



April 19, 2017 — New data from 2016 Q3

DEPRESSION AND SUICIDAL BEHAVIORS

Exploring the link with therapeutic drugs

Emotional problems linked to suvorexant (BELSOMRA) started with missed doses

Very different phosphodiesterase-4 (PDE4) drugs can cause psychiatric problems

Executive Summary

In this issue, we focus on depression and suicidality as adverse effects of therapeutic drugs. One part of our analysis focuses on two newer drugs with notably different medical uses. Apremilast (OTEZLA) is a drug for severe forms of psoriasis, while roflumilast (DALIRESP) is used to treat chronic obstructive pulmonary disease (COPD). But they share a risk of these psychiatric side effects through a common mechanism of action: inhibiting a widely distributed intracellular enzyme called phosphodiesterase-4 (PDE4). Also, a new perspective on risks of suicidal thoughts and behaviors comes through examining some striking cases of suicide and suicidal thoughts after taking suvorexant (BELSOMRA) that began when patients missed a dose or stopped the drug. Separately, we examine serious injuries reported for aspirin.

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 assess drug utilization using dispensed outpatient prescription data from QuintilesIMS.

This issue focuses on the most recently released FAERS reports covering the 12 months ending September 30, 2016, with special attention to the most recent quarter of data, 2016 Q3. In Q3, the FDA received 259,941 new case reports of adverse drug events, a 10% decline from the previous quarter and a 26.6% decline from the same quarter one year earlier. Of special interest are domestic reports with a fatal, disabling, or serious outcome. For 2016 Q3 we identified 70,942 new cases, a decline of 17.7% from the previous quarter, and a similar decline from the same quarter one year earlier. After decades of steady growth in reported events, case report totals have been relatively stable for the past two years. However, in the most recent quarter, declines were seen in practically every category we monitor. Reports from consumers and health professionals, from foreign sources, and those indicating patient deaths all declined.

Numerous Serious Injuries from Aspirin?

Our interest was spurred when an unexpectedly large number of serious adverse drug events in 2016 Q3 were attributed to the ubiquitous and invaluable drug aspirin. For the most recent quarter, aspirin was the primary suspect drug in 2,134 reported cases, including 169 patient deaths and 1,137 gastrointestinal

hemorrhages. In another ranking of the new quarter of data, aspirin accounted for more serious injuries to U.S. patients 75 years and older than any other therapeutic drug.

Further investigation of the aspirin cases provided a reminder of an important principle of drug safety: The risks of any drug need to be examined with close attention to the medical context for its use. In these cases, the aspirin—which inhibits platelet aggregation—was being combined with other potent inhibitors of the blood-clotting process. In addition to mostly low-dose aspirin, the injured patients were also taking rivaroxaban (XARELTO), warfarin (COUMADIN), apixaban (ELIQUIS), or other drugs that also inhibit blood clots. In this report, we focus on aspirin’s contribution to the underlying safety issue of too much blood clot inhibition, and the medical settings in which bleeding risks are highest.

Drugs, Depression, and Suicidal Behavior

After decades of intense controversy, today more than 50 drugs have FDA-required warnings that they may cause suicidal thoughts and actions. Those implicated include not only psychiatric drugs that might have a paradoxical effect in some patients, but also a malaria drug (mefloquine), an acne medication (isotretinoin), and drugs to help people quit smoking. Some experts and drug manufacturers still deny a relationship. In this issue, we examine the evidence for three newer drugs as well as the strengths and weaknesses of the scientific tools available to understand how, why, and when drugs may cause depression, suicidal thoughts, and suicidal behaviors.

Roflumilast (DALIRESP)

Roflumilast (DALIRESP) was approved in 2011 for reducing exacerbations of chronic obstructive pulmonary disease (COPD), and was first in a new class of drugs that worked by inhibiting a widely distributed intracellular enzyme called phosphodiesterase-4 (PDE4). Inhibiting a chemically related enzyme—PDE5—proved effective in erectile dysfunction, and provided the mechanism of action for drugs such as sildenafil (VIAGRA), tadalafil (CIALIS), and vardenafil (LEVITRA).

After FDA reviewers detected a small but unexpected number of suicides and suicide attempts in clinical trials of roflumilast, the agency required a warning and Medication Guide. Our analysis of the most recent 12 months of FAERS reports confirms and extends the evidence supporting the FDA concern, and demonstrates that the cases observed in clinical trials were not random events or the result of some unrelated factor.

Apremilast (OTEZLA)

Apremilast (OTEZLA) was approved in 2014 for the treatment of active psoriatic arthritis, an indication later expanded to include moderate to severe plaque psoriasis. Although targeting completely different disease conditions and based on a different drug effect—on inflammation mediated by the immune system—it shares a basic mechanism of action with roflumilast, inhibiting PDE4.

In its safety assessment of apremilast, FDA reviewers were uncertain whether a small number of cases of depression, suicidal thoughts, or suicidal behaviors was a signal for a drug risk. However, given the agency’s experience with roflumilast, and knowledge that PDE4 was also active inside neurons in the brain, the FDA required a cautiously worded warning in the prescribing information and only limited information for patients. On the other hand, our analysis of the most recent 12 months of FAERS reports identified a strong signal for depression, with more than 600 cases and six times the number expected given the overall number of reports received. In this report, we describe why depression as a side effect may have been underestimated in clinical trials only to emerge prominently in postmarketing surveillance.

Suvorexant (BELSOMRA)

When the FDA approved suvorexant (BELSOMRA) in 2014 for the treatment of insomnia, it was the first drug to block two newly discovered neurotransmitters called orexins. The orexin-emitting neurons send wakefulness signals into the complex neural circuits that regulate sleep and waking cycles. The idea was that blocking these wakefulness signals at night would improve sleep.

To assess the risk of suicidal thoughts and behaviors more accurately, the FDA required the use of a specialized assessment tool to systematically query every study patient about these issues during suvorexant premarket Phase 3 testing. In the highest dose group (and at a higher dose than approved), eight cases of suicidal ideation were identified, compared to none in the group taking a placebo. Based on these and other results from clinical trials, the FDA required a warning about suicidal ideation and depression.

Our analysis of the most recent 12 months of FAERS data confirms and extends the clinical trial evidence that suvorexant may cause suicidal thoughts and behaviors. Among 2,290 adverse event reports for suvorexant we identified 8 completed suicides, 11 attempted suicides, and 19 cases of suicidal ideation.

Suicide Case Adds Perspective

A tragic suicide case reported to ISMP in which suvorexant was the suspect drug—combined with two cases of suicidal ideation from clinical trials—provide new insights into suicidal thoughts and behaviors that may be caused by therapeutic drugs. Do cases that may be related to a drug effect share distinct characteristics? Are there similar cases reported for other drugs?

In a case examined in detail later and reported to the FDA MedWatch program, a 56-year-old IT specialist became aggressive and hostile to his wife soon after receiving free 20 mg suvorexant sample packs from his physician. This behavior was not typical for him. Relations were severely strained after he struck her without provocation one weekend night, something he had never done before. A few days later he committed suicide with a gun in a shed behind the house.

This case report shared four key features with a series of 26 case reports involving varenicline (CHANTIX) and aggression/violence and suicidality. The varenicline cases were investigated by members of the QuarterWatch team and published in a peer-reviewed medical journal. Key features included: 1) An inexplicable and unprovoked act; 2) a victim who was anyone nearby; 3) problems that began soon after starting treatment; and 4) a common resolution in a suicidal act.

After additional inquiry, a possible difference emerged about this suvorexant case. Because of FDA concerns that suvorexant could impair next-day alertness, patients were warned not to take suvorexant unless they could remain in bed for at least 7 hours. The patient in this suicide case frequently missed doses because of his job, and told his doctor his emotional problems appeared on days he didn't take suvorexant. He assaulted his wife on a day after he had skipped his dose. In addition, the FDA reviews describe two clinical trials cases of suicidal ideation that also occurred after treatment was interrupted.

Because of the small numbers of cases, the link to a missed dose or discontinuation should be considered a signal requiring further investigation. However, if this is an important event feature, it is likely to have been underestimated in clinical studies because patients were encouraged to take the drug without interruption during the treatment period.

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, the number of reports reveals 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

Depression and suicidality are important adverse drug events but are more challenging to detect and evaluate than harms with clear physical symptoms or laboratory results. Identifying depression and suicidal ideation depends on how patients describe their thoughts and mood, and how systematically they are asked about these problems. The events identified in preapproval testing of the three drugs examined in this issue were few in number—eight cases of suicidal ideation in one instance and three suicides and two suicide attempts in another. The possibility that suvorexant may cause emotional instability on days when a dose is missed is based on three cases. But when large numbers of patients are exposed to a drug, the number of persons affected can also grow large. In the case of varenicline and suicidal and violent behaviors, Pfizer paid approximately \$300 million in damages to an estimated 2,700 patients exposed to this smoking cessation drug during its first three years on the market.

Given these challenges, the FDA evaluations prior to approval were impressive in the detailed accounting of suicidal thought and behavior cases identified, and in the critical evaluation of a signal for suicidal thoughts and behaviors. FDA medical reviewers were alert to the possibility that new PDE4 drugs for respiratory and skin disorders could plausibly have psychiatric side effects, given their mechanism of action. And given inconsistent results in preapproval clinical testing, the agency correctly opted for warnings. Increased use of its assessment tool for learning about suicidal thoughts and behaviors can improve our knowledge of the risks of future drugs, provided that the number of exposed patients is sufficiently large.

For roflumilast and apremilast, our new assessment of postmarketing evidence confirms and extends the findings of the original FDA reviews based on clinical trial data. In addition, a strong signal for depression linked to apremilast seen in adverse event reporting suggests this effect may have been underestimated in clinical trials. Our findings for suvorexant confirm the risks of suicidal thoughts and behavior already identified, and show the need to investigate further the proposition that the risks of these events may be high during days when treatment is interrupted. The prescribing and patient information for all three drugs should be updated to include the confirming information from postmarket surveillance. Improved warnings for patients are needed for both apremilast and suvorexant.

Our findings about the high bleeding risks of aspirin—when combined with other drugs with anticoagulant effects—provide another perspective on a recurring QuarterWatch theme: drugs with anticoagulant effects are the most dangerous outpatient drug treatments in older adults, with injury rates that can exceed 10% of treated patients per year. Reducing these risks should be a major priority in drug safety. Better information and guidance for physicians about when to combine aspirin and other antiplatelet agents with oral anticoagulants is one useful approach with a high probability of reducing hemorrhages caused by these drugs.

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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 website. (<http://www.ismp.org/QuarterWatch/detailedMethods.aspx>)

The severity of the adverse event is 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 all newly released case reports.

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

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

“The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from 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.[5] When cited in the text, tables, or charts, the brand name of drugs used is normally the one most frequently indicated on the case reports but may account for a small or large share of the actual reports identified. Unless specified, QuarterWatch does not distinguish dose, route of administration, or extended release and other preparations.

In this report, we compare drugs using the MedDRA Preferred Term of “Suicidal Ideation.” This term (rather than completed or attempted suicides) was used to exclude cases where an intentional overdose of a drug (such as acetaminophen) was the means of a suicidal behavior but may not have caused it. To assess signals for drugs with different numbers of reports and different patient exposure, we compare the percentage of reported cases of the event of interest for the study drug with the percentage of events in all other drugs combined using the method of Evans et al.[6] For example, if an event such as nausea occurred in 2% of events for all other drugs combined, but accounted for 4% of events for the drug of interest, we would report that nausea was reported twice as often as expected for the study drug. This comparison is also called the Proportional Reporting Ratio (PRR), and the previous example can be also expressed as a PRR = 2.0.

Results

Report Trends

After literally decades of steady and substantial increases in the number of injuries and deaths reported to the FDA's Adverse Event Reporting System (FAERS), we are starting to observe reduced numbers of reports across most report categories. In 2016 Q3 the FDA received 259,941 new reports of injury in which 1,403 different drugs were identified as primary suspect. The overall number of reports was 10% lower than in the previous quarter; the number of serious injuries occurring in the U.S. was 17.7% lower; and foreign reports of serious injuries were 11.6% lower. In addition, cases initially reported by consumers declined 9.7% and those from health professionals, 9.4%. The total number of reports have now declined in three of the last four calendar quarters.

For many years, much of the rapid growth in FAERS reporting could be attributed to factors that were not related to the safety of the 1.1 billion outpatient prescriptions filled every calendar quarter. Because

companies marketing drugs in the U.S. are required to report all serious cases from any country, globalization of the pharmaceutical industry increased the number of foreign cases flowing into the FDA system. Mandatory submission of manufacturer reports through one electronic portal as well as improvements in the FDA's computer infrastructure increased the number of domestic reports for injuries that were not serious. Despite across-the-board declines in 2016 Q3, the 259,941 new cases were still 4.8 times higher than in the same quarter 10 years ago, when 54,249 new cases were reported.

Category	2016 Q2	2016 Q3	% change
New case reports	288,800	259,941	-10.0%
Domestic, serious	86,191	70,942	-17.7%
Domestic, non-serious	126,392	122,841	-2.8%
Foreign, serious	73,844	65,244	-11.6%
Initial reporter			
Consumer	119,577	107,937	-9.7%
Health professional	81,273	73,649	-9.4%
Report source			
Direct to FDA	14,965	11,688	-21.9%
Through manufacturer	273,835	248,253	-9.3%

However, some of the long-term increase can be attributed to factors both directly and indirectly related to safety. For example, manufacturers today have greater contact with patients for educational and marketing reasons, especially for high-cost biological products and specialty drugs. Reports are increased for these drugs both because of higher risks, and because increased patient contact leads to a higher reporting rate. A steady growth of newly approved drugs with new risks also contributes the total.

The Risks of Aspirin

Given that most people would place aspirin near the bottom of any list of potentially dangerous drugs, we were surprised to discover it at or near the top of several risk rankings for 2016 Q3. Among serious injuries for U.S. adults 75 years and older, it ranked first among regularly monitored drugs, with 730 reports. In a ranking of all regularly monitored drugs and serious injuries in the U.S., it ranked No. 4, with 1,829 reports of death, hospitalization, or other serious injury among 2,134 reports overall. The report rankings remained high when we excluded vague reports, reports from consumers, and reports that might indicate a patient death without investigation of whether the drug might have caused it.

Further investigation revealed this safety signal was a genuine one, but required careful interpretation. Aspirin, in addition to relieving headaches, minor pains, and fever, has a potent effect on the formation of blood clots. In the standard Ivy assay of bleeding time, aspirin increased the time to form a clot from a mean of 5 minutes to 9 minutes, and to as much as 21 minutes in some patients.[7] With this effect in mind, millions of people take low-dose aspirin to prevent heart attacks and strokes, caused when unwanted blood

clots form in arteries supplying blood to the heart and brain. The biological effect is to prevent platelets from clumping together at the site of vascular injury. But in some patients, the adverse effect is unwanted bleeding. The risk of severe bleeding is even greater when an anti-platelet agent is combined with a thrombin inhibitor that prevents formation of the thrombin threads that complete a blood clot.

In the newly reported aspirin cases that drew our attention, aspirin was being combined with one or more of nine potent anticoagulants, notably rivaroxaban (XARELTO), warfarin (COUMADIN), apixaban (ELIQUIS), and enoxaparin (LOVENOX). Not surprisingly, 87.4% of the aspirin case reports indicated hemorrhage had occurred.

The risks of combining blood clot inhibiting agents are high. Our previous study of dabigatran (PRADAXA) reported that combining the drug with a platelet inhibitor such as aspirin doubled the risk of severe bleeding.[8] Studies of apixaban showed that adding aspirin increased the risk of bleeding 2- to 4-fold.[9] Given that long-term administration of anticoagulants such as those combined with aspirin causes bleeding in 10-15% of patients per year,[10] and life-threatening hemorrhages in 2-4% of patients, reducing the risk of anticoagulants continues to be a major drug safety priority. The FDA should sponsor a reanalysis of the extensive clinical trials data on anticoagulants with a goal of identifying appropriate use of dual therapy with aspirin and other antiplatelet agents with anticoagulants.

Drugs, Depression, and Suicidal Behaviors

For more than 25 years, regulators, drug companies, psychiatrists, lawyers, victims, and survivors have debated whether some drugs can cause people to become depressed, violent, or suicidal. The issue first arose to prominence in 1990 with the rapid rise of serotonin reuptake inhibitors (SSRIs) to treat depression. A published scientific report [11] evaluated six patients who became suicidal soon after starting fluoxetine (PROZAC). Court cases involving violence attributed to drugs soon followed. After more than 10 years in which both industry and the FDA mostly denied that drugs could trigger such behavior, the tide began to turn. Starting in 2004 the FDA began adding cautiously worded warnings to many drugs, notably antidepressants and anticonvulsants/mood stabilizers. In 2010 the agency began to require manufacturers to assess this risk in the clinical trials of some new drugs.[12] By 2011 more than 50 drugs had some form of warning about suicidal behaviors [13] and a few have cautious language involving the possibility of violence. From time to time, industry or its allies have pressed to remove suicidal behavior warnings, [14] claiming they have a “chilling” effect on the drugs’ use. In the case of varenicline (CHANTIX), Pfizer succeeded in persuading the FDA to moderate a warning [15] after a two-year campaign. Although the era of outright denial has now ended, surprisingly little is known about these drug-related events, how often they occur, what other factors might contribute, and whether they have telltale characteristics that might indicate a drug role. In this issue of QuarterWatch we focus on three recently approved drugs to explore what can be learned about these adverse drug events with the tools now available.

PDE4: A New Mechanism of Action

Cyclic adenosine monophosphate (cAMP) is a widely distributed enzyme in animal cells and activates various other cellular functions in neurons, the immune system, and blood vessels. cAMP is called a second messenger because it is released when hormones and other signaling proteins trigger receptors in the cell membrane, which releases cAMP.[16] In addition, cAMP can be deactivated by a family of cellular enzymes called phosphodiesterases (PDEs). Therefore, a drug that inhibits PDE in effect stimulates cell activity because the cAMP becomes active longer and in greater concentrations. Among the multiple effects of caffeine is its action as a non-specific PDE inhibitor.[17] However, at least 11 different PDE subtypes have been identified, with the major variants numbered PDE1-PDE5.[18] One became famous. The first PDE5 inhibitor was sildenafil (VIAGRA), which works in some kinds of sexual dysfunction by increasing blood flow to the penis. In a classic example of a drug having many effects—not just the desired effect—PDE5 is also active in blood vessels in the eye, and side effects involving impaired vision and blindness have been reported for sildenafil.[19]

The next major drug target was PDE4. The initial focus on PDE4 inhibitors was based on its high levels of activity in neurons in the brain. Early studies in mice suggested a dramatic improvement in learning and memory.[20] By 2008 PDE4 was on a list of potential neuroenhancers.[21] The first PDE4 inhibitor and prototypical molecule was rolipram, and it was intended to be an antidepressant.[18] However, rolipram failed as an antidepressant, the published reason being unacceptable levels of nausea and vomiting—again because PDE4 is also active in the tissues of the gastrointestinal (GI) tract. It is another example in which a drug targeting a widely distributed enzyme such as PDE4 has many effects beyond the desired one. With further research and testing, other PDE4 inhibitor variants proved to have additional effects deemed beneficial. Roflumilast (DALIRESP) proved to have benefits in COPD and is marketed by AstraZeneca. Apremilast (OTEZLA) was a PDE4 approved for two forms of psoriasis because it apparently retarded inflammatory actions in the immune system. It is marketed by Celgene. However, it was expected that both new PDE4 inhibitors would also have activity in the brain and the GI tract, and in fact both effects were observed.

Signal for Roflumilast (DALIRESP)

The 15-year clinical development of the first approved PDE4 inhibitor, roflumilast (DALIRESP), might be described as a drug with a new mechanism of action in search of a disease to treat. By the time it was approved in 2011, it had been tested in 114 clinical trials enrolling 24,000 subjects, including trials for asthma, osteoarthritis, rheumatoid arthritis, Type 2 diabetes, and allergic rhinitis.[22] For its ultimately approved use—chronic obstructive pulmonary disease (COPD)—it was tested in 18 different trials with 11,965 patients taking the drug or a placebo.

The signal for suicidal behaviors, however, came from a small number of spontaneously reported events in the trials and illustrated the problems that have surrounded the assessment of these events for decades. In the COPD development program, three patients on the active drug committed suicide and two patients attempted suicide, versus none in the placebo group.[22] In a population not being treated for a mental disorder, five cases were deemed large enough for the FDA to require a warning in the prescribing information for physicians, and a mandatory Medication Guide for patients.[23] But five cases were still a small number and the sponsor (then Forest Pharmaceuticals) noted that in some cases the events occurred after treatment was discontinued.[24] In addition, the studies lacked the statistical power to establish a statistically significant effect.

Adverse Event Signal

In the most recent 12 months of data for roflumilast we observed a confirming signal for suicidal and self-injurious behaviors. Among the 176 reports of all types of adverse events were 11 cases in the suicidal and self-injurious behavior High Level Term (HLT) group, including 7 cases of suicidal ideation, 3 suicide attempts, and 1 completed suicide. To compare roflumilast with other drugs, we focused on reports of suicidal ideation; despite the small total number of reports, we found that roflumilast accounted for 7.8 times the number of suicidal ideation reports that would have been expected based on the results for all other drugs combined. In addition, we identified 5 cases of depressive disorders, but this small number could have occurred by chance.

Prescription volume for roflumilast was a mean of 62,000 patients per month, according to dispensed outpatient prescription data from QuintilesIMS. The number of total patients exposed would be larger because of treatment starts and stops during the 12-month period.

In conclusion, the link of roflumilast with suicidal thoughts and behaviors is plausible based on its mechanism of action inhibiting PDE4; events were observed in clinical trials and further confirmed in the latest FDA FAERS reports.

Apremilast (OTEZLA), a PDE4 for Psoriasis

In 2014, apremilast became the second PDE4 inhibitor to win FDA approval, and its initial disease target was entirely different—a severe form of psoriasis called psoriatic arthritis.[25] Given the signal seen for the first approved PDE4, roflumilast, both the FDA and the manufacturer, Celgene, focused on adverse events of depression, suicidal thoughts, and suicidal behaviors. However, the analysis was limited by the relatively small number of patients in the two pivotal clinical trials, a total of 1,493 patients with 998 receiving only one of two dosage levels of the active drug. The number of events related to these psychiatric side effects was also small. Two cases of suicidal thoughts or attempts were identified in the group receiving 20 mg of apremilast, compared to zero in the placebo group. For depression that was severe enough to result in discontinuation, three cases occurred in the apremilast 20 mg group, and zero in the placebo group. However, two FDA reviewers questioned whether these were signals of a drug effect. [26] No similar imbalance was seen in the higher-dose patients, the 30 mg group. This was the opposite of an expected dose-response effect, which predicts more frequent events with increasing doses. Furthermore, just one completed suicide occurred among all the patients in the apremilast testing program, and it occurred in the placebo group. The Phase 3 trials of apremilast were small, lacking the statistical power to accurately assess a possible side effect that might be occurring in 1-2% of the patients.

Despite the ambiguous data from the small clinical trials, the FDA nevertheless required a warning for depression. The prescribing information states unequivocally, “Treatment with OTEZLA is associated with an increase in adverse reactions of depression.” [25] However, in a densely worded clinical trial result summary that followed, the data were aggregated in a manner that implied that the effect was very small, if present at all. A review article, written by two consultants to Celgene, the manufacturer, questioned whether depression was an actual side effect of apremilast, or whether the data were picking up the background rate for depression.[27]

Apremilast Adverse Event Signals

While the clinical trial data for depression were uncertain, postmarketing adverse drug event reporting provided a clear and striking signal that associated apremilast with reports of depression. In the 12 months ending September 30, 2016, apremilast accounted for 631 reported cases of depressed mood disorders (HLT), or 6.3 times the number expected given the total number of reports for this drug ($n = 13,601$). Furthermore, depression reports ranked in frequency just below the three best-documented adverse effects of PDE4 inhibitors, diarrhea, nausea, and headache.[25] In the 12-month totals for all drugs, only one other drug (sodium oxybate) accounted for more reports of depressed mood disorders than apremilast.

We suspect that the depression was underestimated in the Phase 3 clinical trials of apremilast because of the small number of patients studied, and because patients were not asked specifically about depression in a systematic assessment.

Apremilast accounted for an average of 36,000 prescriptions per month in the 12-month period ending in 2016 Q3, per dispensed outpatient prescription data from QuintilesIMS.

Suicidal Thoughts and Behaviors

For apremilast, we identified 68 cases of suicidal and self-injurious behavior (HLT), including 61 cases of suicidal ideation, 4 reports of suicidal behavior or attempt, and 3 completed suicides.

To compare apremilast with other drugs we focused on the 61 reported cases of suicidal ideation and found 1.6 times the number expected. This large total number of cases in one year has scientific weight. Only 17 drugs (mostly antidepressants and anticonvulsants/mood stabilizers) accounted for more reports of suicidal ideation. But given the large number of total reports for apremilast, the PRR of 1.6 times the expected number was only moderately elevated.

Conclusions about PDE4 Drugs

The evidence shows that this new mechanism of action is linked to increased risk of depression, suicidal thoughts, and suicidal behaviors in two drugs targeting notably different medical conditions and not intended for psychiatric patients. In addition to mechanism of action, evidence was seen in clinical trials before approval that led to FDA-required warnings. Our new adverse drug event analysis confirms and extends that evidence from cases reported from a much larger patient population. There were also apparent differences between the two drugs we studied. Apremilast accounted for a strong signal for depression, with a smaller number and proportion of suicidal thoughts and behaviors. Roflumilast, on the other hand, had a stronger signal for suicidal thoughts and behaviors, and only a few postmarketing reports of depression (n = 6).

A Suvorexant (BELSOMRA) Case

A striking report about a case involving both violence and suicide caused us to revisit the newest FDA-approved insomnia medication, suvorexant (BELSOMRA). We previously reviewed this drug in January 2016.[28] While normally QuarterWatch examines computer excerpts of adverse drug events which exclude narrative detail, this new case was reported directly to ISMP in response to our previous review, and we obtained informed consent and additional details to complete an event profile. In accord with ISMP policy, we also submitted the case to the FDA MedWatch program. These are the essential details:

A 56-year-old married man who was an IT worker at an educational institution was prescribed suvorexant for insomnia and provided free sample packs with doses of 20 mg and a Merck patient brochure. Both the patient and his spouse noted that his mood became immediately unstable and he started making angry and aggressive comments to his spouse that were not characteristic of him. Because of his work schedule, he sometimes omitted doses, following the instructions not to take suvorexant unless he could remain in bed for 7 hours. On the days after he missed a dose, the emotional effects were so substantial that he raised the issue with his doctor, but no changes were made in his treatment. On a Saturday in June 2016, the patient had missed a dose. That evening, he and his spouse were being 'goofy' playing with a stuffed animal. Suddenly he "flipped out on me and smacked me. He back handed me on the side of the head," according to the spouse. "This was totally not my husband," she said. This was also not behavior she would tolerate, she said. The next Wednesday after not speaking to each other for the interim, he asked, "Is our marriage in trouble?" A few hours later he went to a shed behind the house with a gun and called 911 to say there was going to be a suicide. Shortly after police arrived he killed himself with gunshot wound to head. His records showed that he had consumed suvorexant for a total of 13 nights over 26 days.

Similar Key Features

This case shared several key features with cases reported for another drug we have examined in depth, the smoking cessation aid varenicline (CHANTIX). In a peer-reviewed publication [29] we identified these key features in 26 cases involving anger/aggression/violence and suicidality in patients trying to stop smoking using varenicline: 1) An inexplicable and unprovoked event; 2) a victim who was anyone nearby; 3) early onset of symptoms, sometimes with the first doses; and 4) ended in suicidal acts in 45% of cases.

In addition, there were differences between the suvorexant and varenicline cases, including a different molecule, a different mechanism of action, and a different patient population. In this suvorexant case, the emotional changes often occurred on days the patient did not take the drug. However, to assess whether the drug (or some other unknown factor) might have been responsible for this tragic event requires examining these questions: 1) Is the effect plausible from the mechanism of action? 2) Were signals seen in clinical trials where all patients are systematically observed? 3) Were additional cases reported as adverse drug events?

Mechanism of Action

Suvorexant was the first drug to be approved that blocked signals from two newly discovered neurotransmitters called orexins.[30] A small number of specialized orexin neurons (around 50,000-80,000) are thought to emit wakefulness signals in the complex cycle of sleep and waking that involves numerous other neurotransmitters, notably dopamine. At night, blocking these wakefulness signals was intended to promote sleep. Dopamine, in turn, is involved in the regulation of sleep, mood, memory, appetite, blood pressure, muscle movements, and sexual functions.[31] One effect of varenicline is to trigger the release of dopamine, and this drug's most frequent psychiatric side effects involve sleep abnormalities. While the mechanisms by which more than 100 known neurotransmitters interact with each other and influence behavior are poorly understood, the available information makes plausible the possibility that suvorexant could cause dangerous or suicidal behaviors in some patients.

Clinical Trials Evidence

The possibility that suicidal thoughts and behaviors might result from a new kind of psychoactive drug was understood by both the FDA and Merck, the manufacturer of suvorexant. In most clinical trials, possible adverse effects are spontaneously volunteered by a patient in response to a vague general question, "Has there been any change in your health since the last visit?" This technique has been shown to underestimate the incidence of side effects by 50-60% or more, compared to specifically asking every patient using some form of a checklist.[32] [33] Starting in 2010, for some suspect drugs the FDA started requiring a specific symptom checklist for suicidal thoughts and behaviors, an instrument called the Columbia Classification Algorithm for Suicide Assessment (C-CASA).[12] Using this instrument in three clinical trials of a higher-than-approved (30-40 mg) dose of suvorexant, eight patients reported suicidal ideation, compared to none on placebo.[34] However, no cases were reported among suvorexant patients taking a lower, 20 mg dose. An FDA reviewer also noted that the suvorexant efficacy trials excluded patients taking antidepressants or with depression symptoms.[35]

The FDA review briefly noted one suvorexant case with many similarities to the case described above, notably that the event occurred on the day after a missed dose and involved both anger/aggression and suicidal thoughts:

A 54-year old female (AN 12362) reported suicidal ideation on Day 91; she had missed Day 90 dose and had been on suvorexant HD [high dose]. After an argument with her daughter, she felt like she wanted to die but had no intention of acting on the thought.[34]

There was no information available on the duration of suicidal ideation in this case.

Another FDA review reported an additional case related to discontinuation of suvorexant:

In a Phase I drug interaction trial (P026), a 21-year-old female without a prior history of suicidal ideation, reported suicidal ideation 4 days after the final dose of trial treatment, suvorexant 40 mg plus paroxetine 20 mg. The event lasted 10 days and was designated mild in intensity. [35]

At the time of approval in 2014, the prescribing information included a cautiously worded warning, "Depression: worsening of depression or suicidal thinking may occur. Risk increases with dose." [36] The Medication Guide for patients warned that patients may experience "more outgoing or aggressive behavior than normal...or worsening of depression and suicidal thoughts or actions," and urged them to inform their doctor if they had a history of depression, mental illness, or suicidal thoughts.

Adverse Event Data

We analyzed 2,290 adverse reports for suvorexant, covering the 12 months ending 2016 Q3. This total showed 40 cases of suicidal or self-injurious behavior (HLT), including 19 cases of suicidal ideation, 11 cases of attempted suicide, and 8 completed suicides. In addition, 38 cases described depressed mood

disorders and disturbances. Narrative information was not available to assess whether these events had similarities to the three specific cases reviewed.

As for the previous drugs, we used reports of suicidal ideation for comparison with other drugs. The 19 suicidal ideation cases occurred 3.1 times more frequently than expected given the total number of reports for suvorexant.

During our one-year study period suvorexant accounted for a mean of 49,000 prescriptions per month, according to data from QuintilesIMS. We would expect the total number of patients exposed to be substantially higher for three reasons. (1) As previously shown, patients frequently complained the drug was ineffective, [28] likely increasing medication stops; (2) The totals did not include free samples, as in the reported suicide case; (3) As with the other drugs, patients might have started or stopped the medication during the study period.

Conclusions

The link between suvorexant and suicidal thoughts and behaviors is plausible based on mechanism of action, at least partially confirmed in clinical trials, with further evidence from postmarketing FAERS reports. We have less evidence—but some specific cases—that anger/aggress/violence and suicidal behaviors sometimes occur when patients miss a dose of suvorexant, even if following safety instructions not to take it unless 7 hours remain before planned awakening. Another possibility is that with a 12-hour terminal half-life and some accumulation with continued use,[28] high-dose suvorexant could remain active during waking hours even a day later, or be a withdrawal reaction. We recommend the FDA and Merck re-examine the available case records to assess possible psychiatric discontinuation effects.

Manufacturer Views

We provided preliminary summaries of our data on suicidal behaviors to the three manufacturers of the drugs examined in this report. Merck told us, “The review of postmarketing reports in Merck’s global safety surveillance database are consistent with the data observed in the suvorexant clinical development program, with no evidence of a new or emerging signal regarding suicidal behavior.”

Adequacy of Current Warnings

Warnings about depression, suicidal thoughts, and suicidal behaviors are important for drugs used to treat medical conditions unrelated to psychiatric disorders such as psoriasis and COPD. Without a warning, many patients experiencing a sudden change in mood or behavior not typical of them would never suspect the drug prescribed for a respiratory or skin problem. Without a warning, a physician hearing a patient report of an unexpected mood change might disregard the drug as a possible suspect. Therefore, we examined the FDA-approved physician prescribing information and any available Medication Guide for patients. Table 2 provides a summary:

	Physician warning	Patient warning*	Postmarket update
Roflumilast (DALIRESP)	Yes	Yes	No
Apremilast (OTEZLA)	Yes	No	No
Suvorexant (BELSOMRA)	Yes	Yes	No

It was encouraging to discover that for all three drugs studied, the prescribing information provided a warning for physicians displayed with reasonable prominence and not buried in a long list of possible adverse events.

The information for patients was mixed. The clearest and most complete warning was in the Medication Guide for AstraZeneca's roflumilast. Its first listed item began "DALIRESP may cause mental health problems including suicidal thoughts and behaviors" and provided six specific examples. We were unable to identify any Medication Guide for apremilast. However, the Otezla web site (www.otezla.com) contained a prominent home page warning: "Otezla is associated with an increase in adverse reactions of depression." The Medication Guide for suvorexant had a warning for patients but it was not prominent, being listed in the eighth section of the guide after admonitions not to drink alcohol and daytime sleepiness. We recommend that all three drugs have Medication Guide warnings for patients similar to those provided for roflumilast.

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