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ISMP

Acute Care ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

QuarterWatch™ (Quarter 3 2017)

Emerging risks with inhaled medications using the Ellipta device, the controversy with antidepressants, and loperamide abuse

The latest issue of ISMP's *QuarterWatch*™ (see box on **page 4**) examines drug safety issues identified by monitoring new adverse drug event reports submitted to the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). New data received during the third quarter (Q3) of 2017 include 291,999 adverse drug event reports from the US and abroad. In this issue, we examine:

- Errors due to confusion with the nomenclature, packaging, labeling, and online instructions for GlaxoSmithKline's line of inhalers using the Ellipta device
- The controversy with antidepressants, with perspectives from a large new meta-analysis published in *The Lancet* and a case study of the newest antidepressant to reach the market, vortioxetine (**TRINTELLIX**)
- Abuse of over-the-counter (OTC) loperamide (**IMODIUM A-D**, others); how it was identified reveals new insights into detecting emerging risks with older drugs

Errors with Breo, Anora, and other "Ellipta" Inhalers

New Ellipta devices. In 2013, GlaxoSmithKline (GSK) introduced **ELLIPTA**, a circular inhaler device capable of combining several active ingredients. The Ellipta brand name for this device was imbedded in the drug names of five products that use the device:

- **BREO ELLIPTA** (fluticasone and vilanterol), for asthma and COPD
- **ARNUITY ELLIPTA** (fluticasone), for asthma
- **ANORO ELLIPTA** (umeclidinium and vilanterol), for COPD
- **INCRUSE ELLIPTA** (umeclidinium), for COPD
- **TRELEGY ELLIPTA** (fluticasone, umeclidinium, and vilanterol), for COPD

Adverse events with inhalers. For the 12 months ending with Q3 2017, we investigated 557 adverse event reports indicating that patients, pharmacists, and physicians were confusing these inhaler products with the same Ellipta device but different active ingredients. Compared to all other drugs examined during this period, 557 reports is a large number. Most of the reported errors involved Breo Ellipta (48%) and Anoro Ellipta (43%). The reports indicated problems in one or more of these categories: name confusion (61.2%), dispensing errors (54.9%), and prescribing errors (15.6%). The product confusion reports indicated issues with both packaging and labeling. Although we saw few error reports for Arnuity Ellipta versus Anoro Ellipta, the similar brand names suggest a potential for confusion.

Causes of confusion. While the ingredient brand names (e.g., Breo, Anoro) are, by design, sufficiently unique to identify the products without the inhaler device information, some practitioners and patients appear to believe the products are named Ellipta or are mixing them up because of the common Ellipta name. A *Safety Brief* in the April 20, 2017, *ISMP Medication Safety Alert!*

Figure 1. Image from website for Breo Ellipta (left) compared to the actual product (right).

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Multivitamin injection label error. The vial label on the single dose **INFUVITE** Adult multiple vitamins injection, manufactured by Sandoz Canada (labeled PremierPro Rx) and distributed by Baxter, lists the folic acid content incorrectly. This is a two-vial product, with each vial containing 5 mL. Both vials are used for a single dose, which is added to 500 mL or 1 L of intravenous (IV) solution. The folic acid content in vial 2 is 600 mcg, but the label incorrectly states 600 mg (**Figure 1**). There is no folic acid in

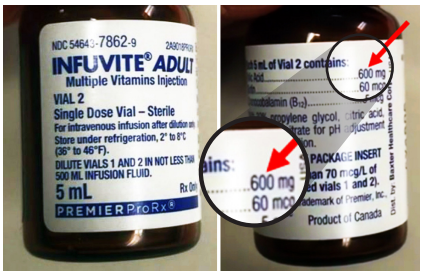

Figure 1. An Infuvite vial 2 label (front on left, back on right) lists the folic acid content as 600 mg, not the correct amount of 600 mcg, per 5 mL.

vial 1. The amount of folic acid in vial 2 listed in the package insert is correct. Sandoz is aware of the label error and is working to alert practitioners and correct the mistake.

HIGH-ALERT

Et "U" JAMA? A letter to the editor in last week's *Journal of the American Medical Association* (*JAMA*) discussed emergency treatment of hyperkalemia with insulin (Rushakoff RJ, Macmaster HW. Improving emergency insulin administration. *JAMA*. 2018;319[18]:1937-8). The authors did a nice job of highlighting the need to standardize the syringe used for IV insulin boluses to the recently available 100 units/mL luer lock syringe without a needle, which facilitates administration via a needleless port, rather than a 1 mL syringe that measures in mL or an insulin syringe with an attached needle. Unfortunately, the abbreviation "U" for units was used throughout the letter when referring to insulin dosing, despite the well known hazard of 10-fold insulin overdoses if the "U" is misread as a zero, especially when

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Acute Care newsletter noted this problem after ISMP received reports of confusion between the various inhalers, particularly when practitioners refer to these products only by the device name Ellipta and not the associated drug brand name. In that *Safety Brief*, we described a dispensing error in which a prescription for Incruse Ellipta was misread, and the more familiar Breo Ellipta inhaler was dispensed. The five products also come in similar packaging, differing only in color, brand name, and ingredient specifications. Once the package is opened, the inhalers are of similar design, shape, and size.

Online instructional videos and other materials for these products further increase the risk of confusion because they do not accurately distinguish between products. If consumers or practitioners visit the product websites to learn how to use this new inhaler device, they are exposed to erroneous and misleading images of the product. For example, at www.mybreo.com/, the image of the Breo Ellipta inhaler is different than the actual product. The web version prominently features only the "Breo" brand name, and the label contains no other information; "Ellipta" is missing, as are the generic drug names, strengths, and other important label information. The online picture of the inhaler label does not resemble the actual Breo Ellipta label except in color (**Figure 1**, page 1).

Worse yet, at www.ismp.org/ext/11, an instructional video about how to use the Breo Ellipta inhaler portrays the device with a label that only reads "Ellipta" (**Figure 2**). This perpetuates confusion between the products using the same Ellipta device but with different active ingredients. Or, it could make patients who watch the video believe they have been dispensed the wrong drug.

Figure 2. Image from Breo Ellipta video instructions only includes the device name on the product label.

Conclusion. GSK and the FDA should re-evaluate the packaging and labeling of the Ellipta inhaler products as a group given that the original proprietary name assessments seems to have underestimated the potential for confusion and error. GSK should also correct the inaccurate product portrayals on its websites.

The Controversy with Antidepressants and a Case Study of Vortioxetine (Trintellix)

Widespread antidepressant use despite limited efficacy. When modern antidepressants were first introduced more than 30 years ago, they were believed to be so effective that they rapidly replaced the standard treatment, psychotherapy. Years later, it was revealed that nearly half of antidepressant clinical trials had failed to demonstrate a benefit, with many trial failures never published by pharmaceutical companies. This helped to trigger new legal requirements for full disclosure of all clinical trial results. Other meta-analyses showed only small differences with placebo, mostly confined to the severely depressed. However, this did not prevent antidepressants from becoming the most widely used psychiatric drugs. While many patients will experience substantial improvement in depression a few weeks after starting an antidepressant, careful measurement of the drug effect itself is revealing. Add this to a longstanding history of reports linking antidepressants to suicidal behaviors in young adults, and the debate about the effectiveness and safety profile of antidepressants continues today.

Reappraisal: "All antidepressants are effective." The latest chapter in this debate came in February 2018 with publication in *The Lancet* of the largest antidepressant meta-analysis to date, which included published and unpublished studies encompassing 116,477 patients enrolled in 522 clinical trials of 21 antidepressant drugs (Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*. 2018;391[10128]:1357–66). The meta-analysis concluded that all 21 antidepressants "were more efficacious than placebo in adults with

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handwritten but even when typed or in electronic order sets. This has occasionally led to harmful or fatal errors. "Units" was fully spelled out in the original manuscript sent to the *Journal*. So, the authors were surprised to learn of the change, which must have occurred during the final editing process since previous versions of the edited letter had not included the change. The authors were mostly focused on getting the message out about the syringes used for IV insulin boluses, not protesting against the *JAMA* editorial policy. However, they have since sent a letter to the *JAMA* editor to inquire why the change was made and whether the editors are aware that "U" is an error-prone abbreviation disallowed by many agencies, including the US Food and Drug Administration (FDA) and The Joint Commission. How unfortunate that some journals still use error-prone abbreviations when most have eliminated them. Biomedical journals should serve as exemplars for patient safety, not set a bad example.

Inconsistent levETIRAcetam unit dose liquid labeling. An issue we first reported in our May 6, 2010 issue is back—inconsistency in the way the concentration of levETIRAcetam is expressed on unit dose cups. The 5 mL oral liquid products packaged by American Health Packaging and some other

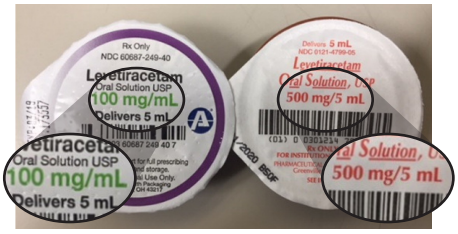

Figure 1. Unit dose cups from different manufacturers do not present the concentration in a standardized format.

companies list the drug concentration as 100 mg/mL rather than 500 mg/5 mL, as Pharmaceutical Associates and other companies do (**Figure 1**). A typical dose for initial treatment in adults is 500 mg BID. Given that this is a unit dose cup, practitioners are used to seeing "500 mg/5 mL" on cup labels. Those who fail to notice the words, "Delivers 5 mL," below "100 mg/mL" might assume they need to give 5 cups for a single dose, leading to an overdose. Because hospitals must often purchase alternative products during shortages, the US Food and Drug Administration (FDA) should not allow

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major depressive disorder." While it was one of the most optimistic and comprehensive assessments of antidepressants published in several years, the clinical trials studied were limited to patients with more severe forms of depression and lasted only 6-8 weeks, even though many people who take antidepressants do not suffer from severe depression and 68% report long-term use. In addition, the only measures of safety were the overall dropout rate and dropouts for adverse drug effects, even though most antidepressants warn about suicidal behaviors in young adults, life threatening serotonin syndrome, precipitation of manic episodes, sexual dysfunction, and other serious adverse effects.

Examination of vortioxetine. To dig a little deeper, QuarterWatch carefully examined the safety and efficacy of one of the 21 antidepressants in *The Lancet* meta-analysis, vortioxetine, as it had a median ranking for efficacy in the meta-analysis, and it is the newest major antidepressant to reach the market (2014). This meant up-to-date FDA requirements and public disclosure of all clinical trial results. The 10 clinical trials conducted to demonstrate efficacy at various doses illustrate the marginal benefits typical of antidepressants. Over 8 weeks, patients receiving both placebo and active drug improved substantially, with depression scores dropping by 34-44% in one large North American pivotal trial. But differences between placebo and treatment groups were small—only 2-3 points on a depression scale of 0-60. Three of 5 trials conducted in the US failed to document a statistically significant benefit, and in 1 unsuccessful trial, the efficacy of an approved antidepressant (**DUL**oxetine [**CYMBALTA**]) used for comparison to vortioxetine also could not be distinguished from placebo. The trials were also limited to patients with more severe forms of depression, where the chances of demonstrating benefit were highest.

To evaluate the safety profile of vortioxetine, QuarterWatch also examined the most recent adverse event data for the 12 months ending in Q3 2017. Vortioxetine had 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 also been reported with other antidepressant drugs. A new signal indicated that vortioxetine might also cause eating disorders (n=69) and weight gain (n=201), mainly from excessive hunger or abnormally large food intake (n=163). The manufacturer, Takeda Pharmaceuticals U.S.A., told us that many of the reports came from an online consumer survey, and might reflect symptoms of major depression rather than a drug effect.

Conclusion. The QuarterWatch review of a typical new antidepressant illustrates that *The Lancet* meta-analysis failed to communicate the marginal efficacy and substantial side effect profiles of antidepressant drugs. Patients' depression indeed improved substantially on vortioxetine treatment, but differences from an inactive placebo were small. Only more severe depression was studied, likely because previous studies in mild and more moderate depression had failed. We also saw a signal for a new side effect not previously prominent: eating disorders leading to weight gain. However, this signal requires further study to establish its validity, patient characteristics, and incidence. Besides antidepressants, it would be hard to identify another class of drugs that, despite decades of use, has more questions about efficacy and the incidence of severe adverse effects.

Discovering a Dangerous New Use for OTC Loperamide

New risk with an older drug. The emergence of a new risk with loperamide (e.g., **IMODIUM A-D**, others), a 40-year-old antidiarrheal drug long available over-the-counter (OTC), begins with a story about a fortunate 39-year-old woman who presented to an emergency department (ED) after experiencing episodes of seizure-like activity. While being evaluated in the ED she experienced two more episodes, one while connected to a cardiac monitor which exposed a life-threatening dysrhythmia. A loperamide overdose was the cause. In this case, the woman had substance abuse issues and had been taking 50 to 100 loperamide (2 mg) caplets a day, instead of the recommended maximum of 4 caplets. Loperamide is an opioid that is 40-50 times more potent than morphine in the gut. But absorption from the gut is poor, and little drug passes the blood-brain barrier at normal doses; thus, it takes a large amount of loperamide to induce a euphoric high or

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situations like this to exist. We recommend purchasing products that only list the amount of drug per container volume (500 mg/5 mL), or affixing an auxiliary label. We have notified FDA and American Health Packaging about the above concern.

Smart pumps may wind up at a different hospital. We recently learned about a smart pump from one hospital that was inadvertently left and used at another hospital after transferring a patient. While both hospitals were part of the same health system and used the same make and model of smart infusion pumps, each had different drug formularies and pump libraries based on the types of drugs, strengths, and/or dosing parameters used for their patient populations. Since the pumps looked identical and operated in the same way, the swap was initially overlooked. The hospital with the wrong pump recognized the problem after a nurse programmed it using a different concentration of oxytocin than used at her hospital. Fortunately, the patient was not harmed before the problem was noticed. Interestingly, some nurses in the health system stated they would never think that the same make and model of infusion pump would contain different drug libraries.

During investigation, the hospital found an identification sticker on the pump, which allowed it to be traced to the affiliate hospital from which a patient had been transferred. Months earlier, the biomedical engineering department at the transferring hospital discovered that they, too, had acquired a pump from the other hospital.

This is not the first infusion pump swap reported to ISMP. In one case, a nurse who needed to administer an infusion of ciprofloxacin was unable to locate the medication in the pump's library. Upon investigation, it was found that the pump belonged to another hospital, which was listed in a poorly visible heading on the pump screen.

To reduce the risk of unnoticed pump swaps, label pumps with the hospital name or be sure the hospital name is clearly visible on the primary infusion screen. Specific procedures for patient transfers should ensure infusion pumps are switched as soon as possible, and those not belonging to the organization are returned. Because of wide

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cope with withdrawal symptoms. The primary medical problem with a loperamide overdose is that it can cause potentially fatal cardiac events including QT interval prolongation, torsades de pointes or other ventricular arrhythmias, and cardiac arrest.

FDA issues warnings. Loperamide was approved in 1976, and because of what was seen as low abuse potential, FDA approved it for OTC use in 1988. But the word got out among substance abusers that if one took 10 to 20 times the recommended dose, the effects would be similar to using opioids such as morphine or oxy**CODONE**. In June 2016, FDA released a Drug Safety Communication that loperamide abuse was causing serious and fatal cardiac events. The warning was apparently based on 48 case reports to FAERS received over 39 years—a small number in a system that captures more than 75,000 serious and fatal injuries per quarter. In January 2018, FDA issued an updated Drug Safety Communication, reporting that it was working with the manufacturers to develop abuse-resistant packaging with fewer doses. However, these communications did not report how many overdoses might be occurring, or how the agency first learned of the issue.

Literature-based post-market surveillance. The primary source of abuse-related harm from loperamide turned out to be published reports in the medical literature prepared by public-minded practitioners—the oldest method of post-market surveillance in place long before adverse event reporting was required. Because literature-based reports are prepared by practitioners for scientific publication, case reports are typically of higher quality than ordinary adverse event reports. 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. An event in which a 19-year-old was found dead at home after hosting a party revealed another problem: standard toxicology screens detected loperamide, but not loperamide overdoses. When the medical examiner reviewed 21 deaths where loperamide had been detected, mass spectrometry established that loperamide overdoses contributed to 19 of the 21 deaths. Poison control centers also reported that loperamide overdoses had doubled between 2009 and 2015. As required, loperamide manufacturers were monitoring the literature and communicating relevant studies to the FDA via the FAERS. An alert FDA staff noticed the case reports, investigated, and followed up with warnings and proposed abuse-resistant packaging.

Conclusion. The way loperamide abuse was identified illustrates new insights into post-market surveillance and detecting emerging risks with older drugs. While FDA acted promptly, published a detailed risk assessment, and followed up with additional action to reduce those risks, it took years to identify the problem of abuse. Even today, the true incidence of overdoses remains unknown. Whether this is a rare but novel form of abuse or a substantial safety issue cannot be determined because of limitations with the entire post-market surveillance system. While voluntary reporting and contributed safety case studies clearly deserve praise, the lack of more effective systematic assessment of emerging drug harm remains a glaring defect not only for older drugs but for all OTC and prescription drugs. Better and more comprehensive systems are needed to assess emerging drug risks, estimate incidence, and support methods to reduce them.

The full QuarterWatch report with references can be found at: www.ismp.org/node/482.

What is QuarterWatch™?

QuarterWatch is an independent ISMP surveillance program that monitors adverse drug events reported to the FDA Adverse Event Reporting System (FAERS). The goal is to identify signals that may represent important drug safety issues. The sheer number of case reports have scientific weight, but because of variation in reporting rates, they reveal little about how frequently events occur and do not prove that the suspect drug caused the event described—only that an observer suspected a relationship. Thus, identified safety issues often require further investigation to determine their frequency and establish a causal relationship to the suspect drug.

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variability in drug libraries, nurses should be aware of the risk of an error if utilizing a pump that has been left behind with a transferred patient. If they cannot find the correct entry in the library, they should investigate rather than opt out of the library and infuse the drug without this important dose-checking safeguard (unless it's an emergency). If rental smart pumps are used, they should arrive at the hospital with a blank library and be loaded with the hospital-specific library prior to use. If interoperability exists, pumps that are foreign to the organization will not function. Although challenging, health systems should work toward standardizing smart pump libraries across affiliated hospitals as much as possible.

Special Announcement

ISMP Program at ASHP Summer Meetings

Join ISMP at the ASHP Summer Meetings and Exhibition in Denver, CO, on **June 4**, from 12:00-1:30 p.m., for a Promotional Theater, **Balancing Unpredictable IV Medication Supply with the Demand for Safe Injection Practices**. Ongoing drug shortages has made safe and effective IV drug therapy extremely challenging. ISMP experts will identify key safety issues and discuss error prevention strategies to implement during drug shortages. Space is limited, and preregistration is encouraged. For details, visit: www.ismp.org/node/1046.

To subscribe: www.ismp.org/node/10

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