

Epidemiologic Trends in Loperamide Abuse and Misuse

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Study objective: Loperamide abuse has been increasing in the United States as a potential alternative to manage opioid withdrawal symptoms or to achieve euphoric effects of opioid use. In June 2016, the Food and Drug Administration warned health care providers and the general public about potential serious adverse outcomes, including cardiac dysrhythmias and death. The purpose of this study is to determine recent trends in intentional loperamide abuse and misuse, reported clinical effects and management, and medical outcomes as reported to poison centers across the United States.

Methods: Loperamide exposures reported to the National Poison Data System indicating intentional misuse, abuse, and suspected suicide between January 1, 2010, and December 31, 2015, were assessed. Demographic and temporal trends, as well as reported clinical effects, medical management, and health outcomes, were analyzed.

Results: There was a 91% increase in reported exposures from 2010 to 2015, of which half were single-agent loperamide use only. Loperamide exposures reported to the National Poison Data System increased at approximately 38 cases per year (95% confidence interval [CI] 32.5 to 42.9; $P < 0.0001$). Fifteen deaths were reported during this time frame, of which 8 involved single-agent loperamide abuse.

Conclusion: Loperamide abuse and misuse are projected to increase in the absence of any methods to reduce exposure or curb abuse. Health care providers should consider the potential for loperamide toxicity when managing patients with opioidlike toxicity. [Ann Emerg Med. 2016;■:1-6.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Loperamide, a synthetic opioid, is a widely used antidiarrheal medication that has been available to the US public as a nonprescription medication since 1988.¹⁻³ At therapeutic doses, it inhibits peristaltic activity through μ -opioid receptor inhibition of the mesenteric plexus of the large intestine.⁴ Loperamide is typically not considered to have abuse potential because it is metabolized rapidly and is rapidly excreted from the central nervous system by p-glycoprotein at recommended doses.^{5,6} Although loperamide is well tolerated in therapeutic doses in adults, it has been reported to cause an opiate-like intoxication in individuals who consumed it in overdose.^{7,8} Recent case reports in the literature have identified individuals recreationally abusing or intentionally taking an overdose of this medication in an attempt to alleviate opioid withdrawal symptoms or to achieve an opioidlike high, resulting in cardiac dysrhythmias and death.⁸⁻¹³ On June 7, 2016, the Food and Drug Administration released a warning about serious cardiac adverse events (eg, QT-interval

prolongation, torsades de pointes, cardiac arrest) associated with higher-than-recommended doses of loperamide.¹⁴

Poison centers across the United States receive a wide range of calls from the general public and health care professionals about thousands of pharmaceutical products, including loperamide. Data collected from these calls are compiled and reported to the National Poison Data System. Overall, the system's data have shown a national increase in intentional loperamide abuse; however, detailed national-level data on epidemiologic trends and medical outcomes have yet to be reported.^{15,16} This study identifies recent temporal trends in intentional loperamide abuse and misuse, demographic characteristics, and medical outcomes as reported to the National Poison Data System.

MATERIALS AND METHODS

The National Poison Data System contains case records from calls reported to all poison centers across the country. Deidentified data from these cases are auto-uploaded to the system every 8 minutes on average.¹⁶ The reason behind

Editor's Capsule Summary*What is already known on this topic*

Loperamide (Imodium) is an opioid medication available over the counter for the treatment of diarrhea. Recently, the Food and Drug Administration issued a warning about serious adverse outcomes of loperamide use, including cardiac dysrhythmias and death. Loperamide abuse has typically been considered nonexistent because the medication does not penetrate the central nervous system well.

What question this study addressed

We describe recent trends in intentional loperamide abuse and medical outcomes as reported to US poison centers.

What this study adds to our knowledge

There were 1,736 human exposures during the study period. The number of exposures increased 91% from 2010 through 2015. Of 15 deaths reported, 8 involved single-agent loperamide abuse.

How this is relevant to clinical practice

Although loperamide is often considered innocuous, health care providers should consider it when managing patients with opioidlike toxicity.

the reported exposure may be unintentional (eg, accidental, environmental), intentional (misuse, abuse, suspected suicide, or unknown), or other (eg, adverse reactions, therapeutic errors).¹⁷ Intentional exposures are categorized as suspected suicidal exposures, misuse, abuse, or unknown intentional exposures. Suspected suicidal exposures are those resulting from the inappropriate use of a substance for self-harm or for self-destructive or manipulative reasons and can include suicides, suicide attempts, and suicide gestures, whether suspected or confirmed. Intentional misuse is defined as an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect. Intentional abuse exposures are from the intentional improper or incorrect use of a substance in which the patient was likely attempting to gain a "high," euphoric effect, or some other psychotropic effect, including recreational use of a substance for any effect. When the exposure is identified as intentional but the motive is unknown, the exposure is categorized as intentional unknown.

Poison centers capture the medical outcome for each case either at management of the case or through follow-up calls. When the medical outcome is known, it is captured as no effect (no symptoms related to the exposure), minor effects (some signs or symptoms that are minimally bothersome and rapidly resolved), moderate effects (more prolonged or pronounced and systemic), major effects (signs or symptoms that are life threatening), or death. When follow-up is not possible (eg, the patient is lost to follow-up, minimal clinical effects are anticipated), poison center staff identify them as "not followed" with anticipated outcomes (eg, minimal toxicity, potentially toxic).

For this study, criteria for inclusion included an intentional loperamide exposure case reported to the National Poison Data System between January 1, 2010, and December 31, 2015. No additional exclusion criteria were applied. Because this was a review of deidentified data collected in the National Poison Data System database, there were no data abstractors, standardized data extraction forms, or assessment of interrater reliability or agreement testing, as seen with chart reviews. Data were analyzed for epidemiologic and temporal trends, and demographic, clinical, and exposure attributes were tabulated. Although cases were not restricted to single-agent exposures (ie, loperamide exposure only), temporal trends, medical outcomes, and therapies provided were assessed between single and polysubstance exposures. Simple linear regression was used to assess the annual change in exposure over time, and χ^2 analyses were used to evaluate differences in categorical data. All data analysis was performed with SAS (version 9.4; SAS Institute, Inc., Cary, NC). This study was deemed exempt by our university's institutional review board.

RESULTS

There were 1,736 loperamide intentional exposure cases during the study period, of which half (50.4%) were single-agent loperamide exposures only (Table 1). Overall reasons for the intentional exposure included intentional abuse (13.1%), intentional misuse (32.8%), suspected suicide (48.8%), and other (5.2%). This distribution, however, varied between single and polysubstance exposures (respective percentages reported): abuse (17.6% versus 8.6%), misuse (53.7% versus 11.5%), and suspected suicide (23.1% versus 75.0%). Male subjects were more likely to intentionally abuse loperamide, whereas female subjects more often used it in reported suicidal attempts ($P<.001$); however, there was no difference in the proportion of cases involving intentional misuse by sex ($P=.57$). Loperamide was most frequently involved in

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