An Updated Focus on Adverse Drug Events
- by Allen Lefkovitz

Adverse Drug Events (ADEs) have been a significant focus of numerous national healthcare organizations, including the Institute of Medicine (IOM), the Centers for Medicare and Medicaid Services (CMS), and the Joint Commission (TJC). Within their “Adverse Drug Event Trigger Tool”, CMS defines an ADE as “an injury resulting from drug-related medical interventions.” CMS has provided both information and tools (including the “Trigger tool”) about adverse events in nursing homes at: www.cms.gov/Medicare/Provider-Enrollment-and-Certification/QAPI/Adverse-Events-NHs.html.

The need for a focus on prevention of ADEs has been strengthened by the study entitled “US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014” published on November 22, 2016 in the Journal of the American Medical Association (JAMA). Dr. Nadine Shehab et al. examined a national surveillance database of U.S. hospitals to further analyze 42,585 emergency department (ED) visits in 2013-2014 that involved ADEs.

Important findings from the JAMA article include:
- Slightly more than 1 in 10 ED visits for ADEs were due to a medication error
- 83.8% of ED visits for an ADE are linked to a single drug (not a combination of drugs)
- 34.5% of ED visits for ADEs occurred in those 65 years and older
- Overall 27.3% of ED visits for ADEs result in a hospitalization; however, for older adults, that rate increases to 43.6%

The top 10 drug classes implicated in both ED visits and hospitalizations from an ED visit are outlined in the figures below.

59.9% of ED visits for ADEs in those 65 years and older were due to anticoagulants, antidiabetic agents, and opioids
Selecting High Priority Targets
Unfortunately, as stated by Shehab et al., “The [four] most common drug classes implicated in ED visits for adverse drug events in the United States are the same ones identified a decade ago – anticoagulants, antibiotics, diabetes agents, and opioid analgesics.” With regard to the increasing attention to the opioid epidemic, it should be noted that even when investigators excluded reports that involved drug withdrawal, intentional self-harm, and recreational drug use or abuse, opioids remained one of the top 5 classes of drugs resulting in both emergency department visits and hospitalizations. Additionally, following the introduction of the newer anticoagulants beginning in 2010 (e.g., Pradaxa), the use of anticoagulants is estimated to have increased by 38%, but the rate of ED visits related to anticoagulants had increased by 57% by 2014. Thus efforts to improve the safe use of each of these drug classes must remain a priority.

In 2014 the U.S. Department of Health and Human Services released the “National Action Plan for Adverse Drug Event Prevention” (the ADE Action Plan) in an effort to reduce preventable ADEs and to increase the awareness about medication safety. The ADE Action Plan identified anticoagulants, antidiabetic agents, and opioids as primary targets. Although Shehab et al. found that 46.9% of all ED visits for ADEs were due to anticoagulants, antibiotics, or antidiabetic agents, when their research examined only those 65 years and older, 59.9% of ED visits for ADEs were due to anticoagulants, antidiabetic agents, or opioids – the identical targets identified earlier by the ADE Action Plan.

As each of these classes are seen as key targets for improving medication safety, specific strategies for improving their safe use have been individually focused upon in past HealthLine newsletters (available on Omniview):

<table>
<thead>
<tr>
<th>Anticoagulants</th>
<th>Antibiotics</th>
<th>Antidiabetics</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 2016</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

The most common ADEs associated with these four classes of drugs were identified in the JAMA article. Close monitoring for these ADEs is strongly recommended:

<table>
<thead>
<tr>
<th>Anticoagulants</th>
<th>Hemorrhage, lab abnormalities (e.g., ↑ INR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Allergic reactions, headache, anxiety, dizziness, syncope, weakness, secondary infections (e.g., Clostridium difficile, candidiasis), GI disturbance</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Opioids</td>
<td>Loss of consciousness, respiratory distress, falls or other injury, altered mental status, allergic reaction, syncope, dizziness, weakness, palpitations, hypotension</td>
</tr>
</tbody>
</table>
Moving beyond drug classes, Shehab et al. drilled down further to the specific drugs involved in ED visits. The top 10 drugs for all patients, as well as for older adults, are outlined below with the drugs in the top four target categories listed in red.

<table>
<thead>
<tr>
<th>Rank</th>
<th>All Patients</th>
<th>Patients ≥ 65 Years Old</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Warfarin</td>
<td>Warfarin</td>
</tr>
<tr>
<td>#2</td>
<td>Insulin</td>
<td>Insulin</td>
</tr>
<tr>
<td>#3</td>
<td>Clopidogrel</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>#4</td>
<td>Amoxicillin</td>
<td>Aspirin</td>
</tr>
<tr>
<td>#5</td>
<td>Aspirin</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>#6</td>
<td>SMX/TMP</td>
<td>Lisinopril</td>
</tr>
<tr>
<td>#7</td>
<td>Lisinopril</td>
<td>Metformin</td>
</tr>
<tr>
<td>#8</td>
<td>Metformin</td>
<td>Glipizide</td>
</tr>
<tr>
<td>#9</td>
<td>Ibuprofen</td>
<td>SMX/TMP</td>
</tr>
<tr>
<td>#10</td>
<td>Rivaroxaban</td>
<td>Dabigatran</td>
</tr>
</tbody>
</table>

SMX/TMP=Sulfamethoxazole/Trimethoprim

Prevention of ADE’s

To open their editorial about the JAMA article, Dr. Chad Kessler and two other physicians stated “Gains in life expectancy in the United States are being eroded at least in part due to the use and misuse of prescribed medications.” They proceeded to state that the Shehab study “suggests that the burden and patterns of adverse health outcomes due to prescribed medications are broader than previously thought.”

In their attempt to address the need for “rethinking and redesign[ing] how medications are prescribed, monitored, and discontinued”, these three physicians state that the three most effective interventions for preventing ADEs are as follows:

- greater involvement and integration of pharmacists;
- meaningful implementation and use of medication reconciliation; and
- inclusion of patients and their caregivers

As stated above, specific strategies for each class have been topics of previous issues of the HealthLine newsletter, but the overarching ideas for prevention of ADEs for each of these classes of medications could be summarized as follows:

- Provide frequent and updated education about proper use
- Ensure routine monitoring of all physical and laboratory parameters affected by use
- Frequently re-evaluate for appropriate use in order to avoid overuse, misuse or duplicate therapy
- Implement non-pharmacological treatment options prior to, and concurrently with the use of pharmacological options
- Be aware of patient-specific risk factors that increase the risk of harm with use
Methotrexate Safety Reminders

Methotrexate is used to treat many conditions including rheumatoid arthritis, psoriasis, and different types of cancers. The methotrexate prescribing information carries boxed warnings for several safety issues (e.g., gastrointestinal, hematologic, pulmonary, and hepatic). As a reminder, methotrexate is considered to be a High-Alert medication due to its heightened risk of causing significant resident harm when used incorrectly. In an effort to reduce the risk of medical errors and harm related to methotrexate, it is recommended that health care providers seek clarification for methotrexate orders described in the table below and in other clinical situations where there is uncertainty, inconsistency, or missing information (e.g., diagnosis for use). This is particularly important during transitions of care.

Methotrexate Scenarios of Concern/Clarification is Required

<table>
<thead>
<tr>
<th>QUESTION ANY ONE OF THESE</th>
<th>RATIONALE</th>
</tr>
</thead>
</table>
| Methotrexate dosed daily  | • For autoimmune conditions such as rheumatoid arthritis, methotrexate is usually administered as one to three DOSES PER WEEK given 12 hours apart. Mistakes involving daily use of methotrexate for rheumatoid arthritis (instead of weekly) has led to fatal toxicity.  
• For oncology, methotrexate is usually administered weekly but may be daily. |
| Methotrexate for autoimmune conditions (e.g., rheumatoid arthritis, psoriasis) without folate supplementation | • In chronic use situations, certain toxicities (e.g., oral and gastrointestinal) may be reduced by folate supplementation. This may not be applicable to cancer indications. |
| Methotrexate in a resident without cancer or an autoimmune condition | • Several medications start with the letters “met” or “meth” and are used for other indications. Ensure that methotrexate was not mistakenly selected during prescribing, transcription, or dispensing. Verify if the resident should be receiving methotrexate or another medication that starts with “met” or “meth” and the intended use and dosing. |
| Methotrexate without regular laboratory monitoring | • Patients receiving methotrexate should be closely monitored so that toxic effects (e.g., myelosuppression, hepatotoxicity, and nephrotoxicity) are detected promptly.  
• During therapy of rheumatoid arthritis and psoriasis, monitor a complete blood count (CBC) at least monthly, and renal function and liver function every 1 to 2 months.*  
• More frequent monitoring is usually indicated during antineoplastic therapy.  
• More frequent monitoring may also be indicated during initiation of therapy, dosing changes, or during periods of increased risk of elevated methotrexate blood concentrations (e.g., dehydration). |
| Orders with the abbreviation “MTX” | • “MTX” is an error-prone abbreviation that should NOT be used because it can be mistaken for mitoxantrone (a medication also used for certain cancers and multiple sclerosis). The complete drug name (e.g., methotrexate) should always be used. |
| Methotrexate weekly orders without the exact day for administration | • Specifying the day of the week helps reduce the risk of medication errors (e.g., once weekly on Wednesdays). In addition, it is recommended NOT to choose Monday as the specified day of the week for once weekly medication administration, as this could be confused with the word ‘Morning’*. |
| Methotrexate in other clinical situations (e.g., drug interactions, dehydration, renal dysfunction) that increase risk of methotrexate toxicity | • Fatalities have been reported as a result of drug interactions that increased the serum concentration of methotrexate leading to methotrexate toxicity.  
• Consider alteration of medication regimens as clinically appropriate. If interacting medications need to be administered, monitor for toxicities regularly. |

*Baseline assessment also includes complete blood count, hepatic enzymes, renal function tests, and chest X-ray (based on the prescribing information). Monitoring recommendations (e.g., frequency) from the American College of Rheumatology [http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines] may vary from the prescribing information.

## Important Drug Interactions with Oral Quinolone Antibiotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction and Monitoring</th>
</tr>
</thead>
</table>
| Sucralfate and select minerals: (e.g., aluminum, iron, calcium, magnesium, zinc, multivitamins) | Interfere with absorption of antibiotic and may lead to antibiotic treatment failure  
*Manage by separating quinolone administration as advised below:*  
- administer ciprofloxacin at least 2 hours before or 6 hours after  
- administer gemifloxacin at least 2 hours before or 3 hours after  
- administer levofloxacin at least 2 hours before or 2 hours after  
- administer moxifloxacin at least 4 hours before or 8 hours after  
- administer ofloxacin for at least 2 hours before or 2 hours after |
| Antidiabetic agents             | *Symptomatic hypo- and hyperglycemia, have been reported with the quinolones.*  
*Additional risk factors include advanced age and renal insufficiency.*  
*Monitor by checking fingerstick blood glucose at least daily for diabetics receiving a quinolone.* |
| Warfarin (Coumadin, Jantoven)   | *Quinolones may increase the anticoagulant effect of warfarin, increasing the risk for bleeding.*  
*Report any signs or symptoms of unusual bleeding from the gums or nose, unusual bruising, red or black, tarry stools, red, pink or dark brown urine, and/or an acute drop in blood pressure.* |
| Corticosteroids (e.g., Prednisone) | *Quinolones cause an increased risk for tendon rupture and tendinitis*  
*Use of oral steroids, age 60 years or older, rheumatoid arthritis, and/or renal failure increase the risk*  
*Discontinue quinolone if the patient experiences pain, swelling, or rupture of a tendon* |

## Regulatory Recap: CMS Adverse Event Trigger Tool:
Thromboembolism related to anticoagulant medication use

- by Carrie Allen

This trigger refers to the risk of a venous thromboembolic event occurring in residents, despite the fact that they are taking anticoagulant(s). Some risk factors for this are: prolonged immobility, recent major surgery, history of previous venous thromboembolism, and consistently sub-therapeutic INR (for those receiving warfarin).

The tool directs surveyors to look for specific documentation such as:
1. Is there evidence the facility routinely monitors lab results of all residents on anticoagulant/antiplatelet therapy?  
2. Is there a system to ensure lab results, including PT/INRs, are appropriately communicated to the physician including when sub-therapeutic values are obtained?  
3. Is there evidence that the facility educates caregivers on risk factors and signs and symptoms that may be indicative of thromboembolism?

Regarding the education of caregivers, CMS lists any of the following signs and symptoms as an indication that thromboembolism may have occurred:
- Pain or tenderness and swelling of upper or lower extremity  
- Increased warmth, edema and/or erythema of affected extremity  
- Unexplained shortness of breath  
- Chest pain  
- Coughing  
- Hemoptysis  
- Feelings of anxiety or dread
# NEW Drug

**Soliqua™ Subcutaneous Injection**

<table>
<thead>
<tr>
<th>Brand Name (Generic Name)</th>
<th>Soliqua [So lee kwa] (Insulin Glargine &amp; Lixisenatide) [GLAR jeen &amp; lix I SEN a tide]</th>
</tr>
</thead>
<tbody>
<tr>
<td>How Supplied</td>
<td>100 units insulin glargine per mL AND 33 mcg lixisenatide per mL in a 3 mL single-use pen.</td>
</tr>
<tr>
<td>Therapeutic Class</td>
<td>Long-acting human insulin analog with a glucagon-like peptide-1 (GLP-1) receptor agonist</td>
</tr>
<tr>
<td>Approved Indication</td>
<td>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide.</td>
</tr>
<tr>
<td>Usual Dosing</td>
<td>Starting dose: 15 units (15 units glargine/5 mcg lixisenatide) SQ once daily if inadequately controlled on less than 30 units of basal insulin or on any dose of lixisenatide; 30 units (30 units glargine/10 mcg lixisenatide) SQ daily if inadequate control on 30 to 60 units of basal insulin.</td>
</tr>
<tr>
<td>Select Drug Interactions</td>
<td>Drugs affecting glucose metabolism; antiadrenergic drugs (e.g., beta-blockers); antibiotics, acetaminophen and oral contraceptives should be taken at least 1 hour before or 11 hours after administration</td>
</tr>
<tr>
<td>Most Common Side Effects</td>
<td>Hypoglycemia, allergic reactions, nausea, nasopharyngitis, diarrhea, upper respiratory tract infection, and headache</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Inject within the hour prior to the day’s first meal. Do not exceed maximum dose (60 units glargine/20 mcg lixisenatide daily). Do not use with other GLP-1 receptor agonists. Monitor potassium in patients at risk of hypokalemia. Not recommended in patients with end-stage renal disease. Has not been studied in combination with short-acting prandial insulin.</td>
</tr>
<tr>
<td>Website</td>
<td><a href="http://www.soliqua100-33.com">www.soliqua100-33.com</a></td>
</tr>
</tbody>
</table>

# NEW Generic Medications

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Date Generic Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bimatoprost 0.03% Ophthalmic Solution</td>
<td>Latisse® Ophthalmic Solution</td>
<td>12/5/16</td>
</tr>
</tbody>
</table>
HealthLine Quiz
- by Steve Law

1. Which drug class is LEAST likely to lead to an ED visit due to an adverse drug event?
   a. Opioids
   b. Anticoagulants
   c. Diuretics
   d. Antipsychotics

2. Which is an effective intervention in preventing adverse drug events?
   a. Greater involvement and integration of pharmacists
   b. Meaningful implementation and use of medication reconciliation
   c. Inclusion of patients and their caregivers
   d. All of the above

3. Which is NOT a potential drug interaction of concern with the Quinolone antibiotics?
   a. Quinolones and sucralfate
   b. Quinolones and warfarin
   c. Quinolones and prednisone
   d. Quinolones and acetaminophen

4. Methotrexate should be dosed daily for the treatment of rheumatoid arthritis:
   a. True  b. False

5. Which of the following signs and symptoms may be an indication that thromboembolism may have occurred?
   a. Unexplained shortness of breath
   b. Pain or tenderness and swelling of upper or lower extremity
   c. Increased warmth and/or erythema of affected extremity
   d. All of the above

6. Which is a TRUE statement about the new medication, Soliqua™ subcutaneous injection?
   a. It contains a long-acting human insulin analog with a GLP-1 receptor antagonist
   b. The starting dose is 15 units SQ twice a day
   c. Acetaminophen should be taken at least 1 hour before or 11 hours after administering Soliqua™
   d. It is indicated to improve glycemic control in adults with Type-1 diabetes mellitus

*Please note, the HealthLine Quiz is designed to help readers retain information that is relevant to their care setting. It is not an approved source of continuing education credits for healthcare professionals.

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Answers to the HealthLine Quiz: 1) c  2) d  3) b  4) a  5) d  6) c