March 28, 2019 ■ Volume 24 Issue 6

ISMP 25 YEARS ADVANCING MEDICATION SAFETY

Acute Care ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

QuarterWatch™ (includes data from Quarter 3, 2018)

Focus on three psychoactive drugs: gabapentin, pregabalin, and pimavanserin

The latest issue of ISMP's QuarterWatch™ (see description in box below) focuses on two older but widely used analogs of the inhibitory gamma-aminobutyric acid (GABA) neurotransmitter and a new type of antipsychotic medication approved for Parkinson's disease psychosis. Key findings include:

- Extensive patterns of potentially unsafe use of the GABA analogs, gabapentin (**NEURONTIN**, others) and pregabalin (**LYRICA**)
- New questions about both the safety and benefits of pimavanserin (**NUPLAZID**)

The following is a summary of the full QuarterWatch™ report, which can be found, with additional references, at: www.ismp.org/node/482.

Report Totals

In the third quarter of 2018, the US Food and Drug Administration (FDA) received 330,912 new adverse drug event reports involving 1,526 different medications. To capture a broader picture, we examined the most recent 12 months of available FDA Adverse Event Reporting System (FAERS) data, ending with September 2018. During this 1-year period, FDA received 1.4 million adverse event reports; 135,196 of the reports were associated with a fatal outcome. However, 43,781 (32%) of the reports of death included no additional information except that the patient died. Whether the drug contributed to the patient's death was not determined in these reports. For perspective, 43,781 is a greater number of deaths than annual US fatalities associated with motor vehicle accidents and twice as many as for homicides. Limited information about reported deaths was also an issue in evaluating pimavanserin, as discussed below. This illustrates the need to update FDA's adverse event reporting regulations and guidances, and to develop protocols for evaluating the possible role of a drug in a patient's death. Managing the risks of therapeutic drugs requires accurate information about serious injuries and deaths to which a suspect drug may have contributed.

Potentially Unsafe Use of GABA Analog Drugs

Gabapentin is approved to treat postherpetic neuralgia in adults and as adjunctive therapy for some forms of epileptic seizures. It is an analog or synthetic form of GABA, a major inhibitory neurotransmitter. A different formulation (gabapentin enacarbil) is approved for postherpetic neuralgia and restless legs syndrome under the brand **HORIZANT**. Gabapentin is so widely used for other purposes that it is

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What is QuarterWatch™?

QuarterWatch™ is the publication of an independent ISMP surveillance program that monitors adverse drug events reported to FDA by manufacturers, health professionals, and the public. The agency releases, for research and data analysis, excerpts of all domestic and foreign reports it receives into the FDA Adverse Event Reporting System (FAERS). The goal is to identify signals that may represent important drug safety issues which often require further investigation to determine their frequency and establish a causal relationship to the suspect drug.

SAFETY briefs

Herceptin Hylecta must be given subcutaneously. HERCEPTIN HYLECTA (trastuzumab and hyaluronidase-oysk) was recently approved by the US Food and Drug Administration (FDA) and will soon be available for adjuvant treatment of human epidermal growth factor receptor 2 (HER2) breast cancer. The new formulation is administered subcutaneously; it contains hyaluronidase, which helps increase the dispersion and absorption of trastuzumab. The usual dose of Herceptin Hylecta is 600 mg/10,000 units per 5 mL (120 mg trastuzumab/2,000 units hyaluronidase per mL) administered subcutaneously over 2 to 5 minutes, once every 3 weeks, alternating between the left and right thigh. No dose adjustments are needed for body weight, and no loading dose is required.

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ISMP is soliciting comments on UPDATED smart pump guidelines

A draft set of guidelines to optimize the use of smart pump technology and its intended safety benefits has been posted on our website for public comment. The guidelines were revised and expanded after ISMP held its second national summit on smart infusion pumps in 2018. The first summit in 2008 resulted in publication of the ***Proceedings from the ISMP Summit on the Use of Smart Infusion Pumps: Guidelines for Safe Implementation and Use*** in 2009. The updated guidelines expand upon critical topics such as infrastructure, the drug library, continuous quality improvement data, clinical workflow, and bi-directional interoperability with the electronic health record. The revised guidelines have already been reviewed by the summit participants and members of the Medication Safety Officers Society, but we would really value your input. To view the guidelines, visit: www.ismp.org/node/1497, and submit your comments and suggested edits by **April 26, 2019**, to: bfobi@ismp.org.

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reported to be taken by more adults (approximately 8.7 million adults take it annually) than any other psychoactive medication except **HYDRO**codone with acetaminophen.

The other GABA analog, pregabalin, is approved for the same indications as gabapentin as well as for fibromyalgia and neuralgia associated with diabetic neuropathy or spinal cord injury. Pregabalin is less widely used (approximately 1.6 million adults take it annually) and, unlike gabapentin, it is designated as a controlled substance (Schedule V). Pregabalin is only available as a brand product, Lyrica, which costs 40 times more than gabapentin (approximately $460 compared to $11.50 per month).

Using data from a large 2016 survey of medical care in the US,[1] we evaluated gabapentin and pregabalin patterns of use. We also analyzed the safety profiles of these two drugs using the most recent 12 months of FAERS data (13,692 total reports) and the literature. Through this analysis, we have identified a pattern of potentially inappropriate and unsafe use so pervasive that addressing it should rank as a major public priority.

Off-label and unapproved use. Both drugs are frequently used off-label to treat other forms of pain, migraine headaches, bipolar disorder, premenstrual syndrome, alcohol withdrawal, and a host of other conditions. Some physicians may use GABA analog drugs "for almost any type of pain," according to an editorial in the *New England Journal of Medicine* warning about the growing use.[2] Another commentary concluded that up to 95% of current gabapentin use could be for off-label indications.[3] The long history of off-label use was partially a result of company marketing campaigns that promoted unapproved uses, which subsequently led to hundreds of millions of dollars in civil and criminal penalties. Investigations connected to this litigation also revealed instances where the scientific literature had been deliberately manipulated to promote increased sales.

Abuse. Another safety concern is outright abuse, either to achieve a euphoric effect or in hopes of potentiating opioids, benzodiazepines, or sedative-hypnotics. In the FAERS data, more than 1,300 reports described withdrawal symptoms, drug abuse, intentional misuse, and overdoses. Hundreds of these reports described fatal overdoses, many of which involved combinations with other drugs known to be abused, notably opioids and anxiolytics. A 2017 survey of overdose deaths in Kentucky showed that 32% had included gabapentin in a cocktail of lethal drugs, most often morphine or fenta**NYL**.[4] Another study of opioid-related deaths in Canada found that 12.3% were also taking gabapentin, which nearly doubled the risk of death compared to those not taking gabapentin.[5] A study in Australia showed an increase in overdose and suicide deaths linked to the increasing use of pregabalin.[6]

Untested concomitant use. GABA analogs are often used concomitantly with other medications, increasing the risk of interactions, overdoses, or inhibition/potentiation of the effects of other needed medications. Our analysis of medication use revealed that half of all patients taking a GABA analog drug were also taking 10 or more other drugs. Specifically, 34.7% of patients taking a GABA analog drug were also sustained users of opioids; 17.8% regularly took another drug that activated GABA receptors (e.g., **ALPRAZ**olam, zolpidem); and 44% regularly took an antidepressant with a GABA analog. Because treatment failure is a common problem with antidepressants, it is possible that GABA analogs are being used off-label on the chance it might increase therapeutic effect. It also appears that antidepressants (mostly tricyclics) and GABA analogs might be combined in hopes of relieving chronic pain.

Other adverse events. In the 12 months of FAERS data, we analyzed more than 2,500 reports signaling that gabapentin or pregabalin was ineffective or had aggravated the condition. Nearly one-third of these reports were associated with an

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While the volume of most drug doses administered subcutaneously is usually no more than 2 mL, the volume of a single dose of subcutaneous Herceptin Hylecta is 5 mL, withdrawn directly from the vial without requiring further dilution. The hyaluronidase component allows larger subcutaneous volumes to be absorbed more quickly.

HERCEPTIN (trastuzumab) by itself has been available since the late 1990s and is administered intravenously (IV) over 30-90 minutes. With Herceptin Hylecta, the larger-than-usual volume per subcutaneous dose may lead practitioners to mistakenly believe it should also be administered IV. This is similar to confusion we have previously reported between subcutaneous-only **RITUXAN HYCELA** (ri**TUX**imab and hyaluronidase) and IV-only **RITUXAN** (ri**TUX**imab). Confusion between these two products has led to IV administration of Rituxan Hycela.

Furthermore, until recently, giving subcutaneous injections of chemotherapy at infusion centers was relatively uncommon compared to IV push doses or infusions, so the risk of route mix-ups is increased, especially when the product is first utilized and practitioners are unfamiliar with it. The advantage of the subcutaneous form of Herceptin Hylecta is that it can be administered in a much shorter amount of time than an IV infusion of Herceptin.

The list of trastuzumab-containing products approved by FDA is quickly growing. For example, **OGIVRI** (trastuzumab-dkst) was approved in December 2017; **HERZUMA** (trastuzumab-pkrb) was approved in December 2018; **ONTRUZANT** (trastuzumab-dttb) was approved in January 2019; and **TRAZIMERA** (trastuzumab-qyyp) was approved earlier this month. (See the Sidebar that follows about the 4-letter suffixes with new biological drugs.) Another formulation is **KADCYLA** (ado-trastuzumab emtansine), which is a conjugate between trastuzumab and emtansine. Ogivri, Kadcyla, Ontruzant, Herzuma, and Trazimera are only administered as IV infusions. None of the trastuzumab products are interchangeable.

By the way, with Herceptin Hylecta, the hyaluronidase component of the brand name

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unapproved indication, particularly with gabapentin. We also identified 729 reports of cognitive impairment, including memory loss, memory impairment, confusion, dizziness, and falls in which these drugs were designated as the "primary suspect drug."

Conclusion. Action is needed to reduce the inappropriate use of GABA analog drugs. Our analysis is consistent with concerns expressed in other scientific forums.[3,5,7] FDA should consider reclassifying gabapentin as a controlled substance (some states have already acted to restrict the drug[8]) and investigate other measures to reduce an overall pattern of unsafe use. Treatment guidelines and physician education are needed to discourage untested use and to increase patient monitoring to ensure prompt discontinuation in cases where the condition is aggravated, interactions occur, or the drug is ineffective.

FDA Reassurance of Pimavanserin Not Warranted

Pimavanserin is approved for treating hallucinations and delusions associated with Parkinson's disease psychosis. Unlike conventional antipsychotics, its primary effects are on serotonin rather than dopamine receptors. The November 2017 issue of QuarterWatch™ raised concerns about both the safety and benefits of this drug, which were also questioned in FDA's initial medical review, resulting in an unheeded recommendation to reject the drug.[9] Since then, other news media have reported additional safety concerns, notably hundreds of reported deaths in the FAERS data. After these safety concerns were raised in a Congressional hearing, FDA conducted a new safety review of pimavanserin. In September 2018, FDA announced the results of this review in a *Drug Safety Communication* (www.ismp.org/ext/181) advising that, "FDA analysis finds no new or unexpected safety risks associated with Nuplazid (pimavanserin)."

We obtained the complete FDA safety reviews, new studies, and the most recent 12 months of FAERS data through September 2018 to conduct a reassessment of pimavanserin. Our results? Rather than being reassured about the safety of the drug, we found weak and incomplete data on patient deaths, new questions about efficacy, and a misleading Boxed Warning in prescribing information that did not adequately inform about the possibility of increased risks and death. Here are the highlights of what we found:

Incomplete death reports. The FDA review focused on 893 reports of death, primarily submitted by the manufacturer, Acadia Pharmaceuticals. Most of the reports had such limited information that FDA safety reviewers could not determine whether pimavanserin contributed to death. Our review of the FAERS data now show 1,339 reported patient deaths since the drug was first approved in 2016 until September 2018, but 522 (39%) cases contained no event description beyond the report term "death." The company told us that its extensive direct contact with patients and caregivers likely led to the discovery of more cases of death than comparable drugs. The problem is compounded by FDA regulations that require a company to report within 15 days of discovering any patient death, whether or not a drug's role was suspected, investigated, or confirmed.

More questions about benefits. In pre-approval testing, pimavanserin did not demonstrate a statistically significant benefit in 3 of 4 clinical trials. Concerns about the lack of benefit with this drug were reinforced by new data from actual clinical use cited in FDA's review. It showed that after just 2 months, 45% of the patients started on pimavanserin had died or discontinued the drug. FDA concluded that the most plausible explanation for the high discontinuation rate had to do with "differences in how patients and their physicians would respond to an apparent lack of efficacy" in the real world as opposed to during a clinical trial. In addition, a large new clinical trial in a different patient population, Alzheimer's patients with psychosis, failed to show treatment benefit after 12 weeks.

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is *Hylecta*, not *Hycela* as it is with the Rituxan subcutaneous product. When referring to Herceptin Hylecta, we caught ourselves a few times saying "Hycela," not "Hylecta."

To prevent errors, it is important to employ barcode technology and to check the vial label to ensure that the drug being prepared and administered is subcutaneous Herceptin Hylecta (trastuzumab and hyaluronidase-oysk) and not IV trastuzumab or IV ado-trastuzumab emtansine. Also, affix a prominent auxiliary warning that states, "Administer subcutaneously in the thigh," on syringes containing Herceptin Hylecta, or utilize the peel-off sticker provided on the vial to label the syringe.

Sidebar: Why are we seeing 4-letter suffixes with new biologics?

What's up with all these 4-letter suffixes appearing alongside newly approved biological medications (e.g., trastuzumab and hyaluronidase-oysk)? In a guidance, ***Nonproprietary Naming of Biological Products*** (www.ismp.org/ext/204), issued by the US Food and Drug Administration (FDA) in January 2017, FDA clarified the need for identifying specific biological products with these suffixes to facilitate pharmacovigilance and safe use. The nonproprietary name for newly approved biological products is now a combination of the core name and a distinguishing suffix attached with a hyphen. This suffix is devoid of any specific meaning and is composed of 4 lowercase letters. The suffix applies to the entire drug name (e.g., the "-oysk" suffix for Herceptin Hylecta applies to the entire name, trastuzumab and hyaluronidase-oysk, not just the hyaluronidase component). The placement of the identifier as a suffix, rather than a prefix, should result in biological products with the same core name being grouped together in electronic databases to help healthcare providers locate and identify these products.

Unlike generic drugs, with biologicals, it's not possible to develop exact copies of the same molecule. Therefore, manufacturers may use slightly variant living organisms or processes to create products referred to as "biosimilars." The 4-letter suffix naming convention will help differentiate various

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Concerns about Boxed Warning. FDA's conclusion that no labeling changes were needed for pimavanserin was based in part on its view that even a substantial increase in mortality among patients taking the drug would be consistent with the existing Boxed Warning. The Boxed Warning says: "**INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.**"

The problem is that this warning applies to a different patient population—elderly patients with dementia rather than patients with Parkinson's disease experiencing hallucinations and delusions. The warning also refers to a different group of drugs, conventional antipsychotics that target dopamine neurotransmitters, and focuses on off-label use of the drug, not that pimavanserin might also increase mortality. A mortality study in Parkinson's patients showed that using conventional antipsychotics more than doubled the risk of death.[10]

Conclusion. Our reassessment of the recent FDA analysis provides no new reassurance that the benefits of pimavanserin treatment outweigh its risks. Instead the post-market data and a new study warrant increased concern. FDA should re-evaluate whether evidence exists to show the benefits of pimavanserin outweigh its risks, and if it does, the agency should clarify the Boxed Warning to say plainly that these risks could apply to pimavanserin.

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FDA Advise-ERR Covers still being applied without the cloNIDine patch

ISMP and the US Food and Drug Administration (FDA) continue to receive medication error reports about patients and caregivers who apply only the adhesive cover to the skin, without the intended clo**NID**ine medication patch. The error has contributed to uncontrolled blood pressure.

The clo**NID**ine transdermal system (**CATAPRES-TTS**) is packaged in a carton containing individually labeled pouches of 4 clo**NID**ine patches and 4 adhesive covers (**Figure 1**, page 5). Application of the adhesive cover is optional; it doesn't contain any drug and should be applied directly over the clo**NID**ine patch *only* if the patch begins to separate from the skin.

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versions of the same biological medication and ensure the safety of patients by identifying the specific product that may be associated with an adverse event.

When a biological nonproprietary drug name is used, it is highly recommended to express the full name, including the suffix, whether the biological is being added to an electronic health record (EHR) or identified in an adverse event report. ISMP also encourages using the brand and nonproprietary names together to provide redundancy and avoid name confusion. Incidentally, **RITUXAN HYCELA** (ri**TUX**imab and hyaluronidase) does not carry the 4-letter suffix because it was approved before the new naming convention was implemented for new originator products. FDA does not plan to add a 4-letter suffix to "grandfathered" biological products (www.ismp.org/ext/203).

HIGH-ALERT

Limited availability of 2,000 mL sterile water bags. Since October 2018, there has been a shortage of small volume sterile water for injection vials. Although the US Food and Drug Administration (FDA) allows extended use dates beyond the original expiration dates for Hospira's sterile water vials (www.ismp.org/ext/175; www.ismp.org/ext/176), the shortage has increased the demand for 250 mL to 3,000 mL bags of sterile water for injection. This has led to intermittent shortages of the larger-sized products as well (www.ismp.org/ext/177).

Additionally, it was previously brought to our attention that Vyaire Medical's Air*Life* 2,000 mL bags and bottles of sterile water for *inhalation* are not as available as the company's 1,000 mL sterile water bags or bottles. If orders for the 2,000 mL bags have been placed, the company says they will start distribution soon. But there will be a 2 to 4 week delay in receiving orders placed in the future. The quantity of 1,000 mL bags is limited, but there are no current distribution delays.

The limited availability of 2,000 mL sterile water bags for inhalation may impact an organization's ability to follow one of our ***Targeted Medication Safety Best Practices for Hospitals*** (TMSBP) (www.ismp.org/node/160). In TMSBP #10, we recommend eliminating 1,000 mL sterile water bags (labeled for "injection," "irrigation," or "inhalation") from all areas outside of the

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In 2010, ISMP published a ***SAFETY*** **brief** about a healthcare provider who applied only the adhesive cover to a patient for several weeks (ISMP. Cover applied without the medicated patch. *ISMP Medication Safety Alert!* 2010;15[22]:2-3). The adhesive cover is larger than the clo**NID**ine patch, which makes it difficult to confirm that the patch is under the cover. Also, while the individual pouches are labeled, the patches themselves are not labeled with the drug name, and the adhesive cover does not state that it does not contain any medication.

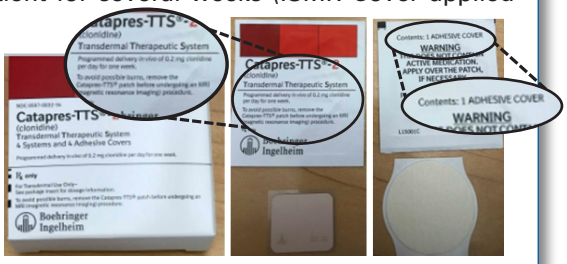

Figure 1. Box of Catapres-TTS-2 (left) containing pouches of individually wrapped clo**NID**ine patches and adhesive covers. The white, round adhesive cover (right) does not contain any drug and should be applied directly over the tan, square clo**NID**ine patch (middle) only if the patch begins to separate from the skin.

Please consider the following points to tell patients and caregivers to help them learn about the appropriate use of the clo**NID**ine transdermal system:

- The clo**NID**ine transdermal system is packaged in a carton that contains both clo**NID**ine patches and adhesive covers.
- The adhesive cover does **not** contain any medication.
- Only apply the adhesive cover if the clo**NID**ine patch begins to loosen from the skin after application during the 7-day period; if used, place the adhesive cover directly over the patch.
- Read the *Patient Instructions*, found in the carton, before using the clo**NID**ine transdermal system.

In inpatient settings, consider adding a note to the medication administration record (MAR) to remind nurses to apply the medication patch and not just the cover. If the adhesive cover is used over the medication patch, it is best to label the adhesive cover with the drug name, strength, and date, *before* applying it. (Note: do not write directly on the medication patch itself because it might affect the delivery of the drug.)

A hospital pharmacist, who recently reported an event, told ISMP that her hospital now dispenses the patch and cover in a zip-lock bag with a label explaining the two components of the product (medication patch and adhesive cover).

ISMP thanks Sarah Thomas, PharmD, and LCDR Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS, at the US Food and Drug Administration (FDA) Division of Medication Error Prevention and Analysis, for providing this ***FDA Advise-ERR****.*

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pharmacy. If sterile water must be stored in patient care areas or brought to the unit for respiratory use, we suggest using 2,000 mL bags to differentiate the sterile water from traditional intravenous (IV) bags containing 1,000 mL, thus decreasing the risk of accidental IV administration of the sterile water. As an alternative, we have also suggested using 3,000 mL bags of sterile water (e.g., for irrigation) or rigid plastic containers of sterile water if used for inhalation. Unfortunately, Air*Life* bags of sterile water are only available in 1,000 mL and 2,000 mL, although the company also provides sterile water for inhalation in rigid bottles (1,000 mL and 500 mL).

If the sterile water bags for injection are being used for reconstitution of dantrolene in malignant hypothermia carts, we recommend providing an adequate supply of sterile water vials if at all possible. During this 2,000 mL limited supply state, if your only alternative is to order 1,000 mL bags of sterile water, consider the use of auxiliary labels that clearly differentiate sterile water bags from IV bags if they must be stored outside of pharmacy.

Special Announcements

Deadline extended for FREE gap analysis

The submission deadline for the ISMP ***Gap Analysis Tool (GAT) for Safe IV Push Medication Practices*** has been extended to **April 30**, so there is still time to participate in this free assessment. Participants who submit their findings anonymously to ISMP by April 30 will receive a gap analysis score and have access to aggregate data. For details, visit: www.ismp.org/node/1188.

FREE ISMP symposia at TSHP meeting

If you are attending the Texas Society of Health-System Pharmacists (TSHP) Annual Seminar in April in **Frisco, TX**, don't miss ISMP's lunch symposia, ***Improving Intravenous Drug Delivery Safety*** on **April 12**. The program, sponsored by Fresenius Kabi, will also be presented at several other state health-system pharmacists meetings later in the year. For details and to register, visit: www.ismp.org/node/1469.

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