ISMP QuarterWatch
Monitoring FDA MedWatch Reports

January 13, 2016 — Data from 2015 Quarters 1-2

NEW SAFETY PERSPECTIVES

Signals for new sleep medication suvorexant (BELSOMRA)
Opioids: Hydrocodone exposure declines while higher potency drugs increase
Update on new diabetes drugs blocking kidney glucose reabsorption

Executive Summary

In this issue we examine safety questions about drugs used in three of the largest patient populations in medicine: A new drug for chronic insomnia, a problem affecting 10-30% of all adults; changes in the use of opioid medications for moderate to severe pain, a near universal issue in most lives at some point; and a new family of drugs for Type 2 diabetes, a disorder for which 21% of those age 65 years or older are currently being treated.

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. 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.

This report is based on combined data from the first and second quarters of 2015, but report trends focus on the second quarter. In the second quarter of 2015 the FDA received 235,540 new reports of injury associated with the therapeutic use of 1381 identifiable primary suspect drugs. The total included 71,825 (30.5%) reports indicating a serious injury in the United States, 57,328 (24.3%) reports of serious injury in foreign countries, and 103,136 (43.8%) domestic cases indicating an injury, but no serious outcome. The second quarter total represented a 16.2% decline from the previous quarter of new information, but an 8.1% increase from the same quarter one year previously. This issue of QuarterWatch features a broader scope of review to include more data and to adapt to changing reporting patterns. Previous issues focused primarily on the subset of domestic cases with a serious outcome.

New Sleep Medication, New Issues

Suvorexant (BELSOMRA) is a novel sleep medication for chronic insomnia and was first marketed in 2015. It blocks the effects of two recently discovered neurotransmitters–called orexins–that send wakefulness signals but are only part of the complex sleep-awake process. The first substantial group of adverse drug event reports provided these key findings:

- Complaints that the drug was ineffective was the predominant problem reported, mentioned in 429 (42.2%) of the total of 1016 reports. This result was understandable given that the FDA, fearing next-day impairment, had required a low 10 mg starting dose that produced minimal benefit in clinical testing.

- Another large group of reports described disturbed sleep, including nightmares, hallucinations, sleep paralysis, and sleep walking.

- A third group of patients reported paradoxical reactions: instead of becoming sleepy, they reported agitation, anxiety, tremors, and palpitations.

Because suvorexant is the first drug exploiting new and complex neurotransmitters and intended for a large patient population, we were also concerned about the limited clinical testing of suvorexant prior to FDA approval. Just 62 patients had taken the drug at the 10 mg dose; only 160 patients were exposed for one year or longer at any dose; and 493 took the maximum recommended 20 mg dose in pivotal trials. In addition, the trials focused on a highly selective patient population and excluded anyone taking virtually any other psychoactive drug, including antidepressants, benzodiazepines, antipsychotics, and ADHD drugs.

Our full analysis of suvorexant examines the tolerability, benefits, and risks of next-day impairment. It also evaluates the problems that may be associated with the drug's 12-hour half-life. The manufacturer, Merck, told us that it believes the first group of adverse event reports did not identify any new safety issues not already reported in the prescribing information for physicians.

Changes in Opioid Use

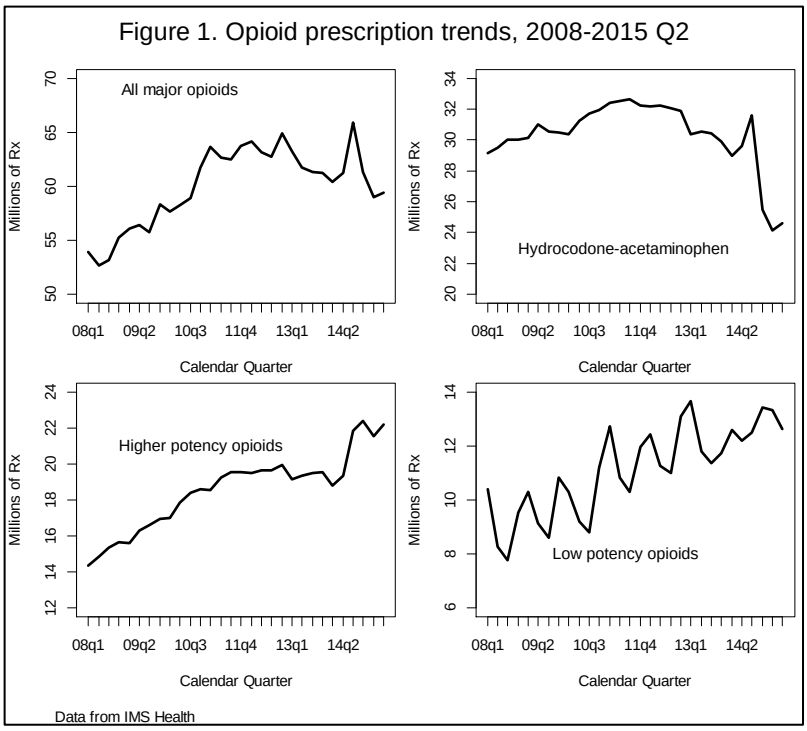
Opioid therapeutic drugs range from fentanyl patches that are 80 times more potent than morphine to codeine products that are the equivalent to one-tenth of a standard 10 mg morphine dose. In 2015 Q2 more than 59.4 million outpatient prescriptions were dispensed for the 13 leading opioid drugs, according to data from IMS Health Inc. We noted several trends in the utilization of these drugs:

- Because of new prescribing and dispensing restrictions, the hydrocodone-acetaminophen combination has fallen from first to third place as the most widely prescribed therapeutic drug in the United States. From a peak of 32.6 million prescriptions in the third quarter of 2011, the hydrocodone combination products had declined by 8 million prescriptions (24.5%) by mid-2015, according to dispensed outpatient prescription data from IMS Health. The decline in utilization is so substantial that it reduced overall usage across the entire opioid drug class. (See Figure 1.) The largest drop in hydrocodone-acetaminophen followed increased restrictions imposed by the Drug Enforcement Administration (DEA).

- Oxycodone prescriptions, on the other hand, have continued a steady increase despite new abuse-resistant formulations, risk management programs, physician education, and other steps to control diversion and abuse. Quarterly dispensed prescriptions increased by 12% since 2011, reaching a total of 15.5 million prescriptions by July 1, 2015.

- The most rapidly growing group of opioids are long-acting, higher potency drugs used for treatment of dependence, and intended to block withdrawal effects without producing euphoric mood changes.

Figure 1. Opioid prescription trends, 2008-2015 Q2



Products with buprenorphine increased 77.4% since early 2011 to reach 3 million prescriptions in the second quarter of 2015.

- Low-potency opioid use–primarily cough medications–also grew moderately. The saw-tooth pattern in Figure 1 indicates seasonal use during the winter quarters.

The Centers for Disease Control and Prevention (CDC) reported 18,893 overdose deaths in 2014 from licit and illicit use of opioids, a 14% increase from the previous year, emphasizing again the public health risks of these drugs.

Update on New Diabetes Drugs

Both prescription volume and adverse drug event reports are increasing rapidly for a new class of drugs for Type 2 diabetes that lower blood sugar by causing the kidneys to excrete some circulating glucose rather than returning it to circulation. They block the protein sodium glucose cotransporter 2 (SGLT2). Three of these SGLT2 drugs are approved: canagliflozin (INVOKANA), approved in 2013, and dapagliflozin (FARXIGA) and empagliflozin (JARDIANCE) which were both approved in 2014.

Despite the lack of long-term data on safety and benefits, these new drugs have moved rapidly into widespread clinical use, according to data from IMS Health. Canagliflozin, first to win U.S. approval, reached 1.1 million dispensed outpatient prescriptions in 2015 Q2, followed by dapagliflozin with 411,000, and empagliflozin with 136,000. Adverse drug event reports over the last 12 months increased roughly in line with patient exposure, with 5484 new cases for canagliflozin, 1805 for dapagliflozin, and 455 for empagliflozin.

We observed increasing numbers of reports of metabolic acidosis–a potentially life-threatening disorder that has been the focus of two FDA Drug Safety Communications. Over the past 12 months we identified 168 possible cases for canagliflozin, 80 for dapagliflozin, and 12 for empagliflozin.

The most frequently reported side effects of all three SGLT2 agents are genital fungal infections. In clinical trials of canagliflozin these infections were seen in 11.4% of females and 3.7% of males. The presence of glucose in the urine and bladder creates a favorable environment for infections, and the FDA also warned of bacterial infections that spread to the kidneys with potentially life-threatening consequences.

Adverse Event Reporting System

Adverse drug events that are not considered *serious* are subject to less rigorous requirements for manufacturers, and have a lower priority for reporting and assessment. In the most recent 12 months of data we identified hundreds of cases of medically significant events that manufacturers had not coded as serious. These cases included events such as hallucinations, sleep walking, and sleep paralysis for a sedative/hypnotic medication; irreversible damage to the motor system for an antipsychotic drug; and depression and anger for a smoking cessation aid with a Boxed Warning about serious neuropsychiatric side effects. These drug manufacturers' reports were also of low quality, with 70% or more lacking the basic information elements of age, gender, and event date.

In the main report that follows we examine the problem and propose solutions. In addition, discovering so many medically significant adverse events that manufacturers did not code as serious led us to change the focus of QuarterWatch to include all reported events rather than limiting our assessment to those cases coded as serious.

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

Suvorexant provides a notable example of four problems surrounding the development, testing, approval, and postmarket surveillance of new psychoactive drugs. (1) It is the first drug to affect a new kind of neurotransmitter that interacts with many others; (2) premarket pivotal trials enrolled small numbers of carefully selected patients; (3) although approved for long-term use, suvorexant was evaluated in small numbers of patients in short duration trials of a few months; and (4) postmarket surveillance was characterized by incomplete manufacturer reports, with a large majority lacking basic data such as age, gender, and event date. Although these limitations are not unique to suvorexant, it means that tens of thousands of patients will be exposed to drugs about which both scientific knowledge and ongoing safety surveillance are limited. Specific safety concerns about suvorexant include whether the warnings against taking the drug with alcohol (CNS effects are additive) and not to drive or engage in any dangerous activity the next day are realistic. In addition, little information exists about long-term effects, notably the extent of accumulation with prolonged use.

Therapeutic drugs containing opioids have been a major safety problem for more than a century. Our analysis shows that additional DEA restrictions on the most widely used opioid–hydrocodone/acetaminophen combinations–was so effective that dispensed quarterly exposure declined by 7.9 million prescriptions. The effect was so large that total population opioid exposure was also reduced. Less reassuring was the steady increase in the use of higher potency opioids such as oxycodone. With 18,893 reported opioid overdose deaths, the sheer numbers rank it among the most important causes of accidental death. By comparison, other deaths in 2013 included 19,974 homicides and 35,369 motor vehicle accident deaths. Controlling the use of opioids is greatly complicated by the lack of alternatives for treating moderate to severe pain, and the widespread need for this treatment. Managing the risks of a product that has substantial hazards but that needs to be widely available for legitimate use is a safety challenge of the first magnitude.

The rapid market uptake of SGLT2 drugs to lower blood sugar in Type 2 diabetes brings new uncertainties about the effects of treatment on the health of hundreds of thousands of older patients. The postmarket surveillance data indicate thousands of cases of genital fungal infections linked to these drugs, mirroring the results of clinical trials, which established a 3- to 4-fold infection risk. To these well-characterized risks are added many fewer but more severe cases of metabolic acidosis and other adverse effects on the kidney. Whether the clinical benefits of these drugs outweigh the increasing evidence of their risks remains uncertain.

Problems with classifying adverse events as serious or not serious constitute still another example of why the FDA urgently needs to update the adverse event reporting system that remains the principal source of new safety information once drugs are approved and marketed. In the report we outline practical steps that can be taken to improve the assessment of whether an event is serious, and enhance the overall quality of manufacturer reports.

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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* 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 serious outcomes were classified as not serious. In a policy change, all new cases were included in the basic analysis. Previous QuarterWatch issues have focused primarily on a subset of adverse events, those that are domestic and coded with serious outcomes. For this reason, event counts in this issue may not be comparable with those in previous issues.

In these data, the adverse events that occur 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 (SOCs) combine the terms into 26 categories. The QuarterWatch database was updated in November 2014 to MedDRA version 17.1.

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

"The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from an IMS Health Inc. information service called the National Prescription Audit™ for 2015 (All Rights Reserved). Such statements, findings, conclusions, views, and opinions are not necessarily those of IMS Health 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 the drug is the one most frequently indicated on the case reports but may account for a small or a large share of the actual reports identified. Unless otherwise specified, QuarterWatch does not distinguish dose, route of administration, or extended release and other formulations.

Results

Report Trends

In the second quarter of 2015 the FDA received 235,540 new case reports from all sources, a decline of 16.2% from the previous quarter but an increase of 8.1% from the same quarter one year earlier. The total included 19,225 (8%) patient deaths, 39,774 (17%) resulting in hospitalization, and 64,184 (27%) classified as medically serious. Although this report includes two quarters of new data, this trend analysis focuses only on the most recent quarter.

We have modified our trend reporting to assess all reports, including foreign reports and cases not classified as serious. Previously we restricted the primary trend analysis to cases that were classified as serious and of domestic origin. Therefore the total of 235,540 includes 57,328 (24.3%) of foreign origin and 103,136 (43.8%) that were not serious.

Using the older QuarterWatch metric limiting the focus to domestic serious reports, we observed a substantial decline in reported events in 2015 Q2. The FDA received 71,825 new domestic, serious case reports, a decline of 23.5% from the previous quarter and 20% from the same quarter one year earlier. Since the long-term trend has been a steady increase, this decline was judged likely to be a fluctuation.

Signals for Suvorexant (BELSOMRA)

New Neurotransmitters Are Found

Suvorexant (BELSOMRA) development began soon after the discovery of a new kind of neurotransmitter. Humans think, act, sleep, and move through the actions of more than 100 different neurotransmitters that transmit signals between 100 billion nerve cells or neurons.[5] Each neuron may receive between 1 and 100,000 signal inputs from other neurons, mostly through one or more neurotransmitters. Typically one specific neurotransmitter serves multiple functions: dopamine mediates functions as diverse as muscle movement, reward/pleasure, sleep, and vomiting. Serotonin can affect emotions, mood, appetite, digestion, and circadian sleep rhythms. Other neurotransmitters provide roughly the same effect but in many different contexts. Gamma-aminobutyric acid (GABA) acts primarily to inhibit other neurotransmitter circuits. Drugs that target GABA receptors to enhance their activity not only have a calming, sedating, and hypnotic effect but also depress the central nervous system (CNS) generally. Most sedative-hypnotics such as zolpidem (AMBIEN) and alprazolam (XANAX) target GABA receptors to enhance its depressant effects on the CNS.

In 1998 two different teams of researchers identified two similar but previously unknown neurotransmitters they named orexins.[6] They seemed to help regulate appetite, sleep and wakefulness. But there were only 50,000-80,000 neurons that synthesized orexins.[7] They were found in the hypothalamus, a large nodule of specialized brain tissue located just above the brainstem. Scientific interest in these obscure new neurotransmitters blossomed when it was discovered that people with a severe sleep disorder called narcolepsy had lost all or most of their orexin-producing neurons. Patients with narcolepsy have severe daytime sleepiness. During nighttime sleep they may experience brief but terrifying hallucinations, muscle paralysis, or periodic leg movements. The idea was that many narcolepsy patients would abruptly fall asleep during the day because they were not getting the regular stream of wakefulness signals from the neurons that produced orexins. But if a drug blocked orexin receptors during the night, it might be an effective way to help people sleep without the complications of impairing numerous other elements of the CNS, as occurs with drugs targeting GABA receptors.

Industry Thinks Blockbuster

The key elements of a blockbuster drug appeared to be in place: A brand new molecular target affecting sleep had been identified. The patient population ranked among the largest in medicine. Insomnia affects around 1 out of 3 adults around the world, according to surveys.[8] In about 10% of adults, insomnia is severe enough to cause daytime distress. At least five research teams (and possibly more) began development programs targeting the orexin receptors in the brain.[9] Almorexant, the first drug to enter substantial clinical trial testing, was discontinued because of undisclosed safety concerns.[10]

Merck's suvorexant was the first to receive FDA approval and reached the market beginning in early 2015.[11] However, thus far the suvorexant launch has produced modest sales, according to data from IMS Health. In the three months ending June 30, 2015, a total of 70,881 outpatient prescriptions had been dispensed. This equals approximately 16,500 patient-days of exposure. Because patients both started and stopped taking the drug during the period, the total number of patients exposed would be higher but would not approach the millions of patients who take other sleep medications.

Suvorexant's Problems

Both substantial problems and notable unanswered questions surrounded suvorexant, based on both animal and human studies. One of the biggest problems concerned an issue that affects many sleep medicines: Is there a dose that increases sleep throughout the night in meaningful amounts without impairing next-day alertness? Merck sought approval of the highest dose tested in pivotal trials, 40 mg, which showed the greatest effect on total sleep time.[12] It increased total sleep time by 45.6 minutes, but about half this effect was accounted for by the placebo.[13] However, the FDA, concerned about potential impairment of next-day driving and alertness, insisted on a 10 mg initial dose,[14] which Merck had abandoned after preliminary studies showed marginal efficacy: It prolonged total sleep time by only about five minutes compared to a placebo, a difference that was not statistically significantly different.[13] The primary outcome results are shown in Table 1.

Table 1. Increased sleep time in minutes

Suvorexant dose	Difference from placebo (p value)		Difference baseline
10 mg*	5.5	NS	38.6
20 mg**	18.4	(< 0.01)	41.3
40 mg**	22.7	(< 0.01)	45.6
Subjective total sleep time at 1 month			

*Clinical Trial P009 **Pooled Trials P028/29

A Long-Acting Drug

Blocking orexin receptors during waking hours might create symptoms similar to narcolepsy as well as impaired alertness. On the other hand, a drug blocking orexin receptors at night had to remain active long enough to sustain any sedating effects during the usual eight-hour period of sleep. Here the earliest pharmacokinetic studies in humans revealed an issue. Suvorexant had an apparent terminal half-life of 12 hours, meaning many patients would still have a therapeutic dose in circulation upon awakening after 8 hours, and substantial amounts remaining during the day. In addition, unlike many sleep medications, suvorexant accumulated with repeated daily dosing and primarily during the daytime rather than nighttime hours. After seven days of administration the apparent terminal half life of 40 mg of suvorexant had grown to 17 hours in elderly men and 20 hours in older women.[15] In Merck's pre-clinical studies of orexin receptors, the company had calculated that a drug would need to block 65-80% of all receptors to achieve substantial sleep efficacy.[16] Based on this theoretical calculation, many patients on a 40 mg dose would experience suvorexant in the therapeutic range for the entire 24-hour period. But the much lower 10 mg dose would fall outside the expected therapeutic range within a few hours of taking the evening dose, the Merck study showed.[16]

Clinical Studies

While precise scientific studies of binding newly designed molecules to target receptors lie at the heart of modern drug development, the human body often behaves differently when administered a narrowly targeted drug. Blocking a specific neuroreceptor is not like turning off the light switch in the bedroom. The body may make adjustments to counter an unexpected chemical intrusion. Especially in the complex changes in sleep states and awakening, the process occurs through the interaction with many other neurotransmitters including histamine, dopamine, norepinephrine, acetylcholine, and serotonin.[5] Thus, it was not immediately clear what the net effects of an orexin blocker would be when administered to humans to enhance sleep.

In many respects the pivotal studies assessing the effects of suvorexant on sleep demonstrated the hoped-for effects. Doses of 20 mg and 40 mg seemed to be well tolerated: 85-90% of treated patients completed the 3-month trials, with only 3-6% discontinuing specifically because of adverse effects.[13] Unlike benzodiazepines and other sleep medications that target GABA receptors, tolerance did not appear to develop. Therefore the benefits seen in the first few weeks were the same and possibly greater at three months. While effect on total sleep time—Merck's primary measure—was less than a half-hour compared to placebo, suvorexant showed evidence of benefit across other secondary measures: amount of time to fall asleep, and the number and duration of awakenings during the night. The benefit was seen by "subjective" measures—e-diaries of patients—as well as in smaller numbers of patients whose brain waves were monitored in a polysomnography lab.

From the perspective of adverse events, one question was whether reasonably complete blocking of orexin receptors might induce the same symptoms seen in narcolepsy. Among the greatest concerns was catalepsy, a complication of narcolepsy in which patients suddenly enter into a trancelike state, usually triggered by strong emotions that might range from laughing to fear.[17] As a result, Merck set up in advance a special panel to adjudicate any suspected cases of catalepsy. The panel reviewed 45 possible cases of catalepsy but confirmed none of them.[13] FDA reviewers were not so sure.[18] They cited one case that they thought could be catalepsy and said the trial might not have captured mild cases of catalepsy. The results were similar for other symptoms of narcolepsy: a few cases of hallucinations just before falling asleep or before awakening; a case of sleep paralysis; a patient who leaped out of bed so suddenly he hit his head against the wall. However, when all discontinuations for adverse events were compared, the discontinuation rate was slightly higher in the placebo group than among those treated with suvorexant. Although relying primarily on assessments of small numbers of individual cases, Ronald Farkas, the FDA team leader, declared that "30 mg and 40 mg seem unsafe" and that "20 mg impairs driving in adults."[18]

As a result of these concerns, and after a supporting advisory committee vote, the FDA rejected the 40 mg dose and approved a 10 mg starting dose, with optional increase to 20 mg. It addition it included strict warnings in the information for patients not to drink alcohol or to "drive, operate heavy machinery, or do anything else dangerous." [11]

Limitations of the Trials

In an article in *The New Yorker,*[19] Merck executives were quoted as objecting to the FDA's safety analysis that focused on just a few specific cases seen in the clinical trials that might have occurred in any systematically monitored group of patients. Scientifically and statistically, this point had merit. However, from a broader perspective, the preapproval trials of suvorexant had so many limitations that it was challenging to draw any valid conclusions about what might happen when a new kind of hypnotic is marketed to a patient population measured in tens of millions. The 10 mg starting dose mandated by the FDA had been tested in only 62 patients for 4 weeks.[13] Here was a drug approved for long-term use, but prior to approval only 160 patients had taken it at any dose for 12 months or more. Testing was more extensive for the 20 mg dose, but the pivotal trials still had monitored only 493 patients taking the drug. Further, the patient population in the pivotal trials had been carefully selected. Notably, it excluded anyone taking psychoactive drugs, including antidepressants, antipsychotics, stimulants for ADHD, mood stabilizers, and anxiolytics. These exclusions

raised three problems: More than 20% of the adult population takes these psychoactive drugs. Insomnia is a key symptom of depression and anxiety, and the drug might have different effects in this population. Finally, these and other excluded drugs also affect neurotransmitters involving sleep, some with sedative effects, some with stimulant effects, and some with both positive and negative effects on sleep in different patients. Another major concern is the long-term effect of a drug that blocked most of the orexin receptors for a large part of every day. Would it induce narcolepsy over the long term? Although harmful and irreversible long-term effects have been seen for other drugs that block different neuroreceptors, there was no scientific evidence yet that this might occur with suvorexant. However, neither could Merck's scientists cite any evidence to exclude such an effect.

Adverse Event Profile

Given the limitations of the clinical trials, the first substantial group of adverse event reports for suvorexant was of particular interest. In the first two calendar quarters of 2015 we identified 1016 adverse event reports identifying suvorexant as the primary suspect drug. The total for this analysis included all reports whether coded with a serious outcome or not, and included 47 foreign reports. (Suvorexant was approved in Japan prior to approval in the United States.) All but 24 of the reports were prepared by Merck, the remainder going directly to the FDA from health professionals or consumers. We judged the quality of the Merck reports as poor: Only 23% contained age, gender, and a partial or complete event date. Just 33% included both age and gender. Our analysis identified six categories of reported adverse effects, with all but one appearing plausible–if not expected–given what was learned in preapproval testing in animals and humans. The ineffective event category excluded terms that indicated some form of insomnia, which is the indication for the drug.

Table 2. Suvorexant reported adverse events

Event Category	Cases (%)*	
Ineffective	429	(42.2)
Sleep disturbance	320	(31.5)
Reduced alertness	286	(28.1)
Paradoxical effect	224	(22.0)
Depression-suicidality	50	(4.9)
Hypersensitivity	31	(3.1)
Total cases	1016	
* One case may have terms in multiple categories		

Reports the Drug Was Ineffective

Overall, 42.2% of the suvorexant reports contained an event term alleging a lack of effect, with most (n = 367) containing the Preferred Term "drug ineffective." We investigated whether the complaints that the drug was ineffective might be related to the lower dose that the FDA had required because of concern about next-day impairment. Where dose was reported, we found the proportion of cases complaining of lack of effect was not statistically different between lower (10 mg or less) and higher doses. (p = 0.931)

Sleep Disturbances

The next largest group of events indicated various forms of sleep disruption. The most frequent terms were nightmare or sleep terror (n = 109), abnormal dreams (n = 93) and various kinds of hallucinations (n = 40). Hallucinations in the daytime are typically symptoms of psychosis, a serious mental disorder. However, in narcolepsy (and the suvorexant clinical trials) brief hallucinations occurred in the period just before falling asleep and at awakening. While only two hallucination events were specifically coded as being of this type, Merck told us the report texts indicated that many of the other cases were of the brief, nighttime variety. Other sleep disturbances were similar to symptoms of narcolepsy, notably sleep paralysis (n = 18), unspecified paralysis (n = 4), and somnambulism (n = 9).

Alertness Impaired

FDA reviewers were concerned that the 12-hour half-life of suvorexant and clinical trials data supported a concern that suvorexant would impair next-day alertness. This was the primary reason the agency insisted that the starting dose be 10 mg instead of the 40 mg that Merck had sought. We identified 286 reported

cases that contained one of many different terms indicating impaired alertness. The most frequent were somnolence (n = 77), headache (n = 67), dizziness (n = 26), and fatigue (n = 19). More severe impairment was indicated in smaller numbers of cases (n = 21), including, amnesia, memory or mental impairment, and confusional state. Other cases indicated consequences of impairment, including road traffic accident, fall, and head injury (n = 5). We did not detect any relationship between a higher dose and more frequent reports of impaired alertness.

Paradoxical Effects

We identified a substantial group of reports (n = 224) indicating that in some patients suvorexant may be causing the direct opposite of the expected hypnotic effects. Instead, patients reported psychiatric symptoms such as anxiety, agitation, irritability, and nervousness. In addition, they reported neurological symptoms that included tremor, restless legs syndrome, muscle spasms, and other movement disorders. Further, we observed numerous cardiac symptoms, including palpitations, chest pains, and other arrhythmias. It was also notable that in these paradoxical cases 30.3% also indicated that the drug had been ineffective in improving sleep. Although these paradoxical effects were not identified in clinical trials, they resemble the paradoxical effects known to occur in some patients taking benzodiazepines either for anxiety or for sleep.[20] Many of these symptoms may also occur in drug withdrawal from cases of benzodiazepine dependence.[21] It is conceivable that some of these cases might be occurring as patients switched from other sleep aids to suvorexant and experienced withdrawal from some other medication.

Depression and Suicidality

The FDA required Merck to conduct direct surveillance of possible suicidal thoughts and actions in its clinical trials, and observed a dose-dependent increase in suicidal thoughts during the trial, but involving only a five suvorexant cases.[13] It also mandated a warning about increased risk of depression and suicidal behaviors. This first group of reports confirmed the evidence seen in earlier clinical trials and included 2 completed suicides, 2 attempted suicides, and 10 cases of suicidal ideation. The total of 41 cases also included reports indicating malaise (n = 14), depression or depressed mood (n = 12). One case could include one or more of these terms.

Symptoms of Narcolepsy

Given that loss of orexin-producing neurons is the cause of narcolepsy, it seemed plausible that blocking most orexin receptors might induce narcolepsy symptoms in some patients. In these reports we observed event terms for all four classic symptoms–sleep paralysis, brief nighttime hallucinations, excessive daytime sleepiness, and catalepsy. What is not known is whether these risks will increase with increasing duration of treatment or dose escalation to increase efficacy.

Other Symptoms

We identified 22 cases indicating various forms of hypersensitivity, both rashes and itching, and angioedema, a rapid swelling of the lips, throat, or other organ. In addition, other mood disorders that seemed unrelated to a stimulant effect were also reported. The largest subgroup of cases was vague, such as feeling abnormal, thinking abnormal or mood altered, altered state of consciousness, or delirium. There were also 80 cases including gastrointestinal complaints and 65 cases indicating a medication error.

Limitations

While the number of adverse event reports was substantial, these reports do not provide a basis for estimating how frequently the reported adverse effects may be occurring. In addition, it not clear how severe these events were from a patient perspective. Merck classified only 85 cases as “serious” under the FDA definitions, and just 28 cases in the United States. This was in part because of so many cases where the drug was deemed ineffective. On the other hand, the company also classified as non-serious cases such as

sleep paralysis (n = 17), hallucinations (n = 32), as well as cases of vomiting, anxiety, agitation, and psychomotor hyperactivity. Finally, in at least 14% of the cases, patients reported taking other psychiatric drugs or sleep medications that might have interacted with suvorexant. This patient population was excluded from pre-approval clinical trials.

Merck's Views

We provided a preliminary summary of our data and discussed our findings with Merck.

The company indicated it was not aware of any particular marketing or educational activity that would have substantially increased the number of reports. The company's view was that the side effects seen in the adverse event reports described events for which adequate warnings already existed in the prescribing information for physicians. The current prescribing information does warn of sleep disturbances, next-day impairment, increased or new episodes of depression or suicidal behavior, and hypersensitivity reactions.[22] The company did not agree with our identification of a paradoxical reaction to the drug involving agitation, palpitations, and stimulation of the CNS. However, it noted that the company continued to evaluate reports on an ongoing basis.

Changes in Opioid Use

Pain is the most common reason patients seek medical care [23] and opioid analgesics are among the most widely used treatments. We surveyed trends since 2008 in the therapeutic use of the 13 most frequently prescribed opioid drugs, accounting for more than 54 million dispensed outpatient prescriptions in the second quarter of 2015, according to data from IMS Health. The patient population ranges from children with coughs to the most severe and intractable cancer pain. In some estimates about 10% of the population takes opioids in any 12-month period, and they are the prescription drugs most widely taken illicitly.[24] In 2011 they triggered more than 855,000 emergency department visits, 23% of the those visits were for adverse effects, and the remainder because of non-medical use or intentional overdoses.[25] Approximately 40% of the population has difficulty initially tolerating opioids, experiencing nausea or vomiting.[26] In continued use 50-90% will experience opioid-induced constipation. Most develop tolerance over time and require escalating doses. Dependence and abuse are major national problems. Nevertheless, especially for serious pain there are few alternatives, and a large majority of opioid prescriptions are for low-potency or short-term use of a few days or weeks.

A 10-Year Debate about Hydrocodone–Acetaminophen

Hydrocodone–acetaminophen (VICODIN, LORTAB, others) is the predominant opioid in medical use. In 2011, and for many years prior, it was the most frequently dispensed outpatient prescription drug of any kind. It was also the most widely used opioid, accounting for 32.4 million prescriptions in the first quarter of 2011, or 51% of the total for the 13 leading opioids. In a year's time, 47 million patients received at least one prescription.[27] It was also a DEA Schedule III controlled substance subject to fewer restrictions compared to fentanyl, morphine, oxycodone, and the other more potent opioids, which are all Schedule II.

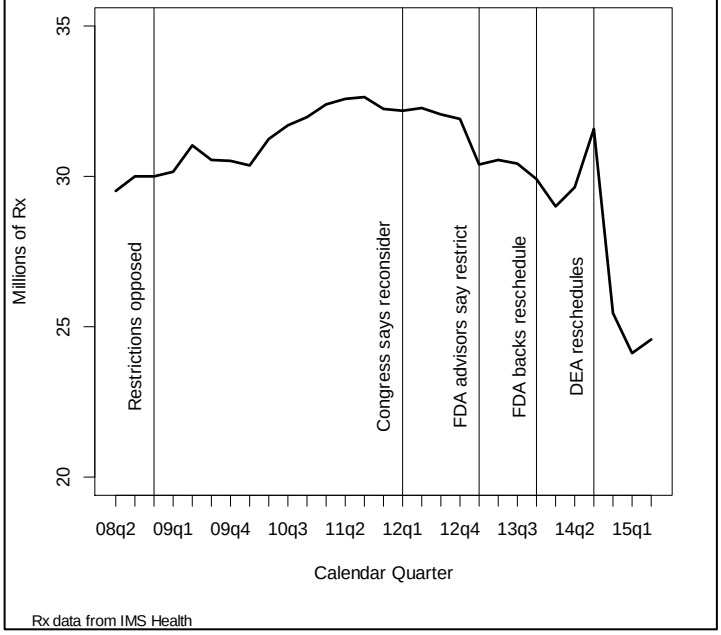
The debate about whether increasing the controlled substance restrictions on hydrocodone combinations would be beneficial lasted for 10 years.[28] In 2004 the Drug Enforcement Administration (DEA) asked the FDA to examine the issue of reclassifying hydrocodone combinations to indicate greater abuse potential. After some deliberation, the FDA recommended in 2008 that it remain in Schedule III (moderate to low potential for abuse). In 2009 the DEA submitted new data seeking reclassification but still no action was taken. In 2012, however, Congress mandated that the FDA reconsider the status of hydrocodone and get input from experts and independent advisors. After getting that input, the FDA recommended reclassification in December 2013.[29] The DEA officially reclassified the drug in August 2014 into Schedule II, which identifies drugs with a high potential for abuse.

The Schedule II category creates substantial restrictions on prescribing and dispensing hydrocodone combination drugs. At the pharmacy it requires separate record-keeping and vaults or safes to store the drug. The physician must provide a written prescription and can't just call in the prescription to the pharmacy, and no refills are allowed. Non-physician providers such as nurse practitioners; physician's assistants, and optometrists are not permitted to prescribe Schedule II drugs. In addition, states may impose additional restrictions such as special triplicate prescription pads.

However, there was also substantial opposition to restricting hydrocodone combinations, both at the FDA advisory committee meeting and in written comments to the DEA. Those with reservations noted that the abuse liability of hydrocodone was lower than that of oxycodone, the most frequently abused prescription opioid. Others feared the restrictions would lead physicians to avoid prescribing an invaluable painkiller and to rely on less effective drugs. There were concerns about limiting use in nursing homes and other settings where non-physicians are more likely to prescribe drugs. The reclassification could also harm patients in pain on weekends when a written prescription might be hard to obtain.

As Figure 2 indicates, the reclassification of hydrocodone products along with previous concerns about abuse have produced a substantial reduction in dispensed prescriptions, so large that total opioid consumption has been reduced. (See Figure 1 on page 2.) From a peak of 32.6 million prescriptions in the third quarter of 2011, dispensed outpatient prescriptions have fallen by 24.6% or 8 million prescriptions. Given that most illicit use of opioids begins when individuals get the drug from family or friends, this substantial reduction in availability could have long-term benefits.

Figure 2. Events-Changes in Acetaminophen-Hydrocodone Prescriptions



Rx data from IMS Health

Oxycodone Exposure Increases

Oxycodone products (OXYCONTIN, others), alone and in combination with acetaminophen (PERCOCET, others), are the dominant higher potency opioid drugs, accounting for 15.5 million outpatient prescriptions in the second quarter of 2014. Oxycodone is available in a large variety of formulations. Strengths range from 5 mg in combination with acetaminophen to 160 mg. It is available in short-acting and extended-release formulations and in abuse-resistant formulations. Although oxycodone prescription numbers are only one-third of those of hydrocodone products, oxycodone accounted for more than twice as many overdose cases in emergency departments.[25]

From 2008 through 2015 Q1, exposure to oxycodone alone nearly doubled, from 3.4 million prescriptions to 6.2 million per calendar quarter. The lower potency combination with acetaminophen was more frequently prescribed, but increases were smaller, from 7.5 million to 9.2 million.

Oxycodone use has also been a primary target of numerous regulatory policies by the FDA, the DEA, and the CDC. [28] The FDA required extended-release oxycodone to be reformulated with increased abuse resistance in 2008. It required an industry risk management program for all long-acting opioids in 2012 that included voluntary training for prescribers. It communicated with all prescribers in 2013 to urge compliance with restrictions and the prescribing instructions. The agency strengthened warnings for all long-acting opioids in 2014. The CDC published draft guidelines intended to reduce prescribing of opioids for chronic

pain in 2015.[21] The DEA, meanwhile, pursued enforcement actions against pharmacies (including CVS and WalMart) for failing to observe legal restrictions, and prosecuted physicians and "pill mills."[30]

Drugs for Treatment of Dependency

Two higher potency opioids–buprenorphine and methadone– are approved in long-acting formulations for treatment of addiction and dependency. As a deterrent to abuse, buprenorphine is combined with naloxone (SUBOXONE, others). In addition, naloxone blocks the effect of other opioids when taken. Long-acting opioids reduce craving and withdrawal effects but the dose is low enough not to create the sought-after euphoric moods.

Buprenorphine products were the fastest-growing among the 13 most frequently prescribed opioids. Since early 2011, dispensed prescriptions for buprenorphine products have increased 77.4%, from 1.8 million prescriptions per quarter to 3 million prescriptions. Methadone exposure, on the other hand, decreased 17.4%, from 980,000 prescriptions to 809,000. These data do not show whether the increase reflects greater numbers of patients with opioid addiction, a higher rate of addiction treatment, or both.

Buprenorphine products are controlled under a specific law–the Drug Addiction Treatment Act of 2000.[31] Although it is a Schedule III opioid, a physician who prescribes it must undertake training, must register with the Department of Health and Human Services, and is limited to treating 30 or 100 patients. Methadone prescribing is limited to certified treatment clinics.

Update on New Diabetes Drugs

Treatment of Type 2 diabetes is a major medical enterprise in the United States, with 21% of adults age 65 and older prescribed a glucose-lowering medication in 2012.[32] Currently patients are treated with at least 10 different classes of drugs and a large number of combinations. Although Type 2 diabetes over the long term results in damage to vision, the peripheral nervous system, and the kidneys, and leads to increased cardiovascular risks, long-term clinical benefits or harms of the drugs are poorly documented because trials have been few, have seldom shown benefits, and may need to last a decade to establish benefits large enough to measure. As a result, diagnosis and response to treatment are based on the biomarker of blood sugar levels, measured as glycosylated hemoglobin A1c (HbA1c).

The treatment of Type 2 diabetes is being transformed by the rapidly expanding use of the newest class of diabetes drugs, agents that cause the kidneys to excrete blood sugar rather than passing it back into systemic circulation. This is achieved by inhibiting sodium glucose cotransporter 2 (SGLT2), a protein found in the kidneys that binds to sugar and transports it back into circulation. Currently, the FDA has approved three SGLT2 agents, canagliflozin (INVOKANA) in 2013; dapagliflozin (FARXIGA) and empagliflozin (JARDIANCE) in 2014.

There are reasons to ask whether many of the mechanisms for lowering blood sugar make sense biologically. The earliest family of oral diabetes medications–sulfonylureas–worked by stimulating the pancreas to secrete more insulin. But is this a good idea in patients whose insulin-secreting cells are already impaired? A second group of agents–the thiazolidinediones–lowered blood sugar by inducing fat cells to absorb more circulating glucose. Was it a good idea in mostly obese patients to induce their fat cells to absorb more sugar, thereby causing additional weight gain? Similar questions could be asked about this new class of drugs.

SGLT2 inhibitor drugs in effect reprogram the kidneys in a fundamental manner. Normally kidneys regulate the fluid and electrolyte balance in the body and filter out waste proteins, but preserve circulating glucose. By blocking the kidney protein that transports sugar through the filtration membranes, the drugs cause some of the circulating sugar to flow instead into the bladder and be excreted in urine. [33] However, the bladder and urinary tract normally do not have substantial concentrations of glucose and this change encourages the development of bacterial and fungal infections, especially in women. In clinical trials,

canagliflozin was associated with genital mycotic infections in 11% of women and 4% of men over a 6-month period. [34] This intervention causes other changes, some apparently positive, others not. It causes weight loss (around 4-6 pounds on the average) and lowers blood pressure by 1-2 mm Hg.[35] On the other hand, it increases low density lipoprotein cholesterol (LDL-C), and impairs the glomerular filtration rates, both by small amounts on the average. Would these substantial changes result in a net benefit or harm over the long-term, life-long period of intended treatment? That pivotal question remains unanswered because long-term exposure has not been assessed in trials of sufficient size and duration.

A Marketing Success

The unanswered questions, however, have not slowed the rapid acceptance of SGLT2 agents into clinical practice. The leading drug currently is canagliflozin, the first approved agent. By the second quarter of 2015 it accounted for more than 1 million dispensed outpatient prescriptions, according to IMS Health. Its growth rate was also rapid, doubling the number of prescriptions in 12 months' time. The second drug approved—dapagliflozin–accounted for 411,000 dispensed outpatient prescriptions and is growing somewhat more slowly. The most recently approved drug–empagliflozin–accounted for 136,000 prescriptions. These totals, however, fall far short of metformin–the predominant medication– which accounted for 20 million dispensed outpatient prescriptions in 2015 Q2.

Adverse Events Linked to Kidney

We assessed all adverse event reports for the three approved SGLT2 inhibitors for the 12 months ending June 30, 2015. The greatest safety concern not understood prior to approval has been a serious and potentially life-threatening condition called metabolic ketoacidosis, and was the focus of two FDA drug safety communications in 2015.[36] [37] Ketones are produced when the body starts breaking down its own fat for energy (instead of glucose), and high levels of ketones are toxic and can cause medical emergencies. Reports of ketoacidosis are increasing, although published clinical details have been few. In its May 2015 communication, the FDA identified 20 cases. In a December 2015 update the agency identified 73 cases. Our most recent adverse event data identifies many additional possible cases, a total 168 cases for canagliflozin, 80 cases for dapagliflozin, and 12 cases for empagliflozin. Because it is not known how many cases go unreported, it is not possible to estimate the incidence of this adverse effect.

As might be expected from the clinical trials data, the adverse event reports for the three SGLT2 drugs include large numbers of cases of fungal or bacterial infections. For canagliflozin, 1464 infection cases (26.7% of all cases) were reported in 12 months; 379 (21.0%) for dapagliflozin, and 93 cases (20.4%) for empagliflozin. While these infections are normally treatable and occur frequently without SGLT2 drug treatment, the relative risk in clinical trials was 3- to 4-fold. Moreover, in some cases the infections may become more serious, spreading into the kidney or urine. The FDA warned in December 2015 that it had identified 19 cases of urosepsis or kidney infections, all of which required hospitalization, including 2 that required hemodialysis because of acute kidney failure. [37]

The adverse event data, using canagliflozin as an example, included other manifestations of renal toxicity including dehydration (n = 173), glomerular filtration rate decreased (n = 116), hyperkalemia (n = 66), and acute renal failure (n = 57).

Adverse Event Reporting System

In preparing this issue of QuarterWatch we encountered numerous examples of manufacturers not coding adverse events as *serious* events with substantial medical consequences. We found coded as "not serious" hundreds of cases that included hypersensitivity reactions, irreversible damage to the extrapyramidal motor system, hallucinations, depression, and genital fungal infections.

Since its founding in 2008, the primary focus of QuarterWatch has been on adverse events coded with a *serious* outcome, which under FDA regulations has a specific meaning: death, disability, hospitalization, life threatening, required intervention to prevent harm and "other medically serious" event.

For manufacturer reporting, the FDA regulations and guidances for non-serious events[2] [38] make it clear that reporting is a lower priority. Manufacturers have no requirement to report foreign events that are not serious, only domestic cases. Domestic cases have to be reported only quarterly for the first three years after approval, and annually thereafter. In a decision dating back to the days when data storage was limited and expensive, the FDA also encouraged manufacturers to seek waivers from submitting non-serious adverse events at all after three years.[36]

Some event outcomes are obvious. If the event resulted in death, disability, or hospitalization, or resulted in an emergency department visit, then the adverse event was serious. Judgment, however, affects what falls into the category of "other medically serious." Here are examples of numerous events with substantial medical consequences coded as not serious, extracted from the cases reported in the 12 months ending June 20, 2015:

Aripiprazole (ABILIFY) is an antipsychotic drug, a class implicated in a form of irreversible damage to the motor system called tardive dyskinesia. In such cases, the patients have uncontrollable involuntary muscle movements of the tongue, lips, fingers, or entire limbs. For aripiprazole we identified 216 adverse event cases for tardive dyskinesia and 147 cases where the drug was reported to induce pathological gambling—all classified as non-serious.

Suvorexant (BELSOMRA) is a new hypnotic medication reviewed in this issue. Cases classified as not serious included hallucinations (n = 31), sleep paralysis (n = 15), and somnambulism (n = 9).

Canagliflozin (INVOKANA) is a Type 2 diabetes drug also reviewed in this issue. Cases classified as not serious included the most frequently reported adverse event for this drug: genital and other fungal infections (n = 788). Also classified as non-serious were urinary tract infections (n = 193), and numerous symptoms of hypersensitivity such as urticaria, rash, and pruritus.

Varenicline (CHANTIX) is a smoking cessation aid with a Boxed Warning about serious psychiatric side effects such as depression and suicidal behavior. It has also been implicated in cases involving violent thoughts and behaviors.[39] The most current 12 months of data for varenicline included cases coded as non-serious for depression (n = 97), agitation (n = 44), and anger (n = 40) as well as hypersensitivity (n = 76).

In addition, these non-serious reports (and a few foreign reports) were of low quality, with a large majority lacking the basic elements of age, gender, and event date. For the aripiprazole non-serious cases only 15% were reasonably complete by this standard; for canagliflozin, only 20% reasonably complete; for suvorexant, just 22%. Varenicline had the best result, with 24% reasonably complete, compared to around 85% of reports sent directly to the FDA without manufacturer involvement.[40]

Conclusions

The FDA can and should take several straightforward steps to clarify the distinction between serious and "not serious" adverse drug events. It needs to clarify the definition of "other medically serious" adverse events, provide examples, and potentially a list of MedDRA terms or groups of terms that should be classified as serious. (Examples include hypersensitivity, depression, and hallucinations.) Given that submissions are now electronic and data storage no longer an issue, the agency should end its policy of giving waivers for the submission of non-serious adverse events after three years. Without the data, the agency cannot detect misclassified cases. In addition, it can require that non-serous foreign reports be submitted. Since these case reports are already being collected by pharmaceutical manufacturers, improving event definitions and making electronic submissions more uniform can be achieved with minimal burden on industry.

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