Potential Adverse Drug Events for Opioid Agents

Potential adverse drug events (pADEs) have been defined in several ways by several agencies in several publications. In many definitions, it is implied that pADEs occur due to medication errors or mishaps. Several definitions state that pADEs are also known as “near misses” or “close calls”. pADEs are medication-related problems (MRPs)/drug-related problems (DRPs)/medication-therapy problems (these may include, but are not limited to, medication errors).

The widely accepted definition of a MRP/DRP is “an event or circumstance involving medication therapy that actually or potentially interferes with the optimum outcome for a specific patient.” The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) defines a medication error as follows: “a medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.”

TMF Health Quality Institute recently developed a pADE data methodology to include Part D (drug data) and specific sets of drug-drug interactions (DDI) for anticoagulants, diabetic and opioid agents. For opioid agents, TMF, with the assistance of the University of Texas at Austin – College of Pharmacy, selected specific opioids and found that when paired with all selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine (Prozac)) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine (Effexor)), these drugs may cause “serotonin syndrome”, and is an opioid pADE drug-drug interaction to monitor.

Signs and Symptoms of Serotonin Syndrome

- Agitation (restlessness)*
- Diaphoresis*
- Diarrhea*
- Disseminated intravascular coagulation†
- Fever above 100.4° F (38° C)
- Hyperreflexia*
- Incoordination (ataxia)*
- Mental status changes
  - Confusion
  - Hypomania
- Multi-organ failure†
- Myoclonus*
- Ocular clonus
- Rhabdomyolysis†

*—Sternbach’s diagnostic criteria require three of 10 signs and symptoms.
†—Extremely severe cases.

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Potential Adverse Drug Event Opioid Drug-Drug Interaction Pairing Table

When pairing any of these drugs…

- Meperidine hydrochloride (Demerol)
- Oxymorphone hydrochloride (Opana)
- Fentanyl (Duragesic, Actiq, Abstral, Fentora, Subsys, Lazanda)
- Codeine and codeine combinations such as acetaminophen and codeine phosphate (Tylenol #3, Tylenol #4), promethazine with codeine, carisoprodol with aspirin and codeine phosphate
- Oxycodone (Roxicodone, OxyContin) and oxycodone combinations such as oxycodone hydrochloride and acetaminophen (Roxicet, Percocet, Endocet, Xartemis), oxycodone hydrochloride and ibuprofen (Combunox)
- Tramadol hydrochloride (Ultram, Ultram ER, Conzip, Ryzolt) and tramadol combinations such as tramadol hydrochloride and acetaminophen (Ultrace)
- Pentazocine lactate (Talwin) and pentazocine combinations such as pentazocine hydrochloride and naloxone HCL (Talwin NX), pentazocine HCL and acetaminophen (Talacen)

…with these SSRIs and SNRIs…

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celexa</td>
<td>Citalopram hydrobromide</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Lexapro</td>
<td>Escitalopram oxalate</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Prozac, Sarafem</td>
<td>Fluoxetine</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Luvox CR</td>
<td>Fluvoxamine maleate</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Paxil, Paxil CR</td>
<td>Paroxetine hydrochloride</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Pexeva, Brisdelle</td>
<td>Paroxetine mesylate</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Zoloft</td>
<td>Sertraline hydrochloride</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Effexor</td>
<td>Venlafaxine hydrochloride</td>
<td>SNRIs</td>
</tr>
<tr>
<td>Pristiq (ER), Khedezla</td>
<td>Desvenlafaxine succinate</td>
<td>SNRIs</td>
</tr>
<tr>
<td>Cymbalta</td>
<td>Duloxetine hydrochloride</td>
<td>SNRIs</td>
</tr>
<tr>
<td>Fetzima</td>
<td>Levomilnacipran hydrochloride</td>
<td>SNRIs</td>
</tr>
<tr>
<td>Savella</td>
<td>Milnacipran hydrochloride</td>
<td>SNRIs</td>
</tr>
<tr>
<td>Symbyax</td>
<td>Olanzapine and Fluoxetine</td>
<td>Atypical Antipsychotic and SSRI</td>
</tr>
</tbody>
</table>

…the patient has an increased risk of serotonin syndrome.