apparent capability to tame a significant infectious disease was a major advance, dismay and consternation greeted the news of what these new treatments would cost. Early news reports noted that sofosbuvir was going to cost $1,000 a pill. QuintilesIMS estimated that in 2015 treating 250,000 patients cost an estimated $19 billion at list prices, or about $125,000 a patient. [21] With more agents on the market and information from confidential price negotiations with government and private payers, a follow-up study suggested per-patient treatment drug cost could often be reduced to approximately $50,000.[22] At published list prices, just one antiviral–ledipasvir-sofosbuvir–accounted for $14 billion in estimated spending in 2015, more than any other prescription drug for any medical purpose.[21] To put the numbers in perspective, the National Institutes of Health spent $4.9 billion on all cancer research in fiscal 2015, and $4.4 billion to study all infectious diseases.[23]

A Safety Problem Emerges

In October 2016 the FDA issued a new warning about a potentially catastrophic side effect that had not been clearly identified in pre-approval drug testing.[24] A Drug Safety Communication warned that in 24 known cases, attempting to suppress the hepatitis C infection with direct-acting antivirals had permitted reactivation of hepatitis B. In this group, three patients experienced liver failure, with two dying and one receiving a liver transplant. Five of the FDA cases were extracted from the published medical literature.

Search for Liver Failure Cases

Following up on this FDA report, we searched the most recent 12 months of FAERS data for acute liver failure cases associated with these new drugs. Acute liver failure is a rare, dramatic, and catastrophic medical emergency that involves sudden damage to so much liver tissue that continued survival is at risk.[25] While most organs are ultimately affected, one critical symptom is encephalopathy–a brain dysfunction that can involve psychiatric disturbances, motor problems, hyperventilation, and even coma. Acute liver failure is rare–a textbook estimate[25] is around 3,000 cases in the U.S. a year–with approximately half the cases attributed to the liver toxicity of acetaminophen, the most widely used over-the-counter pain medication.

Table 4. Terms identifying liver failure

Preferred Term (PT)	Mentions*
Hepatic failure	275
Hepatic encephalopathy	214
Liver transplant	55
Acute hepatic failure	27
Hepatorenal failure	6
Acute on chronic liver failure	4
Coma hepatic	2
Subacute hepatic failure	1

* A report could contain multiple terms

For the 12 months ending June 30, 2016, we identified 524 reported cases worldwide of liver failure in which one of the nine direct acting antivirals was a primary or secondary suspect drug. The case definition, and number of mentions, is shown in Table 4.

The 524 liver failure cases occurred more frequently in males (55%) and in patients with a median age of 61 years. In these reports, 165 cases (31.5%) had an outcome of death at the time the report was submitted. Overall, 90% of the reports were originated by health professionals, including 34 cases extracted from the medical literature with duplicate references excluded. Table 4 shows 55 cases involved liver transplants, but it was not clear whether the transplants were a treatment for liver failure, or whether the event might have occurred in a post-transplant population. These cases reflect the global reported adverse event experience, with 386 (73.7%) from outside the U.S. The primary or secondary suspect drugs are shown in Table 1, reproduced from the Executive Summary.*

Table 1. Primary (PS), Secondary (SS) suspect drugs in liver cases

Drug name	Brand	PS	SS	Total	Percent*
Daclatasvir	Daklinza	74	25	99	18.9%
Elbasvir-Grazoprevir	Zepatier	1	0	1	0.2%
Ledipasvir-Sofosbuvir	Harvoni	116	5	121	23.1%
Paritaprevir combinations	Viekira Pak**	120	61	181	34.5%
Simeprevir	Olysio	16	21	37	7.1%
Sofosbuvir	Sovaldi	91	80	171	32.6%

*Percent of unique cases n = 524. **Includes Technivie, Viekira XR

Limitations

This analysis has several limitations that extend beyond the normal qualifications that apply to adverse drug event data. Notably, these data do not include a medical history of the hepatitis C patients, which could range from asymptomatic patients to those with growing impairment from the fibrotic liver tissue that is the hallmark of the clinical complications of cirrhosis. While the terms that defined our liver failure cases were selected to highlight the acute, catastrophic event, it is possible it might have captured some cases of decompensated cirrhosis reflecting a progression of the underlying disease. On the other hand, 90% of cases were reported by healthcare professionals as a drug-related adverse event and not the natural

* Because of combination therapy, one case could identify 2 or 3 suspect drugs. Paritaprevir combinations identify three similar approved combination drug products, Viekira Pak, Viekira XR, and Technivie.

progression of hepatitis C. Since reporting is voluntary for consumers and health professionals, these totals are unlikely to have captured all the cases that occurred, and therefore provide little indication about how often these events are occurring. Finally, because of the limited number of cases and extensive use of combinations we could not study differences between the various drugs, and notably had just a single case for the newest agent, elbasvir-grazoprevir. Also, there was no data available for the newest agent, sofosbuvir-velpatasvir (EPCLUSA), approved at the end of 2016 Q2.

Antiviral Failure

Although clinical trials of the direct-acting antivirals reported suppressing detectable levels of the virus in a high percentage of cases, we identified 761 reports stating that the drugs failed to work. The Preferred Term to identify such cases was "Drug Ineffective." The patient population was similar to the acute liver failure cases above. From the information available it was not possible to separate cases that represented a relapse from those reporting no initial antiviral effect. This form of treatment failure is consequential, given that the patient is exposed to the risks and expense of treatment, and the drugs are sometimes used in patients starting to suffer clinical complications of hepatitis C with limited options available. In addition, 17 cases also involved liver failure and were included in the analysis above. Our data for insomnia reported above also showed that the direct-acting antivirals accounted for some of the stronger signals among all drugs.

Manufacturer Views

We provided a preliminary data summary to the direct-acting antiviral drug manufacturers and requested input on the data. Gilead Sciences, manufacturer of sofosbuvir and ledipasvir-sofosbuvir, noted its products were approved for patients who were already experiencing liver failure, and this could account for some of the reported cases. Gilead said it had "seen no evidence of a causal relationship between sofosbuvir-based regiments and liver failure." Finally, it noted some cases of virologic failure were not unexpected since the drug was not 100% effective, and that most such cases likely described relapses. Janssen, the manufacturer of simeprevir, told us it believed its drug's adverse event profile was consistent with those seen in clinical trials and reflected in the prescribing information.

Need for Further Investigation

These new data raise more questions than they resolve about the adverse effects of direct-acting antiviral drugs. The FDA's analysis focused on a subset of 24 well-documented cases, including three liver failure cases, where the apparent causal mechanism was reactivation of hepatitis B. This risk potentially can be managed by pre-treatment virologic testing for hepatitis B, as the FDA now recommends. A better understanding of what is occurring in hundreds of additional liver failure cases should be a priority for further investigation. In at least one literature report, liver failure occurred in the absence of hepatitis B,[26] and in other cases this issue was not addressed. In addition to the 524 cases meeting our definition of liver failure, we identified 1,058 additional cases indicating severe liver damage that had apparently not progressed to liver failure.* Still more cases might be identified by early elevated liver enzymes that might signal a direct toxic effect of the antiviral drug treatment. While the FDA analysis has precisely described a small group of cases with a clear apparent cause, these data show it is unlikely that this explains all the cases where treatment results in liver damage rather than benefit. In addition, the antiviral failure cases would benefit from further investigation into likely causes.

* This category was defined as the SMQ "Drug related hepatic disorders- severe events only," but excluded the liver failure cases.

Long-Term Uncertainties

The FDA and pharmaceutical companies were also overoptimistic in labeling as a "cure" the results of a laboratory assay at 12 weeks indicating undetectable levels of the hepatitis C virus genotype. This result is also and more accurately called a sustained virologic response (SVR). To speed approval of the direct-acting antivirals, the FDA reduced the duration of clinical testing from 26 weeks to 12 weeks for some genotypes. And whether traces of the virus might remain to be reactivated a few years later remains poorly studied. Another credible drawback is emerging from earlier studies of antiviral agents in liver transplant patients where recurrent hepatitis is regarded as a major threat and patients are routinely monitored. In one small follow-up study, 35% of transplant patients successfully treated with first-generation agents nevertheless progressed to decompensated cirrhosis.[27] An additional patient treated with the new direct-acting agents followed the same downward path, with deteriorating liver function despite apparent elimination of the virus.[28] If eliminating the virus does not prevent the steady deterioration of liver function, then the value of this treatment is greatly reduced. Hepatitis C is a disease that evolves over decades, with some cases resolving spontaneously, many remaining asymptomatic, and others progressing to cirrhosis, other serious complications, and liver cancer. While direct-acting antivirals should be classed as a major advance, important questions remain unanswered about their long-term effects and appropriate patient population.

The Harms of Antipsychotics Reappraised

Antipsychotic drugs rank among the most toxic known outpatient drugs. With long-term use, they cause injuries, many irreversible, to 40-65% of patients treated. Partly because of these levels of toxicity, treatment failure was the most common outcome of clinical trials conducted in five different medical settings. These are among the conclusions in a newly published comprehensive review in the peer-reviewed scientific journal *Drug Safety*.[29] It was written by two members of the QuarterWatch project team, Thomas J. Moore, project director; and Curt D. Furberg, senior medical advisor. Key findings are summarized here.

The antipsychotic drug class includes 57 different molecular entities, with the first, chlorpromazine (THORAZINE), approved in 1957 and the most recent, brexpiprazole (REXULTI) in 2015. Originally, antipsychotics were among the earliest drugs discovered that appeared to calm many patients with delusions, hallucinations, paranoia, and other forms of psychosis. Most of these agents are also approved for preventing relapse in schizophrenia, and several for treatment-resistant depression or some forms of bipolar disorder. The drugs are extensively used off-label in demented elderly individuals and for behavior control in children. The six most widely used antipsychotics, shown in Table 5, accounted for nearly 54 million prescriptions in 2015, according to dispensed outpatient prescription data from QuintilesIMS.

Table 5. Leading antipsychotic dispensed outpatient prescriptions in the U.S., 2015

Drug name	Brand name	Prescriptions	Year approved
Quetiapine	Seroquel	19,788,379	1997
Risperidone	Risperdal	11,924,021	1993
Aripiprazole	Abilify	9,659,745	2002
Olanzapine	Zyprexa	6,605,620	1996
Haloperidol	Haldol	3,331,036	1967
Ziprasidone	Geodon	2,525,986	2001

Prescription data from QuintilesIMS National Therapeutic Audit

Most of the known harms caused by antipsychotic drugs result from the same mechanism of action that is believed to account for their benefits. While the various drugs have different chemical structures, all of them block normal signaling of dopamine at the D_2 family of neuroreceptors. Modern antipsychotics are engineered to occupy 70% or more of D_2 receptors. The problem is that these receptors are widely distributed throughout the brain and central nervous system and mediate a long list of important body

functions, including mood, sleep, memory, impulse control, decision-making, muscle movement, appetite, blood pressure, and sexual development.

The most visible harm of antipsychotic drugs is impairment of motor control. The most disfiguring variety is called tardive dyskinesia and can involve uncontrollable twitching of fingers, tongue, eyes, and entire limbs. With sustained use, this harm becomes irreversible and untreatable. In a second form of impaired motor control, muscles become rigid or frozen, similar to symptoms of Parkinson's disease, a disorder in which dopamine-transmitting cells are destroyed. When drug-induced, this disorder is called parkinsonism. In a study of newly diagnosed schizophrenia patients treated for approximately one year, 8-13% developed tardive dyskinesia, and more than 40% required medication for parkinsonism. In a broader assessment of harms, a National Institutes of Health (NIH) study of five antipsychotics reported that 66.7% showed moderate to severe harms over approximately 18 months of treatment. The drugs may also cause cognitive impairment, sexual dysfunction, and diabetes.

Even in treating psychosis, the most severe manifestation of schizophrenia, the net benefits of antipsychotic drugs were rated minimal by study investigators, although individual results varied. The most common outcome in clinical trials was treatment failure, defined as discontinuation of the drug for any reason during a study. In six-week trials of quetiapine for acute psychosis, more than 50% experienced treatment failure. In the longer NIH study, treatment failure occurred in 72% of patients. In a one-year relapse prevention study, treatment failure or relapse occurred with haloperidol in 92.6% of patients, and in 69.4% of patients treated with risperidone.

The complete published study examines the scientific evidence in depth, reviews measurement scales used, assesses different outcomes, and investigates the use in different settings that range from treating an early episode of psychosis to use in demented elderly patients. The study concludes, "It is time for regulators and the medical community to conduct an independent scientific and clinical reassessment of the appropriate use of antipsychotic drugs." [29]

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QuarterWatch is published by the Institute for Safe Medication Practices as a public service. It has no regular income, foundation grant, or other dedicated financial support and is provided to the public and health professions without charge. We seek outside peer reviewers for each issue but their identities are not disclosed. QuarterWatch's essential costs are funded from the general budget of ISMP, a non-profit organization dedicated solely to promoting the safe use of medication. ISMP, in turn, is supported by charitable donations, volunteer efforts, foundation grants, and subscription income from its four other medication safety newsletters, for pharmacists in the acute care and ambulatory care settings, for nurses, and for consumers.

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