ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES QuarterWatch
Monitoring FDA MedWatch Reports

May 16, 2018 — New data from 2017 Q3

PERSPECTIVES ON EMERGING DRUG RISKS

How Well Do Antidepressant Drugs Work? Vortioxetine (TRINTELLIX) Case Study
Dispensing Errors, Name Confusion for Breo, Anoro, and other Ellipta Inhalers
Abuse of a Widely Used OTC Drug for Diarrhea

Executive Summary

In this issue, we examine antidepressant drugs with perspectives from a massive new study and illustrated by the adverse event profile and benefits of the newest antidepressant, vortioxetine (TRINTELLIX). Packaging, labeling, and online instructions have all contributed to dispensing errors and name confusion among GlaxoSmithKline's new Ellipta inhalers for asthma and chronic obstructive pulmonary disease (COPD). How the abuse of loperamide (IMODIUM A-D, others), an over-the-counter (OTC) diarrhea medication, was identified and addressed reveals new insights into detecting emerging risks of older drugs.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP). We analyze computer excerpts from the Food and Drug Administration's 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.

In the calendar quarter ending September 30, 2017, the FDA received 291,999 new adverse drug event reports, a 5.4% decline from the previous quarter, but a 4.8% increase from the same quarter of 2016. After many years of steady increase, the volume of reports of injury associated with therapeutic drugs has stabilized over the past 12 quarters. The new reports identified 647 different biological products, prescription, and OTC drugs.

Reports of adverse drug events are voluntary for both consumers and health professionals, who may report possible cases of drug-related injury either to the manufacturer (which must prepare and submit a report to the agency) or directly to the FDA.

Vortioxetine (Trintellix) and the Antidepressant Drug Controversy

More than three decades after the introduction of a new generation of antidepressant drugs, important questions continue to be debated about how well they work, and their safety profile. In the interval, depression is so prevalent and use became so widespread that in some population groups (e.g., women age 40 and older) almost 1 in 4 persons report taking them.

The latest chapter in the ongoing debate began in February 2018 with the publication in the journal *The Lancet* of the most massive antidepressant study to date, encompassing 116,477 patients enrolled in 522 clinical trials of 21 major antidepressant drugs. It concluded that "All antidepressants were more efficacious than placebo in adults with major depressive disorder." It was one of the most optimistic and comprehensive assessments of this drug class published in several years.

To dig a layer deeper, QuarterWatch analyzed the safety profile and efficacy results for vortioxetine (TRINTELLIX). It is the newest antidepressant (launched in 2014), had a name change from Brintellix in 2016, and was widely advertised in early 2018. It also fell right on the midpoint of drug efficacy comparisons reported in *The Lancet* study. We found:

- While the FDA judged it an effective treatment, vortioxetine failed to demonstrate a benefit in 4/10 clinical trials and the trials did not document more benefit than a placebo in U.S. patient subgroups taking the recommended 10 mg daily starting dose in any trial.

- Prescribing physicians and many patients would nevertheless see substantial improvements over the first 6-8 weeks of treatment. In the short-term clinical trials, depression scores improved markedly both in patients taking an inactive placebo and in those on vortioxetine

- The treatment failed in 19%-20% of the vortioxetine patients, those who dropped out before completing 8 weeks of treatment in a pivotal North American trial.

- The most recent adverse drug event data showed substantial numbers of reported cases of aggression/hostility (n = 339), suicidal/self-injurious thoughts and behaviors (n = 155), and sexual desire disorders (n = 160). These adverse effects have been reported for other antidepressant drugs.

- A new signal indicated that vortioxetine might cause weight gain associated with eating disorders, mainly excessive hunger or abnormally large food intake (n = 163).

The manufacturer, Takeda Pharmaceuticals U.S.A., told us that many of the adverse event reports came from an online consumer survey and might reflect symptoms of major depression rather than a drug effect.

This QuarterWatch report also explores why the vortioxetine results are typical of the drug class and why the widely circulated *Lancet* study did not provide a balanced portrait of the risks and benefits.

Dispensing Errors, Name Confusion for Breo, Anoro Inhalers

We investigated more than 500 adverse event reports indicating that patients, pharmacists, and physicians were confusing four inhaler products from GlaxoSmithKline (GSK) with the same new inhalation device but different active ingredients.

Patients with asthma depend on two different kinds of inhalers: To cope with an immediate attack, an albuterol inhaler may provide immediate relief by dilating bronchial passages. But once-a-day inhalers provide long-term treatment intended to reduce the incidence of asthma attacks–and are prescribed to treat airflow obstruction in patients with chronic obstructive pulmonary disease(COPD). Typical ingredients include a corticosteroid to reduce inflammation and a long-acting beta-agonist (LABA), which causes relaxation of bronchial smooth muscles.

Beginning in 2013, GSK introduced a new inhaler device–about the size of a hockey puck–that it brand named “Ellipta,” and would imbed this brand in the drug names of new products: BREO ELLIPTA contains fluticasone (the corticosteroid) and vilanterol (a new LABA). ARNUITY ELLIPTA contains only fluticasone. ANORO ELLIPTA contains umeclidinium and vilanterol. INCRUSE ELLIPTA contains only umeclidinium. All are recommended once-a-day use.

The confusion resulted from these problems: A) Embedding the device name in the brand name, leading the unwary to conclude mistakenly the product name was “Ellipta”; B) Putting the products in nearly identical packages, with similar type size, and with similar device labels; C) Increasing the possible confusion with the online instructional videos and other materials that did not distinguish accurately among products.

The Adverse Event Reporting System

How Abuse of an OTC Diarrhea Remedy Was Identified

Many of us have turned to loperamide (IMODIUM A-D, others) for traveler's diarrhea without knowing that it is an opioid that is 40-50 times more potent than morphine in the gut, but poorly absorbed into the blood with even less passing the blood-brain barrier. But the word got out among substance abusers that if one took 10 or 20 times the recommended dose, the effects would be similar to using the more highly controlled opioids such as morphine or oxycodone. And it was readily available OTC.

The primary medical problem with a loperamide overdose of this magnitude is that it can cause potentially fatal disruption of normal heart rhythm, appearing as short blackouts and seizures in some cases, and death in others. To complicate matters, a standard toxicology screen would detect loperamide but not necessarily reveal the overdose.

Those guessing that identification of this emerging risk might be the result of FDA digital surveillance of millions of electronic health records would be logical, but incorrect. This drug safety problem was identified by the oldest form of postmarket surveillance–publication of case reports and other analysis in medical journals, studies written by public-spirited pharmacists and physicians. But in this case the system worked. Because manufacturers are required to monitor the medical literature, they forwarded these studies to the FDA. An alert FDA staff investigated, and the agency issued two Drug Safety Communications, including a new proposal for abuse-resistant packaging for loperamide.

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

Our assessment of the newer antidepressant vortioxetine provides a detailed profile of its risks and likely benefits, and notes these are typical of other antidepressant drugs. It would be hard to identify another class of drugs that, despite decades of use, has more questions about the patient groups for which its benefits outweigh its risks, and the incidence of severe adverse effects.

We recommend that GSK and the FDA re-evaluate the packaging and labeling of the Ellipta inhaler products as a group, and that GSK correct the inaccurate product portrayals for patients on its web sites.

In the case of emerging abuse of loperamide, the FDA acted promptly, published a detailed risk assessment, and followed up with additional action to reduce those risks. While voluntary reporting and contributed safety studies deserve praise, better and more comprehensive systems are needed to assess emerging drug risks, estimate incidence, and support methods to reduce them.

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Methods Summary

QuarterWatch monitors the safety of prescription drugs and biological products through analysis of adverse drug events reported to the FDA by consumers and health professionals, either directly to the agency or through drug manufacturers. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source.[1] A full description of our methodology is available on the QuarterWatch pages of the ISMP web site. (https://www.ismp.org/quarterwatch/methods)

The severity of the reported adverse event is classified as serious under FDA regulation if the case report specified an outcome of death, disability, hospitalization, required intervention to prevent harm, was life threatening, or had other medically serious consequences.[2] Cases without these outcomes are classified as not serious, and all new cases were included in this analysis unless indicated otherwise.

In these data, the adverse events reported are described by medical terms selected from the Medical Dictionary for Regulatory Activities (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and postmarketing reports.[3] The MedDRA terminology also defines broader categories of adverse events that can include any of a list of more specific and related medical terms. We use these categories, called Standardized MedDRA Queries (SMQs), to identify possible cases of some adverse events.[4] We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that also combine several related but more specific medical terms. High Level Group Terms (HLGTs) combine several related HLTs, and System Organ Classes combine the terms into 27 categories. The QuarterWatch database was updated in November 2017 to MedDRA version 20.1.

To identify signals for various adverse events we also utilize the disproportionality method of Evans [5] to calculate a Proportional Reporting Ratio (PRR). The PRR is similar to the concept of relative risk of the specific adverse event being reported and permits comparison among drugs with notably different total numbers of reports. In this statistical technique, we compare the fraction of a specific kind of adverse event for the suspect drug to the fraction of such events occurring among other comparison drugs in our study period. For example, if reports of hypotension occurred in 12% of all cases of the suspect drug but occurred in only 3% of the cases for the comparison drugs, it would produce a PRR of 4. We also calculate the Yates X^2 value for the comparison and report the probability that the difference might have occurred by chance.

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the most recent version of the case report. The drug names are standardized to drug ingredient names based on the National Library of Medicine's RxNorm terminology.[6] 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.

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

We report the number of prescriptions and patients prescribed selected drugs from our own analysis of published data from the Medical Expenditure Panel Survey.[7] It is the largest publicly available survey of prescription drug use with raw data made available annually by the Agency for Healthcare Research and Quality. The latest available data are for 2015.

Results

Report Trends

The FDA received 291,999 new case reports in the three months ending September 30, 2017, a 5.4% decrease from the previous quarter and 4.8% increase from the same quarter one year earlier. The total included 21,778 (7.5%) cases where the patient died, 44,875 (15.4%) events requiring hospitalization and 78,500 (26.9%) with other serious outcomes. The outcome in the remaining 146,846 cases (50.3%) was not coded as serious and might have involved a less severe injury (nausea, diarrhea), a medication error, or product problem that did not result in injury. In the most recent quarter data, 94.5% of reports were prepared and submitted by drug manufacturers, who learned about the adverse events from consumers and health professionals through product complaints, marketing, educational programs, and on-line activity. In 2017 Q3, the leading manufacturers submitting reports are shown in Table 1.

Table 1. Top 20 sources of adverse event reports in 2017 Q3

Rank	Company	Reports, (% all reports*)	
1	AMGEN	23,732	(8.1)
2	ROCHE	23,028	(7.9)
3	PFIZER	19,469	(6.7)
4	JANSSEN	18,769	(6.4)
5	**FDA-CTU****	16,012	(5.5)
6	NOVARTIS	13,895	(4.8)
7	CELGENE	12,182	(4.2)
8	ASTELLAS	9,658	(3.3)
9	ABBVIE	8,100	(2.8)
10	BRISTOL MYERS SQUIBB	8,047	(2.8)
11	BAYER	7,607	(2.6)
12	TEVA	7,342	(2.5)
13	GLAXOSMITHKLINE	6,888	(2.4)
14	BIOGEN	6,262	(2.1)
15	AVENTIS	5,976	(2.0)
16	ELI LILLY AND CO	5,744	(2.0)
17	MERCK	5,743	(2.0)
18	MYLAN	4,854	(1.7)
19	SANDOZ	4,031	(1.4)
20	ASTRAZENECA	3,773	(1.3)

*Percent of all reports from all sources in 2017 Q3

**Direct reports to the FDA.

Vortioxetine (Trintellix) and the Antidepressant Drug Controversy

More than three decades ago, a new generation of antidepressant drugs was first embraced as so effective that they rapidly replaced the standard treatment, psychotherapy.[8] Years later, it was revealed that nearly half of the clinical trials had failed to demonstrate benefit, and many had been systematically withheld by their pharmaceutical company sponsors,[9] helping to trigger new legal requirements for disclosure of all clinical trials.[10] Other systematic analyses showed small differences from placebo, mostly

confined to the most severely ill.[11] [12] For 15 years the FDA rejected reports that antidepressant drugs appeared to cause suicidal behaviors in some patients. Abruptly, the FDA changed course and required a warning on all drugs to treat depression (whether studied or not) but limited the warning to those 25 years old or younger.[13]

The controversy about true effects of antidepressant drugs did not prevent them from becoming the most widely used psychiatric drugs.[14] In women age 40 and older, about 1 out of 4 persons reported taking antidepressant drugs, with 68% using them for 2 years or more.[15] But the critical studies noted that over 6 to 8 weeks, patients taking an inactive placebo showed improvement similar to those taking an active drug. [12]. But in both treated and placebo groups the improvement in depression scores was substantial.

Reappraisal: "They All Are Effective"

In February 2018, a massive study published in *The Lancet* [16] and widely reported in the media concluded that all 21 antidepressant drugs studied were more effective than placebo. The study was written by an international team of extensively published researchers from Oxford University, Stanford, the Sorbonne, and other famed institutions. It analyzed more clinical trials (522) than any previous meta-analysis, and included both published and unpublished studies, head-to-head comparisons, and placebo-controlled trials. The appendix was the length of a small book (290 pages). It was widely written up in the medical news media, [17] [18] and *The Lancet* reported that it was the most widely read report in more than a month of published studies.

The *Lancet* study compared the percentage of "responders" to treatment between active drugs and a placebo, with responders defined as those with a 50% reduction in depression score over 6- to 8-week trials. The differences between drugs were modest and similar, despite a wide variety of mechanisms of action. The weakest result was for reboxetine (odds ratio (OR) = 1.37), a drug not approved in the U.S., and the strongest result was for amitriptyline, a tricyclic first approved in 1961 (OR = 2.13). Assuming that all the drugs had a beneficial effect on depression, was the difference large enough to matter?

Limitations of the *Lancet* study were important. The drugs were tested in the relatively small subset of patients with moderately severe depression or worse. A majority of patients have less severe forms of depression where treatment effects are smaller or nonexistent, and patients with mild to moderate depression are seldom enrolled in clinical trials. The duration of the clinical trials were 6-8 weeks, even though 68% of U.S. patients taking these drugs report long-term use.[15] The only measures of safety were the overall dropout rate and dropouts for adverse drug effects, even though most antidepressants have warnings or precautions for suicidal behaviors in young adults, life threatening serotonin syndrome, precipitation of manic episodes, sexual disfunction, weight gain, bone fractures, abnormal bleeding, and discontinuation effects.[19]

Enter Vortioxetine (TRINTELLIX)

An alternative approach to the complex meta-analysis is to examine carefully one typical antidepressant, its safety profile, and its largest and most completely reported clinical trials. In the *Lancet* meta-analysis, vortioxetine had the median, or middle ranking for efficacy; its OR = 1.66 compared to placebo, was lower than 10 antidepressants and higher than 10 antidepressants. In addition, it is the newest major antidepressant, launched in 2014 and featuring up-to-date FDA requirements and public disclosure of all clinical trial results.

Vortioxetine Efficacy for Approval

In seeking FDA approval, the sponsor–Takeda Pharmaceuticals U.S.A.–conducted 10 clinical trials of vortioxetine at various doses.[20] The results illustrated the marginal effect typical of antidepressant drugs. The FDA found that 4/10 trials did not provide evidence of a beneficial effect, and in 1 unsuccessful trial an approved comparator (duloxetine/CYMBALTA) also could not be distinguished from an inactive placebo. The efficacy claim depended heavily on foreign trials. Among the 5 trials in U.S. patients, 3 trials failed to

document a benefit. Even in the 2 trials the FDA scored as wins, no benefit was demonstrated at either the10 mg recommended starting dose, or a 15 mg starting dose. The results for this newest antidepressant confirmed and expanded a 2008 study that reported 49% of trials supporting the approval of 12 other antidepressant drugs failed to establish a drug benefit.[9]

Focus on Trial Results

To illustrate the actual results achieved for this typical antidepressant, we focused on the largest vortioxetine trial conducted in the U.S. and scored as a win by the FDA. The results are shown in Table 2 and illustrate several important points.

Table 2. Benefits of vortioxetine in U.S. effiacy trial #316

	Placebo	10 mg	20 mg
Patients studied			
Number enrolled	157	155	150
Percent dropped out*	12%	20%	19%
Results			
Starting MADRS score**	32.0	32.3	32.4
Last MADRS score	21.2	19.3	18.0
Percent improvement	34%	40%	44%
*Did not complete 8 w eeks			
**Severe depression ≥ 35. Moderate = 20-34. Mild = 7-18			
MADRS = Montgomery-Asberg Depression Rating Scale mean value			

The table above, assembled from the published report [21] and FDA statistical review, [22] illustrates these features of antidepressant trials:

- Over 8 weeks typical patient depression scores improved substantially, including those receiving an inactive placebo (34%) or either dose (40%, 44%). Differences *between* placebo and treatment groups were small, and for 10 mg vs placebo could have occurred by chance. The best result was about 3 points better than placebo on a MADERS depression scale of 0-60 in the 20 mg group.

- Treatment failure occurred in 19%-20% taking vortioxetine, who declined to complete the trial primarily because of adverse effects or lack of efficacy.

- The study was limited to patients with more severe forms of depression, where chances of demonstrating benefit are highest.

Safety Profile Enhanced

Over the decades that the FDA has been evaluating antidepressant treatments, the agency has added trial design features to resolve safety questions. One key adverse effect was sexual dysfunction. Early prescribing information for fluoxetine indicated fewer than 3% of patients volunteered information about sexual problems that might be drug-related. But when patients were directly asked about sexual dysfunction, the reported rates were 30% to 80%,[23] depending on the question asked. In response, the FDA began requiring a specific sexual function questionnaire–the Arizona Sexual Experience Scale (ASEX)–rather than relying on information volunteered by the patients at study visits. The results from the 10 trials pooled

together indicated vortioxetine impaired sexual function.[20] Overall, substantially more patients without sexual dysfunction at baseline reported new sexual dysfunction while taking the drug. The degree of sexual dysfunction varied by dose, from 20.0% for those taking a 5 mg dose (a rate similar to placebo) to a maximum of 34.3% for those taking the 20 mg dose.

In another change from earlier antidepressant approvals, the FDA also required systematic evaluation of suicidal thoughts and actions. A more systematic approach revealed that suicidal thoughts were common in this group of patients with moderately severe depression; thoughts of self-harm were approximately similar in all treatment groups, including placebo. For the rare-but-hard endpoint of attempted suicide, two events occurred in those treated with vortioxetine compared to none in the placebo group. These data contributed little to resolve concerns that antidepressants caused suicidal behaviors in some depressed patients previously without these issues. However, the more systematic data also established that among these more severely depressed patients, suicidal thoughts occurred frequently whether they were taking the active drug or a placebo.

Adverse Event Profile

For the 12 months ending 2017 Q3 we identified 1,981 adverse event reports with vortioxetine as the primary suspect drug. The patients had a median age of 39 years, and 69% were female. While the results included 45 cases with a death outcome and 171 cases requiring hospitalization, in 72% of cases the reported adverse effects were coded as not serious (n = 1,422).

The reported cases frequently indicated behavioral changes seen in various degrees for other antidepressant drugs, notably suicide/self-injury (n = 155) and hostility-aggression (n = 339).*

One of the most common side effects was nausea (n = 344), and it mirrored the results seen in the U.S. clinical trial summarized previously. In that trial 27%-29% of vortioxetine patients reported nausea compared to 5% taking an inactive placebo. It also illustrates that adverse event reports accurately reflect drug side effects, but the number of cases may be greatly underreported.

The increased rates of sexual dysfunction seen in clinical trials was also seen in these adverse event reports, with 160 cases indicating sexual desire disorders.

The postmarket data also highlight either a new or more severe side effect not clearly seen in clinical trials: eating disorders and weight gain. We noted these cases, which could include multiple terms in each: Weight increased in 201 cases; excessive hunger (hyperphagia) in 163 cases, and eating disorder, 69 cases.

Company Response

Additional insights into the vortioxetine reports emerged after we shared our preliminary findings on reported adverse drug events with the manufacturer, Takeda Pharmaceuticals U.S.A. The company reported that more than 400 of the reports described above, including many weight gain cases, were obtained from an online consumer survey in which patient views of their experience with vortioxetine were actively solicited. The company also said that changes in appetite and weight could have been part of underlying depression and did not constitute new safety signals.

The company perspective also illustrates key features of adverse event reporting. One reason why manufacturer-submitted adverse event reports have increased over the last decade is because of companies' increased contact directly with patients (in this case through an online survey). We also believe that the *number* of reports provides little information about the incidence of adverse effects, but nevertheless

* Identified using the Standardized MedDRA Query (SMQ), broad scope.

these reports (solicited or not) still indicate a possible association with the drug, especially if they are numerous.

Conclusions

This review of vortioxetine illustrates that the new meta-analysis in *The Lancet* fails to communicate the marginal efficacy and substantial side effect profile of typical antidepressant drugs. The placebo effects were large (32% improved substantially), and the difference from the drug effect might be too small to detect without a sensitive scoring instrument such as used in the trials. Only more severe depression was studied, likely because previous studies in mild and more moderate depression have failed. In these data we also saw a signal for a new side effect not previously prominent in other antidepressant drugs: eating disorders leading to weight gain. However, this adverse event needs further study to establish its validity, patient characteristics, and likely incidence.

Dispensing Errors, Name Confusion for Breo, Anoro Inhalers

We investigated more than 500 reports of drug name confusion or dispensing error concerning four oral inhaler products that GlaxoSmithKline (GSK) markets in the U.S. for asthma or chronic obstructive pulmonary disease (COPD). All four products used the same inhalation device, were promoted with the imbedded brand name "Ellipta," and had similar product labels with same size, shape, and typeface. Labels on the inhaler differed only in color and ingredient specifications. The products are shown in Table 3.*

Table 3. FDA-approved Ellipta inhaler products, 2017 Q3

Brand name	Ingredients	Disease target
Breo Ellipta	fluticasone; vilanterol	asthma, COPD
Arnuity Ellipta	fluticasone	asthma
Anoro Ellipta	umeclidinium; vilanterol	COPD
Incruse Ellipta	umeclidinium	COPD

QuarterWatch extends ISMP's direct national Medication Error Reporting Program (MERP) (https://www.ismp.org/merp) with ongoing surveillance of all medication error reports from all sources in the FAERS data. In this instance, the errors were first reported to ISMP through MERP, and described one year ago in *ISMP Medication Safety Alert! Acute Care*.[24] Reports through ISMP's MERP contain confidential but detailed information about exactly how the medication error occurred. In FAERS reporting, the errors are described in simple event preferred terms (PTs), with the narrative detail excluded for reasons of privacy and confidentiality. On the other hand, the volume of reports in FAERS is much larger than those sent directly to ISMP and later shared with the FDA.

Inhaler devices have been central to the treatment of asthma and other lung disorders for many decades. QuarterWatch estimates that in 2015 more than 15 million persons in the U.S. used an albuterol inhaler to manage acute asthma attacks, and 12 million reported using a fluticasone inhaler product, a corticosteroid that reduces lung inflammation. In 2013, GSK won FDA approval for Breo Ellipta, a combination product for asthma that featured fluticasone and new long-acting beta agonist, vilanterol.[25] It was the first GSK product to feature its new inhaler, brand named Ellipta, a circular shaped device

* An additional product Trelegy Ellipta (fluticasone, umeclidinium, and vilanterol) was approved in September 2017, but too recently to appear in the 2017 Q3 data.

constructed of 28 different parts and capable of combining 2 or 3 ingredients.[26] Three additional products, as noted above, were introduced later using the identical inhaler, and all had the device name embedded in the product brand name (*e.g.,* Anoro Ellipta). GSK reported that by 2016 the company had manufactured 30 million inhalers for worldwide use.[26]

The Adverse Event Data

For the 12 months ending 2017 Q3 we identified 557 reported cases of product confusion or dispensing or prescribing error for the four Ellipta branded inhaler products. This was a large report total of these medication errors compared to all other drugs. The Ellipta error reports are summarized in Table 4.

Table 4. Reported Ellipta product errors, 12-months ending 2017 Q3

	Number,(%)	
Specific product	557	
Breo	268	(48.1)
Anoro	238	(42.7)
Incruse	42	(7.5)
Arnuity	9	(1.6)
Type of Error*		
Product confusion	341	(61.2)
Packaging	173	(31.1)
Label	161	(28.9)
Other	7	(1.3)
Dispensing	306	(54.9)
Dispensed	288	(51.7)
Intercepted	18	(3.2)
Prescribing	87	(15.6)
Prescribed	65	(11.7)
Intercepted	22	(3.9)

*Includes multiple errors reported in 1 case

These data show that product confusion was widespread and linked to the new inhaler device. In addition, it involved all four products using the new inhaler. The confusion was reported as affecting physicians, pharmacists, and consumers.

The Sources of Confusion

Multiple reasons for the confusion were identified, but all were directly or indirectly linked to promotion of the inhaler device under the brand name “Ellipta.” These are the key problems:

- GSK combined ingredient brand name (e.g., Breo, Anoro) with the device name (Breo Ellipta, Anoro Ellipta). The ingredient brand names were, by design, sufficiently unique to identify the product without the inhaler information. But consumers receiving the package might easily believe the primary product name was “Ellipta.” In an FDA product name simulation prior to approval of

Incruse Ellipta, 5/63 practitioners believed the product was called “Ellipta.”[27] In addition, for other inhaler drug products, the device name sometimes comes first (*i.e.,* ACTUAT Flovent, ACTUAT Albuterol)

- The four different products were also provided in packages with identical designs, differing only in color, brand name, and ingredient specifications, all displaying “Ellipta.”

- Once the package was opened, the inhalers were identical, and labels on the inhalers were also of similar design, type size, and shape. Like the package, they differed in brand name, ingredient name, and dose.

- Although we saw few error reports for Arnuity Ellipta versus Anoro Ellipta, the similarity suggests a potential for confusion.

A Problem Made Worse

If consumers or practitioners visited the GSK product web sites to resolve the confusion–or learn how to use this new model device–they would be exposed to erroneous and misleading images of the product. For example, at https://www.mybreo.com/ the image is not what appears on the actual product. The web version prominently features the “Breo” brand name and no other information and does not resemble the actual inhaler label except in color.

Confusion increased for those who wanted information about how to use the new inhaler device with the video at https://www.mybreo.com/copd/about-breo/how-to-use-breo-ellipta.html. The carton (inside the package) says only “Ellipta.” The instructions for using the Breo product in the video show a non-existent product called “Ellipta.” (See Figure 1.) A reasonable person who had been dispensed the correct Breo product who had watched this video could incorrectly conclude they had been dispensed the wrong drug.

Figure 1. Image from Breo Ellipta instructions

Other Inhalers

While the reports for Ellipta products were the most numerous, name confusion reports were also numerous for another fluticasone inhaler product, ClariSpray Nasal Allergy Spray (n = 101). But for all other drugs, there were fewer than 15 reports involving name confusion or dispensing errors in the 12-month data.

Conclusions

We recommend that GSK redesign its web sites for all the Ellipta inhaler products to remove the incorrect product images and add clear links to resolve the confusion. In addition, GSK and the FDA should re-evaluate whether a more complete package and label design is now required, given that the original proprietary name assessments underestimated the potential for confusion and error. Given numerous reports for another inhaler manufacturer as well, the FDA should re-evaluate whether of the entire class of device-delivered drug products needs more consistent and clear brand name rules.

Discovering Dangerous New Use for Loperamide (IMODIUM A-D)

A story about the emergence of a new risk of a 40-year-old OTC drug begins with what happened to an ultimately very fortunate 39-year-old woman.[28] She was delivered to an emergency department in an ambulance after suffering seizure-like activity at work. She had just experienced three episodes in which she would start shaking, lose consciousness, and then awake spontaneously. While being evaluated in the emergency department she experienced two more episodes, one while being examined by a nurse, and another while connected to a cardiac monitor, which revealed the source of the problem. She was experiencing a frequently fatal disruption of normal cardiac rhythm. The cause was an OTC drug that millions of people have used to combat diarrhea, loperamide (IMODIUM A-D, others). But this woman had been taking 50 to 100 caplets a day, instead of the recommended maximum of 4. This episode, and others like it, illustrate new lessons about drug information, drug safety, and postmarket surveillance.

A Common Older Drug

The consumer wanting relief from traveler's diarrhea and reading everything on the bottle or in a package of loperamide would not learn that they were taking an opioid medication that is 40-50 times more potent than morphine–in the gut.[29] But absorption from the gut is poor, and beyond the blood-brain barrier the situation is mostly reversed; it takes a large amount of loperamide to induce a euphoric high.[30] Loperamide was approved in 1976, and because of what was seen as low abuse potential the FDA approved it for OTC use in 1988. A 1997 poison control center study found that nearly 60% of a sample of 216 overdose cases of loperamide were unintentional poisoning of 1-3 year old toddlers.[31] This cross sectional study suggested few safety issues at this time.

The FDA Acts

But in the years that followed, the situation changed. In June 2016 the FDA released a detailed Drug Safety Communication warning that abuse of loperamide was causing serious and fatal disruption of normal heart rhythm.[32] While the warning contained a clear and detailed analysis, it was apparently based on 48 case reports to FAERS received over 39 years. This is a small number in a system that captures more than 75,000 serious and fatal injuries in the U.S. per calendar quarter. In January 2018, the FDA issued an updated Drug Safety Communication [33] reporting that it was working with the manufacturers to develop abuse-resistant packaging with fewer doses. However, these communications did not report how many overdose cases might be occurring, or how the agency first learned of the issue.

Postmarket Surveillance

The primary source for abuse-related harms from loperamide was the oldest method of postmarket surveillance–published reports in the medical literature prepared by public-spirited pharmacists and physicians. Before the FDA began systematically collecting adverse event reports in a database starting in 1968, the medical literature was the primary source for the limited postmarket surveillance that occurred. Because they are prepared by medical professionals for scientific publication, case reports are typically of higher scientific quality than ordinary adverse event reports. But writing and publication can take a year or more. And health professionals were mainly interested in adverse events perceived to be novel. Because of

a decades-old regulation, the FDA is likely to learn of published reports because drug manufacturers are required to monitor the literature and report any cases into FAERS as MedWatch reports.

Thus, beginning around 2014, the medical literature began to feature case reports of near-fatal cardiac disorders linked to intentional loperamide overdoses, similar to the case described above. A case where the 19-year-old subject was found dead at home in Houston after hosting a party [34] revealed another problem: standard toxicology screens detected loperamide, but not overdoses.[35] When the North Carolina Office of the Chief Medical Examiner reviewed 21 deaths where loperamide had been detected, mass spectrometry established that the loperamide overdose contributed to 19/21 cases.[36] A more complete evaluation of loperamide toxicity, written by a team from El Paso, Texas, revealed two additional perspectives: Poison control center reports had doubled between 2009 and 2015; but while postmarket surveillance used the oldest techniques, substance abusers were more advanced, finding out that loperamide was a potent opioid using on-line google searches for “loperamide high.”[29]

Conclusions

The detection of loperamide abuse is a drug-safety episode with both positive and negative features. Public-spirited health professionals identified a new use/abuse of a common OTC diarrhea remedy. The manufacturers were monitoring the literature as required and forwarding relevant studies as adverse event reports. An alert FDA staff followed up with warnings and proposed abuse-resistant packaging. But it also illustrates that postmarket surveillance of OTC drugs relies not only on a voluntary reporting system, but also on health professionals investing substantial time and effort in preparing a report. And while the problem has been detected, analyzed, reported, and action taken, it took years, and how many overdose cases might have occurred remains unknown. Whether this was a rare but novel form of abuse–or a substantial safety issue–could not be determined because of limitations of the entire postmarket surveillance system. The lack of more effective systematic assessment of emerging and known drug harms remains a glaring defect not only for OTC drugs but for all therapeutic drugs. The number of persons injured by specific adverse effects of therapeutic drugs is rarely determined. New and better systems for detecting drug adverse effects continue to develop, but estimating the number of persons harmed and the drugs responsible remains a victim of continued neglect.

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