Pharmacovigilance and Drug Safety Considerations of Loperamide as an increasing drug of abuse: a report of 3 cases and an analysis of the FDA FAERS database from 2002-2022

1Raj Masih, 2Barbra Masih, 3Kaylin Arbaugh, Janaina Rodrigues Dos Santos, 4Michael Philbrick, 5Hunter Pool, 6Himan Bhatia, 7Kshiraj Panchal, 8Alex Mongold, 9Cameron Masih, 10Christian Landis, 11Sidney Cullers

1MD, MPH, FRSPH, Potomac Highlands Mental Health Guild, West Virginia, United States
2MS, LPC, CRC, NCC Prevention Specialist, Department of Substance Use Prevention, Potomac Highlands Mental Health Guild, West Virginia, United States
3BS, Coordinator BUMPS Program, Department of Substance Use Counseling, Potomac Highlands Mental Health Guild, West Virginia, United States
4BS, Research Assistant, Department of Substance Use Prevention, Potomac Highlands Mental Health Guild, West Virginia, United States
5MS, Engineering, Oracle Argus Data Scientist, Morgantown, West Virginia, United States
6MS, Research Assistant, Morgantown, West Virginia, United States
7BS, Information Technology Technician, Potomac Highlands Mental Health Guild, West Virginia, United States

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*Corresponding author: Dr. Raj Masih, MD, MPH, FRSPH, Potomac Highlands Guild, 7 Mountain View Street, Petersburg, West Virginia, 26847, United States. Tel: +1 (304) 668-6329; E-mail: rajm@phgmail.net

Abstract
Loperamide is an anti-cholinergic, opioid, anti-diarrheal drug sold over the counter, that when taken in large amounts can cross the blood-brain barrier and act as an opioid agonist. Thus, it can have similar effects to other opioids such as euphoria, but also respiratory depression. Due to opioid effects and easy accessibility, it is abused and used to manage withdrawal symptoms from other opioids by people with substance use disorders who are not in formalized treatment programs. However, many adverse effects can also happen when loperamide is taken in large quantities including cardiac events such as dysrhythmias, Torsades de Pointes, and cardiac arrest. Loperamide abuse is particularly common in special populations such as those who are pregnant or justice-involved because they undergo frequent drug testing and standard drug screens do not test for it. Since 2002 there has been an increase in reports of severe cases of adverse effects due to loperamide abuse. This increase in adverse events such as cardiac toxicity and even death, combined with the easy accessibility and lack of public awareness of this toxicity makes loperamide abuse very dangerous and challenging to combat. In order to further understand the prevalence of loperamide abuse we conducted a systematic perusal of the FDA FAERS database from 2002-2022 (20 years’ worth of data), looking for adverse event reports for cardiac toxicity, cardiac arrest, substance abuse, overdose, and death. We believe a call to action is needed to place loperamide “behind the counter,” due to large numbers of people abusing it and the prevalence of morbidity and mortality associated with loperamide abuse.

Keywords: loperamide, loperamide abuse, opioid agonist, cardiac toxicity, loperamide toxicity, awareness

Background
Loperamide (Imodium®) is an anti-diarrheal drug manufactured by Mylan®, Teva®, Johnson & Johnson®, Janssen®, and McNeil® among others. It is sold over the counter (OTC) to control acute diarrhea, as well as for symptom reduction in those with inflammatory bowel disease (IBS) and ileostomies. This drug is typically available as a capsule, tablet, or a suspension depending on the strength and dosage. Loperamide works by reducing gastrointestinal motility and decreasing electrolytes and fluid secreted into the bowel. This allows for more absorption and less excretion, decreasing the number of bowel movements while also restoring stool to its normal consistency (U.S. National Library of Medicine, 2018).

Loperamide is generally regarded as safe when taken in therapeutic doses which range from 2-16mg per day. Under normal circumstances when taking therapeutic doses, it only acts as an opioid agonist on the mu-opioid receptors in the gastrointestinal tract to reduce gastrointestinal motility, not in the central nervous system. However, when the dosage exceeds this intentionally or accidentally, or it is taken in conjunction with other prescriptions drugs, such as H2 blockers, the pharmacokinetics of loperamide are altered and it can cross the blood-brain barrier and act on
the mu opioid receptors in the brain. This causes opioid effects in the central nervous system including euphoria as well as possible respiratory depression (Eggleston et al., 2020).

Due to its opioid effect on the brain, taking loperamide in large doses is used to counteract symptoms of acute opioid withdrawal. Thus, it is commonly being misused to provide a euphoric effect or to self-manage opioid withdrawal symptoms. The low cost, easy accessibility, lack of testing, and lack of stigma for loperamide plays a role in its high potential for misuse, and it has even been labeled the “Poor Man’s Methadone” (Wang et al., 2020).

Associated with this misuse of supra-therapeutic doses of loperamide are many adverse effects. Much like other opioids that can cause respiratory depression, there is always a risk of overdose. Loperamide taken in large quantities (typically 50-100 tablets at a time) can also cause cardiac toxicity which can lead to death. The cardiac sequelae of loperamide abuse have been described before by others (Ali, 2020; Betting, 2021; Eggleston, 2020). The manifestations of this cardiac toxicity are commonly seen as QT/QTc prolongation, Torsades de Pointes, other ventricular arrhythmias, and cardiac arrest.

The delivery of oxygen and essential nutrients to relative tissues in the body are dependent upon blood vessels that compose a complex network extended throughout the human body. A unique subset of blood vessels that are responsible for vascularizing the central nervous system (CNS) possess the ability to transport molecules, ions, and mesenchymal-like-cells from the blood to the brain, termed the blood-brain barrier (BBB). The BBB maintains a restrictive nature over drug delivery to the CNS, and, thus, the generation of therapeutics to bypass regulation is a heavily sought-after mechanism. (Daneman & Prat, 2015)

Loperamide is initially absorbed in the GI tract and is later almost completely excreted or metabolized in the liver via cytochrome P450 in the liver (Regnard et al., 2011). Here, loperamide becomes conjugated and is excreted from the body in the form of bile. Loperamide toxicity can also occur when the compound is coupled with a cytochrome P450 inhibitor. Cimetidine, a known H2 antagonist, competitively inhibits histamine binding to H2 receptors blocking the activity of cytochrome P450 (National Institute of Diabetes and Digestive and Kidney Diseases, 2012). Consequently, when loperamide is co-ingested with cimetidine or any H2 antagonist, increased loperamide serum levels are observed and loperamide has a far greater potential to enter the blood and cross the blood-brain barrier (Larsen et al., 2018). Consequently, loperamide serum levels accumulate and overwhelm the P-Glycoprotein essential for excretion of loperamide from the brain.

Although the exact mechanism of cardiac toxicity resulting in fatality caused by loperamide abuse is unknown, it has been postulated to be linked to the human ether-a-go-go-related (hERG) gene channel. This channel functions by pumping potassium out of the cardiac cell to repolarize action potential and retain the electrochemical gradient across the cell. Loperamide abuse has been linked to loss of function within this channel resulting in potential lethality to the user (Ali et al., 2020).

Reported symptoms vary across the range of increased exposure, while intestinal discomfort is listed on the minor end of the scale, repeated seizures and unconsciousness is noted prior to death on this range of symptom severity (Eggleston et al., 2020). While this drug is available over the counter and is anecdotally proven to effectively mitigate symptoms of opioid withdrawal, when abused and taken irresponsibly the drug can cause lethal arrhythmias resulting in death.

There has been an increase in reported loperamide abuse in the last decade. Cases have been reported with the self-management of opioid withdrawal symptoms and from those attempting to achieve the euphoric effects of opioid use. The increase in cases from 2010 to 2015 resulted in 15 deaths, eight of which occurred from a single use of the drug (Vakkalanka et al., 2017).

This increase in cases is also likely due to the easy accessibility, low cost, and lack of testing for loperamide compared to other opioids. People in justice-involved monitoring programs can get this drug easily over the counter at a drugstore for a low price, while still circumventing any drug testing they must complete. Due to its opioid effects when taken in large quantities, it is an ideal option to combat the withdrawal symptoms that opioid users can experience when they abruptly stop using opioids. This makes it a very appealing option to populations receiving frequent drug screens, such as pregnant opioid users, and those who are justice-involved. This also makes it a potentially dangerous deadly drug with lethal outcomes due to lack of awareness of toxicity.

Commonly referred to as “loping”, people with opioid use disorders routinely take large doses of loperamide to achieve opioid euphoric effects (60-200 mg at a time) (Schifano&Chiappini, 2018). Loperamide produces a euphoric effect and alleviates opiate dependency and opiate withdrawal symptoms when ingested at doses higher than 50 milligrams. At supra-therapeutic levels, loperamide is described as a “lope high” and give effects “better than oxycodone” (Schifano&Chiappini, 2018). It has been reported on drug forum threads that the oral ingestion of forty-four 2 milligram tablets (88 milligrams) of loperamide felt as “someone who’s taken too many tramadol in too little of time trying to achieve a high multiple times a day”. It was noted that there was a substantial decrease in breathing after ingesting high amounts of loperamide. When taken at doses ranging from 50-800 milligrams, loperamide has been reported to be similar or better than any opioid (Drugs-Forum, 2012). To those who do not have a tolerance for opiates, a large dose of loperamide gives the user an uncomfortable and/or uneasy sensation. If the user has a tolerance for opiates, loperamide becomes a dangerous coping mechanism for other withdrawal symptoms. Coined “poor man’s methadone” by the American Journal of Forensic Medicine and Pathology, the use of this over-the-counter drug has grown in popularity among populations with opioid use disorder (OUD) (Vera, 2016).
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Wang and associates (2020) described a case of a pregnant woman who was being treated for suspected peripartum cardiomyopathy. Due to her cardiac symptoms, a C-section was performed at around 32 week’s gestation. It was later discovered she had been abusing loperamide, taking around 40 mg daily, which was believed to be the cause of her cardiac dysfunction. If the large doses of loperamide had been identified as the cause sooner, in this case, it is likely that an emergency C-section could have been avoided (Wang et al., 2020).

**Case 1:**

The patient was a 23-year-old Caucasian female with a history of opioid use disorder for over four years. Her family reported that she had been purchasing and consuming large quantities of loperamide over the counter “for irritable bowel syndrome” symptoms. The patient had a three-month history of multiple emergency department visits for abdominal pain, sweating, dizziness, and feeling faint. On the day of her demise, she had visited the emergency department with a chief complaint of feeling lightheaded, dizzy, and heart-racing. She also reported leg swelling associated with the symptoms. In the emergency department she was diagnosed with viral syndrome and cellulitis of her legs. She was discharged to outpatient follow up with her primary care Physician for the symptoms. 6 hours later, the patient was brought back to the emergency department in cardiac arrest and was noted to have torsades-de-pointes dysrhythmia. CPR and advanced cardiac life support interventions were performed for 107 minutes without avail, and she was pronounced dead. The subsequent autopsy performed revealed the cause of death to be loperamide toxicity with a serum level of 774 MG.

**Case 2:**

The patient was a 44-year-old Caucasian male with a 12 plus year history of documented opioid use disorder including the use of heroin, prescription opioids, and fentanyl. After a recent incarceration for theft, he was placed on state probation. The family reports that the patient had been regularly attending 12 step recovery meetings in the community and had passed all urine drug screens performed by probation.

After his sister had not heard from the patient for over two days, she went to his house to make sure he was OK. She had to force the door to the house open, and upon entering noticed the patient lying on the floor in a state of rigor mortis. The coroner confirmed that the patient had been dead for at least 48 hours, and the cause of death was loperamide toxicity. Postmortem serum loperamide levels were found to be 505 MG.

**Case 2:**

The patient was a 38-year-old Caucasian female with an extensive history of opioid use disorder who was on parole following incarceration. She presented to a behavioral health agency requesting help for acute withdrawal symptoms because of over two years of loperamide abuse. The patient reported that she would consume between 50 to 100, 2 mg loperamide tablets every day, as this would prevent opioid withdrawal symptoms. Recently she had become symptomatic with palpitations, dizziness, lightheadedness, and anxiety. She wished to enter a medical detoxification facility for detox from loperamide. She reported that she was successfully able to abuse loperamide while on parole because this did not show up on standard 12 panel urine drug screens. She was transported to a local emergency department for medical clearance and no substance was detected in her urine through a standard 12- panel urine drug screen as this is not routinely tested for.

**Methods**

To understand the global prevalence of adverse events (AE) associated with loperamide we conducted a detailed analysis of the FDA FAERS database. The FDA FAERS database contains adverse event reports, medication error reports, and product quality complaints that have been submitted to the FDA to help support the post-marketing safety surveillance of drugs. Sources of these reports include patients, prescribers, family members, literature sources, and marketing authorization holders (MAH). Our analysis was performed using medDRAstandardized codes and five-level-hierarchy within a 20-year period from 2002 until 2022. Our parameters included a perusal of documented AEs sub classified by seriousness criteria as established by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E2A Guidelines) and then further by the medDRA five-level hierarchies including System Organ Class (SOC), High-Level Group Terms (HGLT), High-Level Terms (HLT), Preferred Terms (PT), and finally into the most granular Lowest Level Terms (LLT).

We specifically searched for AEs that were reported under the following key terms:

1. Death
2. Cardiac Arrest
3. Cardiac Dysrhythmias
4. Torsade-de-Pointes
5. QTc prolongation
6. Ventricular Dysrhythmias
7. Intentional Misuse
8. Abuse
9. Drug Dependence

10. Overdose

We then utilized statistical analyses including Pearson’s Chi Square testing to further elucidate any relationship between gender and AEs and AEs and outcomes in the FDA FAERS database.

Results

Detailed analysis of the FDA FAERS database revealed that from the year 2002 through 2022 there were 18,183 total cases of adverse events involving loperamide. Of these cases, 1,095 were reported cases of off label use, 974 cases were drug abuse, 895 cases were overdose, and 743 cases were intentional product misuse (Figure 1). In terms of the ICH serious patient outcomes, there were 1,454 deaths, 118 cases resulting in disability, 3,399 cases of hospitalization, 893 cases were defined as life-threatening (Figure 2). In reviewing patient genders involved in loperamide toxicity, there were 10,438 cases involving females and 5,990 cases involving males (Figure 3). In terms of distribution by year, there were 4,566 cases reported in 2015, 1,480 cases reported in 2016, 1,483 cases reported in 2020, and 451 cases reported in 2022 (Figure 4). In terms of worldwide presence, the United States led the world in top number of toxicity reports with 13,484 (Figure 5). Canada was next with 885, followed by France with 643, followed by United Kingdom with 433 (Figure 5). To achieve further granularity, we looked at the top system organ class terms. Within the system organ class (SOC) terms there were 9,460 adverse events under injury and poisoning, and 2,399 cases under cardiac disorders (Figure 6). When assessing the top high-level group terms in adverse events (HLGTs), there were 2,337 cases for off-label and intentional product misuse, 1,619 cases of overdose, 1,259 cases of cardiac arrhythmias, and 1,131 cases of cardiac disorders (Figure 7). Additionally, there were 1,130 cases of poisoning (Figure 7). A review of the top high-level terms (HLT), revealed there to be 1,480 overdoses, 1,222 substance-related and addictive disorders, 1,140 cases of disturbances in consciousness, and 974 cases of poisoning and toxicity (Figure 8).
Figure 2:

Figure 3:
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Figure 4:

Figure 5:
Figure 6:

![Top System/Organ Class (SOC) Terms]

Figure 7:

![Top High-Level Group Terms (HLGT)]
Discussion

In analyzing the 4,884 cases from the FDA FAERS system organ class level, 45.8% of the cases were females and 54.2% were males. 65.6% of patients with loperamide toxicity were hospitalized, 28.8% cases were fatal, and 5.6% suffered life-threatening events. A Pearson Chi-Square Test was performed which revealed a p-value of less than 0.05, which was indicative of a statistically significant association between gender and the system organ class (SOC). This can be further inferred to mean that there was a relationship between gender of the patient and cardiac disorders, injury, poisoning, and overdose.

In reviewing the high-level group terms (HLGTs) 3,733 cases of adverse events associated with loperamide were reviewed. 71.8% of patients were hospitalized, 21.6% of patients died, and 6.6% of patients had a life-threatening event. Once again there was a statistically significant association between cardiac arrhythmia and the gender of the individual (female greater than male), additionally there was a statistically significant association between patient outcomes and cardiac arrhythmia. These outcomes were assessed for correlation to different variables using the Pearson’s Chi-Square test. Two statistically significant associations could be seen through this data analysis. The first had been between cardiac arrhythmia and the gender of the individual (female greater than male), additionally there was a statistically significant association between patient outcomes and cardiac arrhythmia.

In reviewing the High-Level Terms (HLTs), statistical analysis reveals that loperamide toxicity was seen in 57% of men and 43% of women. Utilizing gender as a differential variable, it was found across male and female genders that there was a statistical significance between disturbances in consciousness, overdose, poisoning and toxicity, and substance related and addictive disorders (p-value less than 0.05).

In reviewing the preferred term cases, 1,406 cases of adverse events associated with loperamide were reviewed. Statistical analysis revealed that 38.1% cases were females, and 61.9% cases were males. 59.7% of cases were drug abuse, 1.2% were intentional product use issues, and 39.1% were overdose. Outcomes were 36.3% death, 59.3% hospitalization, and 4.4% life threatening events. A Chi-Square Test was performed with a p-value less than 0.05, which revealed a statistically significant association between gender (Male > female) and patient outcomes. However, a Chi-Square Test performed between gender and reaction showed a p-value greater than 0.05, therefore, it was concluded that this did not represent a statically significant association between gender and reaction. This meant that prevalence of abusing the drug, intentionally misusing the product, or overdosing was independent of patient gender.

Conclusion

We utilized a detailed cross-sectional analysis of the FDA FAERS database from 2002-2022 to elucidate the true prevalence of loperamide toxicity in the context of people who abuse loperamide for its opioid effect. Our analysis revealed an unexpectedly high number of adverse events occurring in association with loperamide use and abuse including cardiac dysrhythmia, overdose, poisoning, and death. We believe that a broader call to action is needed to bring about awareness to healthcare providers, pharmacists, and the general population.
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regarding the potential for serious adverse events occurring with abuse of loperamide above standard doses. It is important that healthcare professionals, OB-GYN clinicians, probation and parole officers, substance use treatment providers, and people involved in mental health and behavioral health counseling to understand the potential severity of toxic events associated with loperamide abuse. We believe that routine testing of loperamide should be incorporated into standard urine drug screening panels for substances of abuse due to the potential for severe toxicity from this substance. We believe it is also necessary to inform the public about the dangers and risks of using supra-therapeutic doses of loperamide, and potential toxicity that can occur with this. We believe that based on this analysis and the prevalence of severe toxicity including death, cardiac dysrhythmias, overdose, and poisoning that a call to action is needed. We believe this call to action should involve, in addition to a robust awareness campaign, policies and practices to place loperamide “behind the counter”, similar to pseudoephedrine to preclude bulk purchases, and thereby limit toxicity associated morbidity and mortality.

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