LOPERAMIDE SAFETY IN OKLAHOMA

Loperamide Misuse

Oklahoma Osteopathic Association 123rd Annual Convention

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May 4th, 2023 1pm -1:30 p.m.

Objectives

- 1. Describe the history of loperamide misuse
- 2. Review the basics of loperamide dosing
- 3. Describe the clinical presentation of a loperamide overdose and associated cardiotoxicity
- 4. Discuss national initiatives to mitigate misuse
- 5. Introduce the Loperamide Safety Campaign

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Consumer Health Group Warns of Loperamide Abuse, Misuse

January 09, 2019, 08:47 am <u>News Staff</u> – The Consumer Healthcare Products Association (CHPA) wants to ensure family physicians know that improper use of loperamide (Imodium) -- specifically, taking it at very high doses -- can have serious, even fatal, cardiac effects.

In response to this concern, CHPA has launched a <u>Loperamide Safety education</u> <u>campaign</u> that offers clinical resources such as <u>fact sheets for general health care</u> <u>professionals</u>, <u>emergency health care professionals</u> and <u>mental health care</u> <u>professionals</u>, as well as <u>for patients</u>. <u>Additional resources for clinicians</u> include FDA drug safety communications and journal articles and case studies about the drug.

Loperamide is an important FDA-approved antidiarrheal medication sold both in OTC formulations and by prescription that is used safely every day by millions of people, said CHPA.

However, recent data suggest that a small but increasing number of people are taking extremely high doses of loperamide in a misguided attempt to self-manage opioid withdrawal or to achieve a euphoric high.



Loperamide (also sold under the brand name Imodium®) is a prescription and over-the-counter medication approved by the U.S. Food and Drug Administration to relieve the symptoms of diarrhea. Loperamide is safe and effective when used as directed. A small but growing number of individuals are intentionally misusing loperamide by consuming very high doses in an attempt to self-manage their optoid withdrawal or to achieve a euphoric high.

There are currently no treatment protocols for loperamide abuse or toxicity. However, it is important to recognize this issue and address it appropriately with patients who may be abusing or who may be at risk for abusing loperamide. Taking very high doses of loperamide can lead to serious cardiac events and death.

https://www.aafp.org/news/health-of-the-public/20190109loperamideabuse.html. Accessed 4/23

Loperamide Overview

- Loperamide, a safe and effective treatment for acute and chronic diarrhea, was first manufactured in 1969, marketed in 1977 (C-V), and approved for OTC use in 1988. The drug:
 - Treats many types of diarrhea except for invasive bacterial diarrhea
 - Decreases the number of bowel movements and reduces water in stools
 - Is a critical medication for adults and children with minor gastrointestinal issues.
- No alternative treatment has a comparable benefit/risk profile.
- The World Health Organization includes loperamide on its Essential Medicines list.
- Brands include Imodium[®] and other private labels.

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Loperamide Misuse Background



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Basics of Loperamide and Dosing

- Loperamide is a peripheral mu-opioid receptor agonist.
- At therapeutic doses (max of 16mg/day (Rx), 8mg/day (OTC)), loperamide:
 - Binds to gut wall opioid receptors, slows intestinal motility, thus allowing absorption of electrolytes and water
 - Inhibits the release of acetylcholine and prostaglandins, which results in reduced propulsive peristalsis and increased intestinal transit time
 - Is a substrate for *P*-glycoprotein, thus limits central nervous system (CNS) penetration
 - Has low oral bioavailability (<2%)
- At supratherapeutic doses (70–800 mg up to 1600 mg/day), loperamide:
 - Is known as a "poor man's methadone" (available online and on the shelves)
 - Allows users to self-treat opioid-withdrawal symptoms and produce euphoria

Basics of Loperamide and Dosing (Cont.)

- Loperamide is a substrate through CYP3A4, 2C8, 2B6 and CYP2D6 pathways.
- CYP3A4 inhibitors (statins, azole, cimetidine), CYP2D6 inhibitors (SSRIs), and *P*-glycoprotein inhibitors (methadone, verapamil) could prevent metabolism, increase serum concentrations, and increase CNS absorption.
- Genetic polymorphism of reduced *P*-glycoprotein activity might increase loperamide concentration by 50%.
- Loperamide is lipophilic and highly protein bound (95%).
- Its half-life is 11 to 34.8 hours.

Loperamide-Induced Toxicity

- High dose loperamide inhibits potassium, calcium and sodium channels.
- Cardiotoxicity complications: QT prolongation, Torsades de Pointes, QRS prolongation, ventricular dysrhythmias, syncope, cardiac arrest, and death
- CNS and respiratory depression: pinpoint pupils, unresponsiveness and hypoventilation
- N-desmethyl metabolite of loperamide can contribute to cardiotoxicity.

Management and Treatment

- Monitor for CNS and respiratory depression
- Monitor for serum electrolytes (potassium, calcium, magnesium)
- Provide continuous cardiac monitoring
- Monitor vital signs, pulse oximetry, and EKG
- For acute overdose (within 2–4 hours), consider administering activated charcoal
- To reverse respiratory depression, administer **naloxone** and can be repeated at 2 to 3 minute intervals.

Management and Treatment (Cont.)

- Provide supportive care for cardiotoxicity:
 - For QRS widening, administer bolus doses of IV sodium bicarbonate
 - For QTc prolongation, administer IV magnesium sulfate, IV potassium chloride, and IV calcium chloride
 - Cardioversion or defibrillation

Long-term treatment of Loperamide Misuse

- Buprenorphine, buprenorphine/naloxone
- Behavioral therapy and psychosocial support

Loperamide Misuse

- Epidemiologic trends from 2010-2015:
 - 91% increase in loperamide exposure
 - 1/3 of cases occurring in teens and young adults
 - 1,736 intentional loperamide exposures (abuse, misuse, suspected suicide and others)
 - Approximately 38 cases/year, including 15 deaths
- Loperamide abuse, toxicity, and deaths in the U.S. remain rare, according to the U.S. Food and Drug Administration's (FDA) Adverse Avent Reporting System (FAERS), which showed:
 - 18 deaths from 2012 to 2017
 - 11 deaths in 2017 and 13 in 2018

Cardiac Effects Reported in Loperamide Overdose Cases (National Poison Data System, 2009–2015)



ECG = electrocardiogram; v tach = ventricular tachycardia; v fib = ventricular fibrillation.

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Not a "Gateway"

- Loperamide is not a "gateway" drug to opioid abuse.
- Medical literature and FDA report that loperamide abuse is associated with patients who have preexisting opioid use disorder.

FDA 2016: "The majority of reported serious heart problems occurred in individuals who were intentionally misusing and abusing high doses of loperamide in attempts to self-treat opioid withdrawal symptoms or to achieve a feeling of euphoria."

Intentional Loperamide Exposures

Volume of Intentional Loperamide Exposures Reported to Poison Control Centers *January 2015 through December 2021*



Volume of Online Posts About Loperamide Misuse



Yearly Post Volume

No. of Posts

Year

Volume of Online Posts About Loperamide Misuse

- Talk about heroin to methadone withdrawal
- Use grapefruit juice to help with CYP3A4 inhibition
- Use prescription medications to enhance the CNS-related effects of loperamide: ketoconazole, fluoxetine, atorvastatin, clarithromycin, ritonavir
- Use OTC medications such as famotidine, cimetidine, omeprazole
- Use energy drinks containing quercetin and quinine

Oklahoma Data vs. National Data

- State-specific data is difficult to find, although Oklahoma Poison Centers collect and report to the American Association of Poison Control Centers.
- The Oklahoma Medical Examiner's Office conducts its own lab tests.
- In a Sept. 15, 2020, Interim Study Report, Dr. Byron Curtis, chief toxicologist for the Oklahoma Medical Examiner's Office, noted:

✓ "Saw first case in 2013 ... via normal tox screenings using outside lab."

✓ "Saw cases again the following year ... so developed our own tox testing."

✓ "Overall, [there were] 14 deaths from 2013 to 2016."

FDA Drug Safety Communications

In 2016 and 2018, FDA released two Drug Safety Communications on loperamide, which:

- ✓ Warned about the serious heart risks of extreme doses.
- ✓ Asked for packaging changes to encourage safe use.

"Black box warning: Cases of Torsades de Pointes, cardiac arrest, and death have been reported with the use of a higher than recommended dosages of IMODIUM."

"Heart alert: Taking more than directed can cause serious heart problems or death."

Packaging Changes

- FDA and industry announced new loperamide packaging changes in September 2019.
- Changes were implemented marketwide, both online and in stores.

Solid forms of OTC loperamide are now:

- Sold only in unit-dose blister packages.
- Available in a maximum of 48 mg per pack (24 count).

FDA Drug Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse

FDA limits packaging for anti-diarrhea medicine loperamide (Imodium) to encourage safe use

FDA Drug Safety Communication

FDA In Brief: FDA approves new packaging for brand-name over-thecounter loperamide to help curb abuse and misuse

Loperamide Safety Campaign



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CHPA and Industry Response

- In 2016, the Consumer Healthcare Products Association (CHPA) created the Loperamide Task Group to focus on loperamide abuse and misuse solutions.
- CHPA and the task group developed the Loperamide Safety campaign, a national awareness and prevention campaign.
- In 2021, CHPA developed the first state pilot campaign, Oklahoma Loperamide Safety.

National Campaign Approach

- Provide data-driven and responsible content
- Encourage prevention efforts and reinforce safe use
- Focus on educating healthcare providers who are most likely to treat patients with loperamide cardiotoxicity or interact with patients who are at highest risk of abuse
- Minimize potential behavioral contagion by targeting consumers who are likely already aware of loperamide misuse and are searching for information about loperamide

Oklahoma Campaign Approach

- Replicate the national campaign model at the state and local levels
- Customize resources and materials for the Oklahoma campaign
- Develop relationships with local experts and stakeholders

Oklahoma Campaign Objectives

- Prevent loperamide abuse and misuse while minimizing the risk of contagion
- Educate healthcare providers about loperamide abuse and its connection to opioid use disorder and the risk of serious cardiac events
- Educate at-risk consumers about the risks of abuse
- Promote the safe use of loperamide

Campaign Strategies

The five strategic pillars of the integrated campaign are:

- ✓ Website: Provide resources and information on LoperamideSafety.org.
- ✓ Third-party outreach: Reach healthcare providers through organizations and medical associations.
- ✓ Digital marketing: Reach healthcare providers through paid digital media and ads on LinkedIn.
- Key opinion leaders: Invite leaders to champion campaign messaging.
- Social listening: Monitor online conversation about loperamide abuse and misuse.



Oklahoma Campaign Audiences

Healthcare providers

- Behavioral health specialists
- Emergency medicine specialists (emergency department physicians, nurses, physician assistants, nurse practitioners, and emergency medical technicians).
- Pharmacists
- Gastroenterologists
- At-risk consumers

Campaign Website for Healthcare Providers



Oklahoma-specific website for healthcare providers: LoperamideSafety.org

Campaign Webpage for At-Risk Consumers

UNDERSTANDING THE RISKS OF MISUSING LOPERAMIDE **Oklahoma-specific** webpage for at-risk Loperamide (also sold under the brand name Imodium®) is a prescription and over-thecounter (OTC) medicine approved by the U.S. Food and Drug Administration to relieve the consumers: symptoms of diarrhea. LoperamideSafety.org/ Loperamide is safe at approved doses: a maximum of 8 mg per day for OTC use or as instructed by your healthcare provider. consumers Taking more than the approved dose can result in serious heart problems and death. If you or someone you know is taking more than the recommended dose of loperamide and experiences any of the following symptoms, discontinue loperamide use immediately and call 911. Fainting

Unresponsiveness

. Irronular heartheat or chest pain

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UNDERSTANDING THE RISKS OF MISUSING

LOPERAMIDE IN OKLAHOMA



Loperamide (also sold under the brand name Imodium*) is a prescription and over-the-counter (OTC) medicine approved by the U.S. Food and Drug Administration (FDA) to help relieve symptoms of diarrhea. Loperamide is safe at approved doses: a maximum of 8 mg per day for OTC use or as instructed by your

Taking more than the approved dose can result in serious heart problems and death.

If you or someone you know is taking

- more than the recommended dose of loperamide and experiences any of the following symptoms, discontinue loperamide use immediately and call emergency services.
- Symptoms to Watch For:
- » Fainting
- Unresponsivene Ø Gastrointestinal complication

» Irregular heartbeat

If you believe that you or someone you know may have a substance use disorder, call 2-1-1 for free,

TO LEARN MORE about loperamide, visit KNOWYOUROTCS.ORG/INGREDIENT/LOPERAMIDE

For patients and consumers.

Collateral Development – Fact Sheets



Campaign

fact sheets

providers

Collateral Development – Video

Determine of the signs of

The video features Jeanna Marraffa, PharmD, and loperamide misuse survivor Katharine Rayland, RN.

Video for healthcare providers

Paid Media – Healthcare Providers

CHPA

LinkedIn ads targeting healthcare providers



Ads drive healthcare providers to the Oklahoma Loperamide Safety website homepage and the healthcare provider resources webpage, where they can learn about loperamide abuse and download resources.

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2,117 followers

Paid Media – At-risk Consumers

Google search ads targeting at-risk consumers



Ads drive users searching for loperamide abuse-related terms to the Oklahoma Loperamide Safety webpage for at-risk consumers, LoperamideSafety.org/consumers.

Conclusions

- When used at therapeutic doses, loperamide is safe.
- People with opioid use disorder are turning to alternatives to treat withdrawal or to achieve a euphoric high.
- Loperamide misuse is uncommon.
- More research is needed on the mechanisms of toxicity.
- Collaborative efforts for translational research are paramount.
- Educating healthcare providers is one step toward preventing deaths from loperamide cardiotoxicity.

Visit LoperamideSafety.org to download fact sheets and read the latest scientific literature.

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Thank you!

References

- Reinert JP, Dunn RL. Management of overdoses of loperamide, gabapentin, and modafinil: a literature review. Expert Rev Clin Pharmacol. 2019:12(9):901-908
- Wu PE et al. Clinical Review: Loperamide Toxicity. Ann Emerg Med. 2017;70(2):245-252.
- Stanciu CN, Gnanasegaram SA. Loperamide, the "Poor Man's Methadone": Brief Review. Journal of Psychoactive Drugs. 2017 Jan-Mar;49(1):18-21. DOI: 10.1080/02791072.2016.1260188. PMID: 27918873.
- Vakkalanka JP, Charlton NP, Holstege CP. Epidemiologic trends in loperamide abuse and misuse. Ann Emerg Med. 2017;69(1):73-78.
- Understanding loperamide abuse. Loperamide safety. www.loperamidesafety.org/home-1. Accessed on 4/18/23.
- Imodium (loperamide) [package insert]. Raritan, NJ: Janssen Pharmaceuticals; 2016.
- De La Cruz, A et al. Pharmacist Review of Loperamide Abuse. <u>https://journalce.powerpak.com/ce/pharmacist-review-of-loperamide-abuse</u>. Accessed on 4/18/23.