University of Illinois Hospital & Health Sciences System
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Jan/Feb 2016

RxPress

Vol 17 No 1

TABLE OF CONTENTS

Key updates to Beers Criteria in 2015

The American Geriatrics Society released the updated version of Beers Criteria for Potentially Inappropriate Medication Use in Older Adults in October 2015. The Beers Criteria attempts to identify and raise awareness on medications that may be inappropriate for use in elderly patients. This guideline should not be applied to palliative patients. The last revised version of Beers Criteria was released in 2012. A review panel performed comprehensive literature search and selected over 1,100 studies for full review from preliminary abstract screening of over 6,700 studies. Key changes that pharmacists should be familiar with include recommendations regarding nitrofurantoin, proton pump inhibitors (PPIs), Z-drugs, and new tables.

Nitrofurantoin

This recommendation is considered to be the most controversial as the updated Beers Criteria lowered restrictions for nitrofurantoin use to patients with creatinine clearance (CrCl) less than 30 ml/min or chronic use. The Beers Criteria 2012 stated that this medication should not be used in patients with CrCl < 60 ml/min. The main concern is possibility of irreversible pulmonary fibrosis, liver toxicity, and peripheral neuropathy with nitrofurantoin. The changed recommendation was based on the results of 2 retrospective studies.

Proton pump inhibitors (PPIs)

Proton pump inhibitors (PPIs) were added to the updated Beers Criteria with a recommendation to not use them for longer than 8 weeks. Patients may use PPIs beyond this timeframe if they require chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) or oral corticosteroids for their pre-existing conditions. Other conditions that permit use of PPIs for longer than 8 weeks include Barrett's esophagitis, erosive esophagitis, and hypersecretory conditions. Multiple studies and five systematic reviews and meta-analyses showed that prolonged intake of PPIs increases risk for *Clostridium difficile* infection, decreased bone density, and bone fractures.

New tables

Two new tables have been added: renal dosing of medications and drug interactions. Renal dosing table provides several medications that require dose adjustment in patients with decreased renal function. The table does not contain any anti-infective medications as the criteria's main focus is on medications for chronic use. The recommendations also do not include specific doses and only provide CrCl threshold at which medication doses should be reduced. The drug-drug interactions table provides only key interactions where concomitant medication use should be avoided. Both of these tables are not meant to be comprehensive lists.

Z-drugs

Nonbenzodiazepine benzodiazepine receptor agonist hypnotics, sometimes referred to as Z-drugs, should be avoided in all elderly patients and patients with dementia or cognitive decline. Z-drugs include eszopiclone, zaleplon, and zolpidem. These medications may cause delirium, falls, fractures, and increased emergency department visits. The benefits from these medications are minimal with studies showing only small improvements in sleep latency and duration.

Other notable medication changes

Antiarrhythmic medications in Class Ia, Ic, and III were removed from the list to avoid because the new data showed that rhythm control can be as beneficial as rate control. Amiodarone, dronedarone, disopyramide, and digoxin are still not recommended as first-line agents for atrial fibrillation. Desmopressin was added to the list of medications to avoid due to risk for hyponatremia.

Demystifying Drug Supply Chain Security Act (DSCSA)

The Drug Supply Chain Security Act (DSCSA) was signed into law on November 27, 2013 with a goal of protecting public from counterfeit, stolen, contaminated, and illegal medications by tracing medication distribution. This act would also improve efficiency for removing recalled medications from the distribution process. The DSCSA affects manufacturers, wholesale distributors, dispensers, which are mainly pharmacies, and repackagers. Over the next 10 years, the Food and Drug Administration (FDA) will release regulations, guidance statements, and guidelines for database creation facilitating compliance with this law. By November 27, 2023, interoperable electronic system for tracking medication distribution should be implemented among various parties.

The key components of the law consist of product identification, product tracing, product verification, detection and response, notification, wholesale licensing, and third-party logistics provider licensing. Product tracing, product verification, detection and response, and notification are the components that apply to pharmacies. Pharmacies must establish processes and systems for:

1. Tracking medications when ownership of medications is transferred between various organizations (product tracing);
2. Verifying that medications match the identifier assigned by manufacturers or repackagers (product verification);
3. Investigation and steps to quarantine medications that are suspected to be illegitimate (detection and response);
4. Reporting to the FDA if illegitimate medications are present (notification).

July 1st, 2015 was the original deadline for pharmacies to comply with product tracing, which was eventually postponed to November 1, 2015. Recently, this deadline has been postponed again to March 1, 2016 because the FDA realized that independent pharmacies and health systems may need more time to implement processes, tracking systems, and electronic software programs. For example, some pharmacies expressed concerned with the original deadlines because many manufacturers finalized their drug tracking templates only at the end of May 2015. This new deadline of March 1, 2016 is applicable only to pharmacies and not to manufacturers, wholesale distributors, and repackagers. However, as of July 1st, 2015, pharmacies are responsible for capturing and maintaining information on acquired medications and engaging in transactions only with legitimate trading partners. January 1st, 2015 was the deadline to create systems and processes for verification and handling medications that are suspected or confirmed to be illegal.

The law still does not address several issues that face hospital and health-care system pharmacies. For example, guidelines for “loan-and-borrow” situations between pharmacies and first responders do not exist. The tracking requirements for medications falling under 340B drug pricing program are lacking as well. Several pharmacies have expressed these concerns to the FDA and hope more guidance will be provided over the next 8 years.

Key dates for pharmacists to know:

Date	Action
November 27, 2013	The Drug Supply Chain Security Act (DSCSA) signed into law
January 1, 2015	Implementation of systems and processes to detect, respond to, and notify the FDA if illegal medications are present
March 1, 2016	Full compliance with product tracing regulations by pharmacies
November 27, 2023	Complete implementation of DSCSA and electronic interoperable medication distribution tracking system

Government actions to address the opioid epidemic

The Centers for Disease Control and Prevention (CDC) has drafted a guidance on prescribing of opioids for chronic pain in the primary care setting. The purpose of the guideline is to improve efficacy and safety of opioid use for chronic pain, enhance prescriber-patient communication on expectations and adverse effects, and reduce risks for overdose and death. The guideline encourages responsible prescribing at a time when the United States is dealing with an epidemic of prescription painkiller abuse and overdoses. From 1999 to 2013, the amount of opioids prescribed has quadrupled, and people who died in the United States from overdose related to opioids quadrupled to 16,000. This equates to 44 deaths daily.

In developing their guideline, the CDC considered clinical evidence from a 2014 systematic review performed by the Agency for Healthcare Research and Quality, as well as contextual evidence on alternative treatments, benefits and harms, values and preferences, and resource allocation. The CDC recommendations fall into 3 categories: determining initiation and continuation of opioids; identifying, dosing, monitoring, and discontinuing opioids; and assessing and addressing safety concerns with opioids. Some of the major recommendations that come from the guideline include the following:

- Preference should be given to nonpharmacologic and nonopioid therapy for treating chronic pain.
- Prescribers should establish realistic treatment goals with patients, and consider how opioids will be discontinued before initiating them.
- Immediate-release (IR) opioids are preferred over extended-release/long-acting (ER/LA) opioids when initiating opioid therapy.
- Prescribers should use additional precautions

when prescribing ≥50 morphine mg equivalents (MME)/day, and they should avoid prescribing ≥90 MME/day.

- Efficacy and safety should be evaluated within 1 to 4 weeks of initiating opioid therapy or increasing dosage, then at least every 3 months thereafter.
- Prescribers should consider offering naloxone to patients who have a history of overdose, substance abuse disorder, or are on daily dosages of ≥50 MME.
- Prescribers should review the state prescription drug monitoring program data at opioid initiation and at least every 3 months to help determine if a patient is at risk for overdose.
- Prescribers should use urine drug testing before starting opioid therapy and then at least annually thereafter.
- Prescribers should avoid prescribing opioids to patients also taking benzodiazepines.

The Food and Drug Administration (FDA) issued a special report in February 2016 that supports the CDC's draft guidelines on prescribing opioids. The report also highlights the issues associated with prescription opioid abuse, emphasizing the need to address the opioid epidemic while still providing effective treatment for those with chronic pain. The FDA has asked the National Academy of Medicine to help them review and revise their policies on opioid review, approval, and monitoring. The FDA will also be discussing their current Risk Evaluation and Mitigation Strategies for ER/LA opioids, with the possibility of expanding them to IR opioids. Manufacturers of ER/LA opioids may have expanded requirements for postmarketing data so that safety, misuse, and abuse with these products are more clearly delineated. The FDA will also work more closely with the National Institutes of Health on development of non-addictive alternatives (both pharmacologic and nonpharmacologic) for treatment of pain. The FDA Pediatric Advisory Committee will create evidence-based guidelines and policies for opioid use in children. Lastly, together with the Health and Human Services and industry, the FDA will develop a better evidence base for understanding the phenomenon of pain and how best to use opioids in the long-term setting.

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Switching between oral formulations of posaconazole

On January 2016, the Food and Drug Administration (FDA) released a safety announcement that oral formulations of posaconazole (Noxafil) are inappropriately switched and do not have 1 to 1 conversion. Currently, two oral formulations of posaconazole are available on the market: oral suspension (released in 2006) and delayed-release tablets (released in 2013). Delayed-release tablets are approved only for prophylaxis of *Aspergillus* and *Candida* infections in immunocompromised patients while oral suspension has the same indication and also additional indications for treatment of oropharyngeal candidiasis and oropharyngeal candidiasis that is not responsive to itraconazole and/or fluconazole treatment.

The table lists approved doses of oral posaconazole for prophylaxis of Candida and Aspergillus infections:

Oral formulation	**Dosing for prophylaxis of *Aspergillus* and *Candida* infections in immunocompromised patients**
Posaconazole oral suspension	Take 200 mg (5 ml) three times a day
Posaconazole delayed-release tablets	Take 300 mg twice daily on the first day, and then continue with 300 mg once daily

Pharmacists and other healthcare providers must be aware of labeled posaconazole dosing recommendations depending on type of oral formulation used. Delayed release-tablets have higher bioavailability than oral suspension of posaconazole. If converted incorrectly between oral formulations, patients may experience either supratherapeutic or subtherapeutic posaconazole levels. Subtherapeutic levels increase risk for insufficient prophylaxis for fungal infections while supratherapeutic levels may result in adverse events such as diarrhea, vomiting, edema, shortness of breath, heart and liver problems.

To date, the FDA has received 11 case reports with inappropriate conversion between the two oral formulations of posaconazole. One case resulted in death while another patient was hospitalized. In the case report involving death, a patient was inappropriately switched between oral formulations at a pharmacy, and his posaconazole levels fell into subtherapeutic range. The patient passed away from stroke related to *Aspergillus* infection.

Pharmacists and healthcare providers must exercise caution when switching patients between different oral formulations of posaconazole and remember that dosing differs based on the formulation utilized.