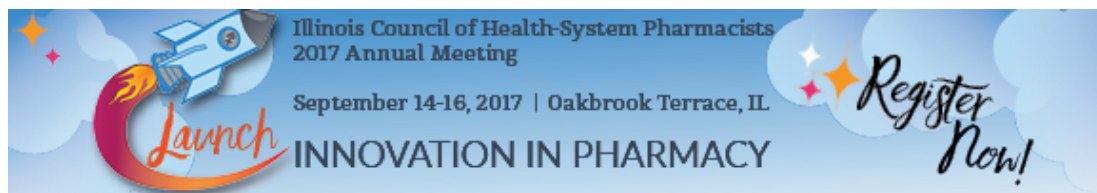




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## Educational Affairs

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### Loperamide: An Old Drug with Rising Concern

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#### Introduction:

Loperamide (Imodium®) is a synthetic opioid antidiarrheal medication that has been widely available over-the-counter since the 1980s.<sup>1</sup> Its chemical structure is similar to opioid analgesics. The prescribing information for loperamide states an “extremely low abuse potential,” which may contribute to a misconception about its safety, even at supratherapeutic doses.<sup>2</sup> At recommended doses, loperamide inhibits peristaltic activity in the large intestine. However, at supratherapeutic doses, loperamide is able to cross the blood-brain barrier and provide the euphoric effects commonly sought after in opioid abuse.<sup>1</sup> Loperamide has become known as a “poor man’s methadone” and is used both recreationally to achieve the same euphoric effect common to opioids and to avoid drug withdrawal. Recent evidence from the National Poison Data System has shown an increasing trend in intentional loperamide overdoses, leading to rising concerns over its opioid toxidrome and other serious toxicities such as life-threatening cardiac arrhythmias and death.<sup>1,3-8</sup>

#### Pharmacology:

Loperamide acts as a mu-receptor agonist, which decreases peristaltic activity. The recommended dose is 4 mg orally after the first loose stool and then 2 mg after each additional loose stool, not to exceed 16 mg per day, per the package insert.<sup>2</sup> Despite its opioid properties, it was once believed to have limited abuse potential due to its poor central nervous system (CNS) penetration. Loperamide is a known substrate for P-glycoprotein (P-gp), which limits its penetration into body tissues, particularly the CNS.<sup>7</sup> This exerts a protective mechanism by minimizing drug concentrations. It is also a substrate through the CYP3A4 and CYP2D6 pathways.<sup>3</sup> Concomitant ingestion with CYP3A4 inhibitors (e.g. statins, -azoles, cimetidine, grapefruit juice), CYP2D6 inhibitors (e.g. SSRIs) or P-gp inhibitors (e.g. methadone, verapamil, quinidine) could prevent metabolism, facilitate increased serum concentrations and increase CNS absorption of loperamide.<sup>7,9</sup> Loperamide has been reported to produce QTc prolongation and may also cause QRS widening, leading to ventricular tachycardia.<sup>10-13</sup> The U.S. Food and Drug Administration (FDA) also released a statement warning against the use of approved doses due to misuse or abuse because of this adverse

effect.<sup>14</sup> Notably, documented cases of QTc prolongation and other cardiac disturbances were in patients who had no previous cardiac history and were not on other QTc prolonging agents.<sup>10-13</sup>

#### Illinois Poison Center Data:

The Illinois Poison Center (IPC) managed 137 total loperamide exposures from 2014-2016. Of these, 18 patients overdosed for the purpose of abuse, withdrawal prevention, or treatment. Characteristics of these loperamide exposures include:

- Patients ranged from 18-60 years of age, with a mean age of 31 years.
- Loperamide doses ranged from 36 mg once to 400 mg per day for six years.
- 11 cases resulted in hospital admission.
  - Five of these cases required critical care unit admission.
  - No cases resulted in fatality.
- Three cases included respiratory symptom response with naloxone administration. However, these patients still required critical care unit admissions.
- Nine cases reported cardiac abnormalities.
  - Six of those cases reported EKG changes, including QRS widening, QTc prolongation, ventricular tachycardia, and cardiac arrest.
    - One patient presented with a QRS interval of 112 ms and a QTc interval of 726 ms.
    - Another patient presented with a QRS interval of 146 ms and a QTc interval of 526 ms.

#### Management:

- Patients should be monitored for CNS and respiratory depression.
- Laboratory evaluation requires monitoring of serum electrolytes, including potassium, calcium and magnesium.
- Vital signs, pulse oximetry and EKGs should be assessed. Continuous cardiac monitoring is recommended.

#### Treatment:

- If the patient is awake and alert, has a protected airway and has ingested loperamide within one to two hours prior to emergency department (ED) presentation, consider giving activated charcoal.
- There is no evidence for the use of dialysis, hemoperfusion or urinary alkalization to increase the elimination of loperamide from the body. Loperamide is highly protein bound (97%).
- To reverse respiratory depression, the patient should be given 0.4 mg of naloxone with repeat dosing as needed. Titrate carefully to prevent intubation but not cause opioid withdrawal in patients with chronic abuse. It is critical to note that naloxone may correct CNS and respiratory depression; however, it will not correct cardiac toxicity.
- Supportive care for cardiotoxicity/arrhythmias:
  - QRS widening: Bolus doses of IV sodium bicarbonate (50-100 mEq) to alkalinize arterial pH to 7.45-7.55 if the QRS complex is wide.
  - QTc Prolongation: Because hypokalemia, hypomagnesemia and hypocalcemia may contribute to a widened QTc interval, the following are recommended:

- Magnesium Sulfate IV 1-2 grams to maintain magnesium > 2 mg/dL. Additionally, magnesium sulfate is the first-line choice if the patient develops torsades de pointes.
- Potassium Chloride IV 20-40 mEq to maintain potassium > 4 mEq/L.
- Calcium Chloride IV 1 gram over two to five minutes; repeat as needed.
- In refractory cases, transvenous/transcutaneous pacing has been used.
- Defibrillation.

### Discussion:

Loperamide's widespread availability, low cost and large package sizes may contribute to misuse of this over-the-counter product.<sup>7</sup> For example, one big box retailer offers 400 caplets for the price of \$7.59. With increasing incidence of loperamide overdoses, healthcare professionals should be aware of loperamide's abuse potential, especially in patients who have a significant history of narcotic use or methadone maintenance therapy.

The potential for loperamide abuse should be considered when evaluating patients with a history of substance abuse who present to the ED with a drug overdose. However, screening for use could be difficult, as routine drug screens do not detect synthetic opioids.<sup>15</sup>

For immediate assistance in managing known or suspected overdose, pharmacists can call the IPC at 800-222-1222.

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