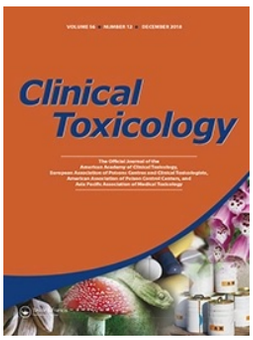

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REVIEW

Loperamide toxicity: recommendations for patient monitoring and management

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ABSTRACT

Who: This position statement is a collaborative effort by the American Academy of Clinical Toxicology (AACT) and the American Association of Poison Control Centers (AAPCC) and has been endorsed by the American College of Medical Toxicology (ACMT). The position statement describes loperamide misuse, proposed mechanisms of toxicity, adverse clinical effects, and recommendations for the acute monitoring and management of patients with loperamide toxicity.

Why: Use of high-dose loperamide for its euphoric effects and to self-treat opioid use disorder (in place of evidence-based therapies, like buprenorphine or methadone), is increasing. Despite reports in the medical literature and lay press, many remain unaware of high-dose loperamide use and how to manage patients with loperamide-associated toxicities.

Target audience: Providers in Emergency Medicine; Prehospital; Intensive Care; Internal Medicine; Primary Care; Gastroenterology; Addiction Medicine; Pharmacy

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KEYWORDS
Loperamide; cardiac toxicity; substance use disorder

The position of the AACT and the AAPCC, endorsed by the ACMT, is as follows:

Loperamide is a nonprescription antidiarrheal that is safe when taken in therapeutic doses; but when taken in large quantities or combined with medications that alter its pharmacokinetics, it exerts opioid effects in the central nervous system. These include, euphoria, central nervous system depression, miosis, and respiratory depression. Patients with respiratory depression may be treated with naloxone. A continuous infusion of naloxone may be used for patients with recurrent respiratory depression. When taken in large doses, loperamide also causes cardiac toxicity, manifesting primarily as conduction disturbances and dysrhythmias. Conduction abnormalities include, but are not limited to, QT prolongation, QRS prolongation, polymorphic ventricular tachycardia, Torsades de Pointes (TdP), and Brugada pattern. Management includes close cardiac monitoring and standard Advanced Cardiac Life Support (ACLS) measures for life-threatening dysrhythmias. For patients with recurrent dysrhythmias, additional treatments such as transvenous pacing or amiodarone can be considered. Providers should include loperamide toxicity in their differential diagnosis for patients with a history of opioid use disorder with a new cardiac conduction disturbance. While individual practitioners may differ in their management of patients with loperamide toxicity, these are the positions and recommendations developed by the AACT and AAPCC, and endorsed by ACMT, after review of the issue and scientific literature, and are current at the time of this writing.

Methodology

Initial recommendations are based on the opinion and clinical experience of the task force members. The authors performed a literature search and review prior to drafting this position statement. Additionally, the authors reviewed data for all loperamide exposures reported to the United States National Poison Data System (NPDS), which receives data from 55 regional Poison Centers, to the Canadian Association of Poison Control Centres (CAPCC), which receives data from 5 provincial Poison Centres, and from a recent publication [1] of data from the ACMT Toxicology Investigators' Consortium Registry (ToxIC), which receives patient data from toxicology bedside consultation from approximately 40 USA sites. These exposures were reviewed for demographic information and details of the exposure, including dose, time course, observed clinical effects, medical management, and reported medical outcomes. This document was reviewed and approved by the AACT Board of Trustees and the AAPCC Board of Directors and endorsed by the ACMT Board of Directors.

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Background

Opioid use disorder is a public health issue with significant impact in North America. The United States Centers for Disease Control and Prevention (CDC) preliminary statistics for 2017 report 49,068 deaths associated with opioid overdose, corresponding to a death rate of 15.1 persons per 100,000 population [2]. Opioid-related deaths have also increased in Canada, with almost 4,000 deaths in 2017 and a death rate of 10.9 persons per 100,000 population [3]. Despite increasing death rates in the United States and Canada, opioid related deaths in Latin American and the Caribbean remain well below the global average according to the United Nations Office on Drugs and Crime [4].

Loperamide is a safe and effective antidiarrheal agent when used at recommended therapeutic doses (2–16 mg daily) [5]. When loperamide became available without prescription in 1988, it was described as being "free of abuse potential" [6]. Loperamide exerts its antidiarrheal effect through inhibition of intestinal peristalsis via mu-opioid receptor agonism, calcium channel blockade, calmodulin inhibition, and reduction of paracellular permeability.

At therapeutic doses, loperamide has minimal central nervous system (CNS) activity because first-pass metabolism limits its oral bioavailability and p-glycoprotein extrusion limits CNS penetration [7]. However, in the presence of supratherapeutic dosing or pharmacokinetic manipulation, loperamide may reach CNS mu-opioid receptors and exert opioid effects. P-glycoprotein, an ATP-dependent drug pump, effluxes absorbed loperamide back into the intestinal lumen, into bile, and out of the CNS [8]. Concomitant use of loperamide with p-glycoprotein inhibitors is reported to increase loperamide's CNS activity [9]. Additionally, use of CYP 3A4 or 2C8 inhibitors is reported to increase loperamide's oral bioavailability [10,11]. Examples of xenobiotics reported to be used for pharmacokinetic manipulation include: quinine, proton pump inhibitors, famotidine, cimetidine, gemfibrozil, and itraconazole [9,11–13]. Additionally, there have been cases of CNS depression, respiratory depression, and fatalities following ingestion in infants, possibly due to their developmental lack of effective p-glycoprotein function [14–17].

High-dose loperamide

High-dose loperamide use was first reported in online-based forums as early as 2005, with approximately 70% of individuals reporting use of the drug to treat opioid withdrawal symptoms and 25% for its euphoric effects [18]. Between 2010 and 2015, there was a 91% increase in the number of loperamide exposure calls reported to the United States National Poison Data System (NPDS) [13]. Google trends, a measure of Internet search popularity, also shows an increase in search volume for the term "loperamide" during the same time frame [19,20]. Since 2010 there have been numerous cases reports and case series of high-dose loperamide use and subsequent toxicity published in the medical literature [3,13,20,21].

Poisoning databases have shown an increase in loperamide exposures in the United States and Canada. From January 1, 2012 to September 30, 2018, the NPDS reported 6606 cases of single substance exposures to loperamide (Table 1). The majority of exposures were reported to be unintentional (69%, $n = 4574$) and most resulted in no effect or minor effect (77%, $n = 5062$). There was also an increase in the number of cases of loperamide exposures reported as intentional "misuse" or "abuse", from 92 cases in 2012 to 272 cases in 2017 (Figure 1). There were 18 deaths reported during this time frame, including six deaths in 2018. During the same period of time, the CAPCC received 737 calls for single substance exposures to loperamide. The majority of exposures were unintentional (77%, $n = 569$) and resulted in no toxicity or minor effects in most cases (77%, $n = 565$). Major effects occurred in 14 cases and there were three deaths reported. The frequency of cases reporting "abuse" or "misuse" also increased during this time period, from 10 cases in 2012 to 20 cases in 2018 (data reported through September) (Table 2 for definitions of classification of clinical effects).

From January 2010 to December 2016, the ACMT Toxicology Investigators' Consortium Registry reported 26 cases of loperamide exposure. Intent was reported in 18 cases, with a majority being due to either "misuse" or "abuse" ($n = 12$, 67%). Additionally, 50% ($n = 6$) of patients who indicated loperamide "misuse" or "abuse" reported using it to avoid withdrawal symptoms. In these cases patients reported ($n = 4$) daily loperamide doses ranging from 160–400 mg to mitigate withdrawal symptoms. Cardiac dysrhythmias were reported in 23% ($n = 6$) of patients, 5 of whom were reported single-agent exposures, and all of whom reported doses of at least 200 mg. There were no deaths reported in this cohort [1].

Loperamide cardiac toxicity

Cardiac toxicity associated with loperamide and its metabolite, n-desmethyl-loperamide, are likely caused by inhibition of both cardiac delayed rectifier (hERG) potassium channels and cardiac sodium channels [22–24]. Both QT and QRS interval prolongation have been reported, with QT prolongation being more common [22,24–27] Although a

Table 1. Poison control center loperamide experience.

	AAPCC[a]	CAPCC[b]
Number of exposures from 01/01/2012 to 9/30/2018	6606	737
% Unintentional (*n*)	69% (4574)	77% (569)
No or Minor Effect (of cases followed to known outcome)	40% (2632)	20% (148)
Not followed (clinical effects not expected or no more than minor effect possible)	37% (2430)	57% (417)
Moderate or major effects	9.7% (641)	6.2% (46)
Deaths	18	3

[a]55 U.S. Poison Centers; [b]5 Canadian Poison Centres.

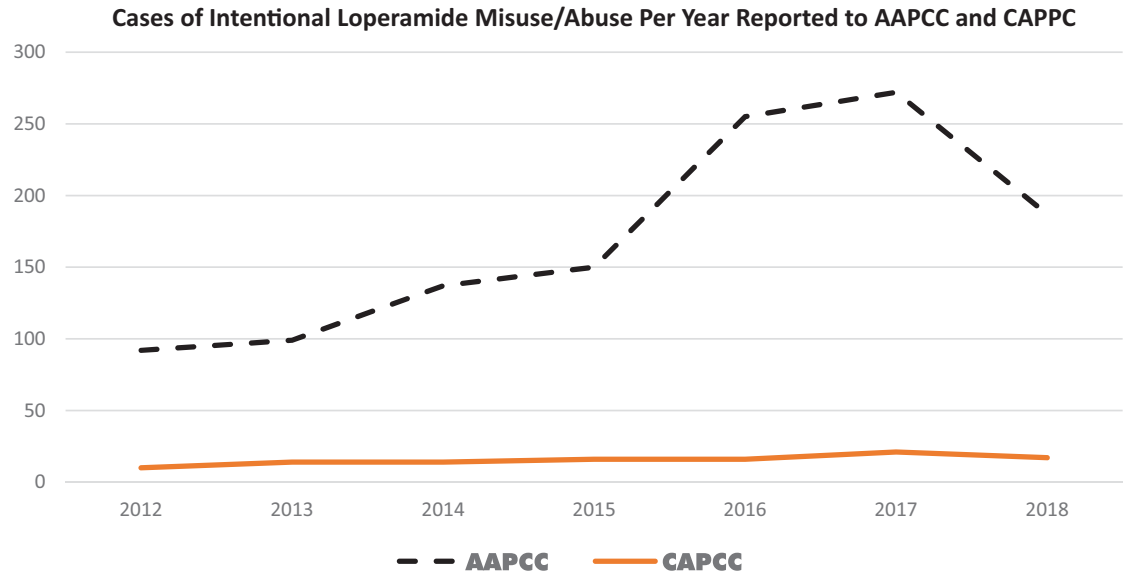

Figure 1. Loperamide misuse/abuse cases per year.

Table 2. Definitions of medical outcome from poison center data.

Description	Definition
No effect	The patient developed no symptoms as a result of the exposure.
Minor effect	The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms resolve rapidly and the patient returned to a pre-exposure state of well-being. Some examples: • Mild GI symptoms • Sinus tachycardia without hypotension
Moderate effect	The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Some examples: • Acid-base disturbance • Disorientation • Hypotension that responds to treatment • Single seizure which resolve spontaneously or readily responds to treatment
Major effect	The patient has exhibited symptoms as a result of the exposure which were life threatening. Some examples: • Repeated seizures • Ventricular tachycardia • Cardiovascular instability • Cardiac or respiratory arrest • Ventricular fibrillation • Unconsciousness
Death	The patient died as a result of the exposure or as a direct complication of the exposure where the complication was unlikely to have occurred had the toxic exposure not preceded the complication.

Adapted from the American Association of Poison Control Centers National Poison Data System Manual.

dose–response curve for cardiac toxicity has not yet been defined, the available clinical data suggest cardiac toxicity requires serum loperamide concentrations several fold higher than those that occur with therapeutic antidiarrheal doses [11,28,29].

Both opioid intoxication and cardiac conduction anomalies are known toxic effects of loperamide. However, it is important to recognize that these effects can, and do, occur independently of one other. Our clinical experience suggests life-threatening cardiac conduction abnormalities are often observed in the absence of opioid toxicity.

Loperamide fatalities

From 1976 through 2015, the United States Food and Drug Administration's (FDA) MedWatch database revealed 48 cases of serious cardiac adverse effects and 10 deaths. The median daily dose of loperamide in these cases was 250 mg (range: 70–1600 mg) and four cases reported concurrent use of a p-glycoprotein or CYP 3A4 inhibitor [13].

Loperamide associated deaths have been further detailed by the North Carolina Medical Examiner's Office, which reported 19 fatalities associated with loperamide toxicity [30]. Most of these fatalities listed loperamide as the primary cause of death (89%, $n = 17/19$), but it is not known if these deaths occurred secondary to cardiac or respiratory toxicity [30]. Two additional fatalities associated with high-dose loperamide use reported postmortem blood loperamide concentrations of 77 ng/mL (cardiac blood) and 140 ng/ml (femoral blood) [28]. It must, however, be noted that postmortem blood concentrations cannot be compared directly to those in living persons.

Treatment

Treatment of patients with loperamide toxicity is largely supportive and based on individual patient conditions. In addition to airway support, patients with respiratory depression after acute overdose should receive naloxone [15]. A starting dose of 0.4 mg naloxone is recommended, with dose titration to achieve stable respiratory status. A continuous naloxone infusion, titrated to maintain adequate respirations, may be necessary due to the prolonged duration of loperamide in overdose [31].

In the absence of contraindications, it is reasonable to administer a single dose of activated charcoal within the first several hours after an acute overdose [32].

Standard ACLS [33] measures should be used to manage patients with loperamide associated cardiac dysrhythmias. Synchronized cardioversion should be used for patients with ventricular tachycardia and hemodynamic instability and asynchronous cardioversion (defibrillation) should be used for patients with ventricular fibrillation or ventricular tachycardia without pulses. Patients with TdP or polymorphic ventricular tachycardia, who do not have spontaneous resolution of their dysrhythmia, should be treated with asynchronous cardioversion. Magnesium (2 grams) should be given intravenously (IV) over 5–20 minutes once there is a perfusing rhythm. Additionally, amiodarone or transvenous pacing can be considered for patients with recurrent dysrhythmias.

Electrolyte abnormalities, including potassium, calcium, and magnesium, should be corrected to prevent further QT prolongation. An empiric bolus of IV sodium bicarbonate 1–2 mEq/kg may be administered in patients with QRS widening and stable ventilatory status. However, the efficacy of this treatment remains unknown. It is imperative to monitor serum potassium, sodium, and pH closely in patients receiving sodium bicarbonate. Sodium bicarbonate induced hypokalemia should be corrected to prevent further QT interval prolongation. Although evidence is lacking, it is the opinion of the task force that in the event of cardiovascular collapse not responsive to standard treatment measures, extracorporeal membrane oxygenation (ECMO) or the administration of IV fatty acid emulsion, may have a role in treatment [29,34,35].

The duration of cardiac toxicity may be prolonged and patients may require several days of observation and treatment [31]. Patients with any evidence of new ECG abnormalities should be admitted and observed until these changes are resolved.

Additional recommendations

The AACT, AAPCC and ACMT recognize the challenge of providing patient care recommendations for a topic with limited data that is driven primarily by case reports and case series. However, it is essential that healthcare professionals are able to recognize and manage the toxicities of high-dose loperamide. It is important to consider high-dose loperamide use in the differential diagnosis of patients with unexplained syncope or a prolonged QT, especially in the setting of an opioid use disorder.

General Recommendations:

For Clinicians

- For patients with suspected loperamide toxicity, contact your regional Poison Center at 1-800-222-1222.
- Patients chronically using high-dose loperamide for its euphoric effects or to mitigate opioid withdrawal symptoms should be assessed for opioid use disorder and receive evidence-based treatment.
- Pharmacies should be aware that the purchase of large quantities of loperamide by a single consumer may pose an imminent health risk.

For Public health officials

- Educational campaigns are needed to increase awareness of loperamide misuse and subsequent risk of cardiac toxicity.
- Strategies analogous to other over-the-counter medications with lethal overdose potential, such as pack size limitations, should be considered.
  - We agree with the recent action taken by the US FDA to limit over-the-counter brand name loperamide products (Imodium A-D, Imodium Multi-Symptom Relief, and Be Health Loperamide HCl Capsules). These changes allow no more than 48 mg of loperamide to be sold in a carton and require each capsule or tablet to be packaged as an individual dose. The FDA is continuing to work with generic and liquid over-the-counter loperamide manufacturers to develop a strategy that supports safe loperamide use.

For Researchers

- Additional *in-vitro* and *in-vivo* research is needed to determine a loperamide dose-response relationship and to better characterize the mechanisms by which loperamide causes cardiac toxicity.
  - This is a key area for interdisciplinary collaboration and translational research.

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Disclosure statement

Dr. Palmer reports compensated participation in an expert panel meeting by the CHPA Loperamide Expert Panel prior to the preparation of this manuscript.

Dr. Marraffa reports to serve in an expert panel by the CHPA Loperamide Expert Panel. She did not receive financial compensation for this role.

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