I. Combined Loperamide Surveillance Report:

Report A: Misuse and Abuse of Loperamide in the United States as Reported to the RADARS® System Survey of Non-Medical Use of Prescription Drugs

Report B: National Poison Data System Summary of Loperamide Containing Product Exposures

SPONSOR:	Johnson & Johnson Consumer Inc., McNeil Consumer Healthcare Division 7050 Camp Hill Road Fort Washington, PA 19034
SPONSOR CONTACT:	Leslie Shur, D.O., F.A.A.P. Director, OTC Global Medical Affairs Global Medical Affairs Leader—Analgesics
TARGET DRUG SUBSTANCES:	Loperamide
PROGRAMS:	National Poison Data System RADARS® System Survey of Non-Medical Use of Prescription Drugs
REPORTING COUNTRIES:	United States
PRINCIPAL INVESTIGATORS:	**Jody L. Green, PhD, CCRP** Denver Health and Hospital Authority Rocky Mountain Poison & Drug Center 777 Bannock Street, Mail Code 0180 Denver, Colorado 80204 (United States)
REPORT DATE:	30 June 2017

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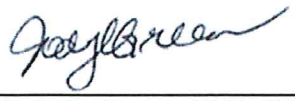
Principal Investigator:



30 June 2017

Jody L. Green, PhD, CCRP — Date

Report Prepared By:

30 June 2017

Kate M. Reynolds, MPH — Date

II. Integrated Executive Summary

There have been reports of massive overdose of loperamide resulting in serious cardiovascular events. Reports from the United States regarding the use of loperamide to self-treat opioid withdrawal or to induce euphoria have been the subject of recent medical literature. Moreover, reports from United States poison centers have highlighted the association between loperamide abuse and cardiovascular toxicity[1]. Existing data sources provide valuable ways to understand this type of behavior and the associated risk with cardiovascular toxicity. This combined surveillance report provides a summary of data collected via two data programs: A) Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System Survey of Non-Medical Use of Prescription Drugs Program, and B) National Poison Data System (NPDS). Data on non-medical use (NMU; this is defined on the survey as ever using loperamide "for any reason other than what was recommended by a doctor/dentist/pharmacist/the package insert"), misuse and abuse of loperamide have been collected throughout the United States from the Survey of Non-Medical Use of Prescription Drugs Program during 3rd quarter 2016. The NPDS report provides a summary of all loperamide-containing product exposures reported to United States regional poison centers between 2012 and 2015. This report also utilizes nationwide sales data to provide further context for the association between loperamide availability and both NMU of loperamide and reports of loperamide exposure.

- Extrapolated data from the Survey of Non-Medical Use of Prescription Drugs Program suggest that 2.5% of adults in the United States endorsed NMU of loperamide sometime during their lifetime (weighted estimate: 6,160,074) and 0.7% of adults in the United States endorsed NMU of loperamide in the last 90 days. Comparable data from the NPDS show that intentional abuse (intentional improper or incorrect use of a substance where 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) or intentional misuse (intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect) of loperamide was associated with 12.4% of all reported loperamide exposures.
- When reports of NMU were evaluated in the context of product availability, there was an estimated rate of 1.5 endorsements for loperamide NMU in the last 90 days per 100 sales units (i.e., tablets, gelcaps, liquid equivalents) sold. When NPDS reports of intentional abuse or intentional misuse of loperamide were evaluated in the context of product availability, rates per one million units (i.e., tablets, gelcaps, liquid equivalents) sold ranged from 0.030 (0.023, 0.038) to 0.173 (0.146, 0.205). This equates to 1 exposure for every 5.8 to 33.3 million units (i.e., tablets, gelcaps, liquid equivalents) sold. In both programs, the rates of NMU or intentional abuse or intentional misuse of were very low.
- While younger age was associated with both lifetime NMU of loperamide and NMU of loperamide in the last 90 days, NPDS intentional abuse and misuse exposures were more likely to involve an adult patient (89.1% ≥12 year of age) than exposures involving unintentional exposures (exposures resulting from an unforeseen or unplanned event; 70.2% <12 years of age). This is likely due to the unintentional category of exposures including pediatric accidental unsupervised ingestions (47.5% of all exposures). In both data programs, use of other substances was associated with increased NMU, intentional abuse, and intentional misuse of loperamide. Likewise, oral routes were most common with NMU, intentional abuse, and intentional misuse of loperamide, with other routes less frequently endorsed or reported.

- Strengths of both data programs include national representativeness through either nation-wide coverage or national estimates calculated using a weighting schematic. Particular strengths of Survey of Non-Medical Use of Prescription Drugs include the richness of the survey data to capture detailed patient characteristics, reason for use, and routes of administration of NMU of loperamide in the general population. The survey captures data from those who do not report NMU allowing for identification of potential risk factors. Particular strengths of the NPDS data system include standardized data collection methods, structured database, and timely reporting. NPDS data can be tracked over time and include actual experiences with the use, abuse, and misuse of loperamide.
- Limitations of both data programs include reliance on self-report as well as self-selection bias due to voluntary participation and spontaneous reporting. Limitations specific to the Survey of Non-Medical Use of Prescription Drugs include that reason and route for proper use of loperamide are not captured, so estimates of proper use cannot be calculated. Specifics about misuse for diarrhea are not captured. The NPDS system is limited by the nature of spontaneous reporting, which may lead to the under-reporting of some types of exposures. In addition, the use of sales data in both programs should be considered as a proxy for drug utilization-based rates as there is no accurate way to measure doses of loperamide actually used.

III. Table of Contents (Combined Report)

IV. Individual Program Reports

Report A: Misuse and Abuse of Loperamide in the United States as Reported to the RADARS® System Survey of Non-Medical Use of Prescription Drugs

Report B: National Poison Data System Summary of Loperamide Containing Product Exposures

1 Misuse and Abuse of Loperamide in the United States as Reported to the RADARS® System Survey of Non-Medical Use of Prescription Drugs Program

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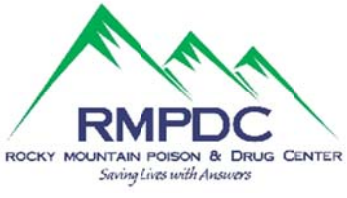
TARGET DRUG SUBSTANCES:	Loperamide
PROGRAMS:	RADARS® System Survey of Non-Medical Use of Prescription Drugs Program
REPORTING COUNTRIES:	United States
PRINCIPAL INVESTIGATORS:	**Jody L. Green, PhD, CCRP** Denver Health and Hospital Authority Rocky Mountain Poison & Drug Center 777 Bannock Street, Mail Code 0180 Denver, Colorado 80204 (United States)
REPORT DATE:	30 June 2017



2 Executive Summary

There have been reports of massive overdose of loperamide resulting in serious cardiovascular events. Reports from the United States regarding the use of loperamide to self-treat opioid withdrawal or to induce euphoria have been the subject of recent medical literature. This type of aberrant behavior is difficult to study and is not often detected in randomized controlled trials. Existing data sources provide valuable ways of better understanding abuse and misuse of medications. One avenue by which this can be monitored is through the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System Survey of Non-Medical Use of Prescription Drugs Program. Data on non-medical use (NMU; defined on the survey as ever using loperamide 'for any reason other than what was recommended by a doctor/dentist/pharmacist/the package insert'), misuse, and abuse of loperamide have been collected throughout the United States from the Survey of Non-Medical Use of Prescription Drugs Program and are presented in this report. Additionally, this report includes national sales data that presents NMU of loperamide in the context of drug availability.

- Extrapolated data from the 3rd quarter of 2016 Survey of Non-Medical Use of Prescription Drugs Program suggest that 2.5% of adults in the United States endorsed NMU of loperamide sometime during their lifetime (weighted estimate: 6,160,074), and 0.7% of adults in the United States endorsed NMU of loperamide in the last 90 days. In context of the commercial availability of loperamide, there was an estimated rate of 1.5 endorsements of last 90 day NMU per 100 sales volume (e.g. tablets, soft gels, or liquid equivalents) of loperamide sold in the United States.
- Results from this survey suggest that in the general population, loperamide has been misused (i.e. self-reported non-medical use to 'self-treat pain' or 'treat a medical condition other than pain') by an estimated 2.3% of adults, abused (i.e. self-reported non-medical use for 'enjoyment or to get high') by 0.1% of adults, and non-medically used to 'prevent or treat withdrawal symptoms' by 0.1% of adults. See Appendix A for a comprehensive list of survey response options for reasons for NMU.
- Compared to survey respondents who did not endorse lifetime NMU of loperamide, respondents endorsing lifetime NMU of loperamide were more likely to be younger in age (average 42.7 years versus 46.7 years), reside in the South, to be Hispanic, to report mid-range household income ($50,000 - $100,000), to be a current healthcare professional, and to score higher on the Drug Abuse Screening Test (DAST-10).
- Compared to respondents who did not report NMU of loperamide in the last 90 days, respondents endorsing recent NMU of loperamide were more likely to be younger in age (average 39.3 years versus 46.7 years), to be Hispanic ethnicity, to report mid-range household incomes ($50,000 - $100,000), to score higher on the DAST-10, and were less likely to be female or former or current military.
- Endorsing multiple drugs of abuse was found to be a risk factor for recent NMU, misuse, abuse, and non-medical use of loperamide to prevent or treat withdrawal symptoms. Approximately 1 in 3 respondents who endorsed NMU of loperamide in the last 30 days also endorsed NMU of prescription opioids or use of any illicit drugs in the last 30 days. Of respondents who endorsed lifetime NMU of loperamide, the top 2 of 5 possible endorsed reasons were to 'treat a medical condition other than pain' (56.6%) or to 'self-treat pain' (39.0%).The most commonly endorsed route of administration for NMU of loperamide was swallowing (88.2%). Other less frequently endorsed routes of administration were chewing and then swallowing (12.2%), dissolving in mouth (7.1%), inhalation (5.2%), injection (5.6%), and other route (5.7%).
- Strengths of the survey data used in this report include a large sample size that is weighted to the distribution of adults in the United States, richness of the survey data to

capture detailed patient characteristics, reason for use, and routes of administration of NMU of loperamide in the general population. The survey captures data from those who do not report NMU, allowing for identification of potential risk factors. Limitations of this program include reliance on self-reporting as well as self-selection bias due to voluntary participation and registration to participate in an online survey panel. An additional limitation is that reason and route for proper use of loperamide are not captured, so estimates of proper use cannot be calculated. Specifics about misuse for diarrhea are not captured.

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4 List of Tables

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6 List of Acronyms

CI	Confidence Interval
COMIRB	Colorado Multiple Institutional Review Board
DAST-10	Drug Abuse Screening Test
IRI	Information Resources, Inc.®
IQR	Interquartile Range
NMU	Non-Medical Use
RADARS® System	Researched Abuse, Diversion and Addiction-Related Surveillance System
RMPDC	Rocky Mountain Poison & Drug Center
SD	Standard Deviation

7 Glossary of Terms

95% Confidence Interval (CI)	A range that is estimated to contain the true population estimate (e.g. mean, percentage) in 95% of all samples.
Abuse	Self-reported non-medical use of loperamide for which the respondent reported a reason for non-medical use of loperamide "for enjoyment or to get high."
Census Regions of United States	Northeast, South, Midwest, West
Drug Abuse Screening Test (DAST-10)	A 10-item yes/no instrument that yields a quantitative index of problems related to drug abuse Scores are collapsed into 5 categories based on degree of problems related to drug abuse: 0 – No problems related to drug abuse reported 1-2 – Low level 3-5 – Moderate level 6-8 – Substantial level 9-10 – Severe level
Denominator	In a given analysis, the value representing the total population of interest.
Endorsement	Any report of non-medical use of a specific drug or of a specific event (e.g. one respondent may have multiple endorsements of drug products, route of administration, source of drug acquisition, reason for use).
Illicit Drugs	Includes cannabis (recreational and medical use), cocaine powder, crack cocaine, ecstasy (e.g. MDMA), GHB/GBL, non-pharmaceutical amphetamine (e.g. speed), non-pharmaceutical fentanyl (e.g. China white, Apache, China girl, etc.), heroin, ketamine, and mephedrone.
Interquartile Range (IQR)	A measure of variation of a given variable of interest displayed as the range of Q1 to Q3. Data are divided into quartiles: Q1 = 1st quartile, 25% of data falls below this number Q2 = 2nd quartile (Median), 50% of data falls below this number Q3 = 3rd quartile, 75% of data falls below this number
Loperamide	Loperamide is an active pharmaceutical ingredient found in medications such as Imodium® that are approved for over-the-counter sales in the United States to help control symptoms of diarrhea.
Mean	The average; the sum of observed values divided by the number of observations.
Median	The middle value of all respondents, 50% of respondents fall above the median, and 50% of respondents fall below the median.
Misuse	Self-reported non-medical use of loperamide for which the respondent reported a reason for non-medical use of either "to self-treat pain" or "to treat a medical condition other than pain".

N	Sample size
Non-medical use (NMU)	Use of a non-prescription medication for any reason other than what was recommended by the study respondent's doctor/dentist/pharmacist/the packet insert.
Numerator	In a given analysis, the value representing the sub-set of interest in the population.
Opioids	Includes the active pharmaceutical ingredients buprenorphine fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, sufentanil, tramadol, or tapentadol. For purposes of this report, discussion of 'opioids' is limited to non-medical use of prescription opioids.
Prevalence	Measurement of individuals (e.g. percentage) who endorse non-medical use of loperamide during a specific time period.
p-value	The probability of obtaining a given result by chance alone. Generally, p-values that are less than 0.05 are treated as 'statistically significant' (less than a 5% probability that a given result is from chance alone).
Rate	The drug utilization measure used in this report is number of standard units of loperamide sold. The rate is calculated as the weighted number of non-medical use of Loperamide endorsements (numerator) divided by the measure of drug utilization (denominator).
Respondent	A unique individual who completed the Survey of Non-Medical Use of Prescription Drugs Program survey. Respondents should be interpreted at the case level.
Sales volume	Number of single and combination ingredient tablets, soft gels, liquid equivalents, or oral solutions / suspensions sold as reported by IRI.
Sample	A subset of the population.
Standard deviation (SD)	A measure of variation or dispersion of data around the mean. A low standard deviation means there is little spread of values around the mean, whereas a high standard deviation means there is a wider range of values around the mean.
Statistical significance	Implies that the observed result was unlikely to have occurred by chance alone; usually based on a p-value less than 0.05.
Unweighted	The actual number of respondents who completed the Survey of Non-Medical Use of Prescription Drugs Program survey.
Weighted	The number of adults in the United States that are represented by the responses given in the survey.

8 Introduction

There have been reports of intentional overdose of loperamide resulting in serious cardiovascular events. Reports from the United States regarding the use of loperamide to self-treat opioid withdrawal or to induce euphoria have been the subject of recent medical literature. This type of aberrant behavior is difficult to study and is not often detected in randomized controlled trials. Existing data sources provide valuable ways of better understanding abuse and misuse of medications.

This report utilizes data from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System Survey of Non-Medical Use of Prescription Drugs Program to study rates of non-medical use (NMU), misuse, and abuse of loperamide among the general population and to characterize associated behaviors and outcomes. For the purposes of this report, surveillance in the United States will be described.

9 Objectives

9.1 Non-Medical Use of Loperamide

The primary objective of this report is to estimate NMU of loperamide among adults in the United States general population. The primary analysis focuses on respondent characteristics and endorsement of multiple drugs for those who do and do not endorse NMU of loperamide. In addition, this analysis examines NMU of loperamide in context of drug availability using national sales data.

9.2 Reasons and Routes of Non-Medical Use of Loperamide

A secondary objective of this report is to examine the self-reported routes of use among respondents who endorsed NMU of loperamide within their lifetime. The analysis focuses on percentages of respondents who endorsed each reason for NMU and route, as well as the relationship between respondents' endorsement of reason and route.

9.3 Loperamide Misuse, Abuse, and Prevention or Treatment of Withdrawal Symptoms

An additional secondary objective of this report is to examine endorsements of loperamide for misuse, abuse, and prevention or treatment of withdrawal symptoms among the general adult population. The analysis focuses on respondent characteristics and history of illicit drug use and NMU of opioid drugs among respondents who misused, abused, and used to prevent or treat withdrawal symptoms.

10 Methods

10.1 RADARS® System Survey of Non-Medical Use of Prescription Drugs Program

10.1.1 Overall Study Design and Plan

The RADARS System provides post-marketing surveillance of prescription and over-the-counter medication abuse, misuse, and diversion to pharmaceutical companies, regulatory agencies, and policy making organizations. The RADARS System is comprised of programs that gather data from several unique populations along the spectrum of drug abuse. The RADARS System Survey of Non-Medical Use of Prescription Drugs Program in the United States is a large-scale, repeated, cross-sectional online survey. The Survey of Non-Medical Use of Prescription Drugs Program was designed to study NMU of medications among the general population and to characterize associated behaviors and outcomes.

The Survey of Non-Medical Use of Prescription Drugs Program survey is a self-administered, online survey. This detailed survey is used to gather information about respondent demographics, lifetime use and NMU of prescription and over-the-counter drugs, frequency of NMU, reasons for NMU, route of administration for NMU, source of drug acquisition for NMU, and price paid through illicit channels. Lifetime NMU on the survey is defined as ever using the product for any reason other than what was recommended by your doctor/dentist/pharmacist/the package insert. Endorsements of reason for NMU (to self-treat pain, to treat a medical condition other than pain, for enjoyment or to get high, to come down, to prevent or treat withdrawal symptoms, and other) or routes of administration (swallowed, chewed and then swallowed, dissolved in mouth, inhaled, injected, or other) were limited to any respondent who selected “Yes, I have used this medication” for NMU of loperamide. See Appendix A for a comprehensive list of survey questions pertaining to loperamide from the Survey of Non-Medical Use of Prescription Drugs Program 3rd quarter 2016 survey in the United States.

The survey also gathers information about tobacco, alcohol, and illicit drug use, substance abuse treatment, history of chronic and acute pain, mental health, and doctor shopping. Lifetime illicit drug use includes any of the following during the respondent’s lifetime: cannabis (medical or recreational use), cocaine powder, crack cocaine, ecstasy (e.g. MDMA), GHB/GBL, non-pharmaceutical amphetamine (e.g. speed), non-pharmaceutical fentanyl (e.g. China white, Apache, China girl, etc.), heroin, ketamine, and mephedrone. Survey respondents also complete the Drug Abuse Screening Test (DAST-10) if they endorse lifetime NMU of any prescription or over-the-counter medication, or any lifetime use of an illicit drug[1]. This scoring system measures the degree of problems related to drug abuse. DAST-10 scores were categorized according to the degree of problems related to drug abuse: None (0), Low (1-2), Moderate (3-5), Substantial (6-8), and Severe (9-10).

The data collection period for the Survey of Non-Medical Use of Prescription Drugs Program 3rd quarter 2016 United States survey opened on 08 July 2016 and closed on 18 August 2016. Non-probability quota sampling was used to provide a proportional distribution of survey respondents across census regions of the United States (Northeast, South, Midwest, and West) and an equal distribution by gender. Survey respondents were recruited through an online survey panel company which sends email invitations to complete surveys in exchange for modest compensation. Panel members are individuals who self-select to sign up to complete

surveys in exchange for points, which can be redeemed for modest compensation. The email invitations sent to panel members do not include any information about the topics included in the survey. The overall response rate of invitations sent to participate in the Survey of Non-Medical Use of Prescription Drugs Program 3rd quarter 2016 survey in the United States was 11%. During the study period, there were 44,649 people who received an email invitation and initiated the survey, of which 236 (0.6%) were under 18 years old or over 110 years old, 4,569 (10.2%) did not agree to the confidentiality agreement, and 3,773 (8.5%) were in a region/gender strata that had already met its sampling quota and were not allowed to complete the survey. Additionally, 3,736 (8.4%) respondents partially completed the survey, 940 (2.1%) completed the survey in under two-fifths the median completion time, and 845 (1.9%) provided invalid responses, resulting in 30,523 completed surveys that meet the panel company's inclusion criteria. Once collected, the de-identified survey data are transmitted from the panel company to Rocky Mountain Poison & Drug Center (RMPDC) for analysis.

10.1.2 Data Quality Assurance

RADARS System staff perform steps to ensure the integrity of the final cleaned data set. At the completion of each survey, the data are downloaded as an SPSS file from a secure hosting site and stored in their raw format on RMPDC's secure server. After the raw data file has been downloaded to RMPDC's secure server, it is locked to preserve the original dataset; a secondary analysis dataset is created from the raw dataset.

Exclusion criteria are then applied to data deemed implausible. Respondents are excluded from the analysis dataset if he/she endorses: 1) use of all illicit drugs in the past 7 days and 2) NMU of all opioid, benzodiazepine, or stimulant products in the past 7 days. In 3rd quarter 2016, one respondent was excluded. Two programmers independently apply exclusion criteria and compare resulting datasets to ensure quality control. These data rules are applied to create the final analysis dataset.

10.2 Other Data Sources

10.2.1 Census Data

The most recent population estimates, made publicly available by the United States Census Bureau[2], were used to calculate post-stratification weights for the Survey of Non-Medical Use of Prescription Drugs Program data. Total 2015 population counts were calculated for the residential adult (ages 18+) United States population in all fifty states and Washington, D.C. The residential population includes all people currently residing in the United States including military personnel. These data were stratified by the four main census regions (based on state), gender, and 10 year age categories (with youngest age group as ages 18-24 and the oldest age group as ages 65+).

10.2.2 Information Resources Inc.® (IRI)

Total loperamide multi-outlet sales (consisting of sales from sources such as grocery, drug, military, and chain stores) in the form of sales volume of loperamide-containing products (single and combination ingredient products; tablets, soft gels, liquid equivalents, oral solutions, or oral suspensions) data were obtained from IRI (Information Resources, Inc.®). IRI uses a proprietary projection methodology to extrapolate from the observed data to total multi-outlet sales in the US. The most recent sales data available for analysis are from 2015. Analysis for this report used data from the 4th quarter 2015 (05 October 2015 through 27 December 2015) in order to

align the most recent possible sales data with the Survey of Non-Medical Use of Prescription Drugs Program 3rd quarter 2016 survey in the United States. These data are used as a proxy for drug utilization-based rates to provide an assessment of NMU in relation to the commercial availability of loperamide.

10.3 Data Analysis and Reporting

10.3.1 Weighting Scheme

Population-based weighted estimates provide an assessment of the overall public health burden associated with reported drug use. This approach is a valid measure of understanding the impact on the United States population. Post-stratification weights are applied to the raw data from the Survey of Non-Medical Use of Prescription Drugs Program to represent the distribution of adults (age 18+) in the United States by census region, gender, and age. The 2015 census population estimates for the United States were used to calculate these weights.

10.3.2 Variables of Interest

The primary outcomes of interest are endorsements of NMU of loperamide within a respondent's lifetime and within the last 90 days, 30 days, and 7 days. NMU was further classified by reason for NMU as misuse, abuse, and prevention or treatment of withdrawal symptoms. All instances of misuse, abuse, or prevention/treatment of withdrawal symptoms are by definition NMU (use in ways other than indicated in the package insert or for nonprescription products the drug facts label). Abuse is defined as the NMU of loperamide for enjoyment or to get high.
Misuse is defined as the NMU of loperamide in order to self-treat pain or treat a medical condition other than pain. This may or may not include NMU of loperamide for reasons such as the treatment of diarrhea. Respondents are not asked about diarrhea specifically in this survey; see Appendix A, question 4 for the exact wording of options for reasons for NMU of loperamide.

Secondary outcomes of interest include self-reported reasons and routes of use among respondents who endorsed NMU of loperamide within their lifetime. Reasons available for selection on the survey include: to self-treat pain, to treat a medical condition other than pain, to get high, to come down, to prevent or treat withdrawal symptoms, or other reason. Open-ended text fields from respondents who selected "other reason" for NMU of loperamide were recoded to the appropriate category, when possible, and included in the analysis (e.g. a response of "diarrhea" in the open-ended text field for a reason for NMU of loperamide was recoded as "to treat a medical condition other than pain", a response of "pain" was recoded as "to self-treat pain", and a response of "can't remember" was left as "other reason"). Routes of administration available for selection on the survey include: swallowing, chewing and then swallowing, dissolving in mouth (e.g. between cheek and gum, under the tongue), inhalation (snorting or smoking), injection, or other route. Respondents were able to select multiple routes and reasons associated with NMU of loperamide. Open-ended text fields regarding route of administration were also recoded where appropriate.

See Appendix A for a comprehensive list of survey questions pertaining to loperamide from the Survey of Non-Medical Use of Prescription Drugs Program 3rd quarter 2016 survey in the United States.

Risk factors of interest included general demographics (age, gender, residence, race, and ethnicity), current or former military service, current enrollment as a college student, current

work as a healthcare professional, DAST-10 score, and endorsement of multiple drugs. Endorsement of multiple drugs included lifetime use or past 30 day use of any prescription opioids (NMU only), heroin, or any illicit drugs. Illicit drugs included cannabis (recreational and medical use), cocaine powder, crack cocaine, ecstasy (e.g. MDMA), GHB/GBL, non-pharmaceutical amphetamine (e.g. speed), non-pharmaceutical fentanyl (e.g. China white, Apache, China girl, etc.), heroin, ketamine, or mephedrone.

10.3.3 Statistical Analysis

Risk factors of interest among survey respondents were summarized using descriptive analyses. These analyses were stratified by lifetime and recent NMU of loperamide. Among those who endorsed NMU of loperamide, the reason and routes given were analyzed. Since respondents could endorse multiple reasons and routes, the proportions will not add to 100. Among respondents who only report one reason for use, the route of administration could be directly correlated to that reason. In order to ensure that estimates were not distorted by a few survey responses, we reported only route and reason estimates with sufficient data (e.g. any combination of route and reason with at least 30 respondents who selected the particular reason).

Risk factors of interests were also explored using descriptive analyses stratified by misuse, abuse, and prevention or treatment of withdrawal symptoms of loperamide. Means and standard deviations (SD) or medians and interquartile ranges (IQR) were calculated for continuous variables while prevalence and 95% confidence intervals (CI) were calculated for categorical variables. Comparisons of select estimates were calculated using Wald chi-square tests for categorical variables and t-tests for continuous variables to determine whether there was a statistically significant difference in respondent groups.

A rate of endorsements of NMU of loperamide to sales data was calculated as a proxy for drug utilization-based rates to provide an assessment of NMU in relation to the availability of loperamide. This approach accounts for the bias towards endorsements of more readily available medications. The rate and 95% CI used in this report is the weighted number of endorsements for NMU of loperamide during the past 90 days (3rd quarter 2016), divided by the volume sold during the 4th quarter in 2015. Rates are rescaled per 100 volume (e.g. tablets, soft gels, liquid equivalents, oral solutions, or oral suspensions).

All calculations and analyses were conducted using survey procedures to account for the survey design and weights in SAS, version 9.4 (SAS Institute, Cary, NC, USA).

10.3.4 Institutional Review Board / Ethics Committee

The study protocol was reviewed and approved by the Colorado Multiple Institutional Review Board (COMIRB) prior to the initiation of the Survey of Non-Medical Use of Prescription Drugs Program in the United States. COMIRB granted the Survey of Non-Medical Use of Prescription Drugs Program approval on 05 July 2016. Participation in this survey is voluntary and all respondents are informed that their answers are both confidential and anonymous.

10.3.5 Investigators and Study Personnel

The principal investigator of this study is Jody L. Green, PhD, CCRP.

11 Results

11.1 Summary of Results

11.1.1 Demographics and Risk Factors for Non-Medical Use of Loperamide

There were 30,522 respondents included from the 3rd quarter 2016 launch of the Survey of Non-Medical Use of Prescription Drugs Program after exclusion criteria were applied (Figure 9.2.1.1). After weighting, these data represent 247,773,709 adults in the United States. Overall, an estimated 6,160,074 (2.5%; 95% CI: 2.3, 2.7) adults in the United States have ever non-medically used loperamide.

Compared to those who do not endorse NMU of loperamide, those who endorse NMU were more likely to be younger in age, report living in the South, to be Hispanic, report mid-range household income ($50,000 - $100,000), report being a current healthcare professional, score higher on the DAST-10, and endorse ever using an illicit drug; they were less likely to be current or former military (Table 11.3.1.1). Similar patterns persisted when comparing recent NMU of loperamide (in the last 90 days) compared to those who did not endorse NMU within that last 90 days. Respondents who endorsed recent NMU of loperamide were also more likely to be younger in age (average age 39.3 years versus 46.7 years), to be Hispanic, have mid-range incomes, and score higher on the DAST-10; they were less likely to be female, with a lower income, and be current or former military (Table 11.3.2.1).

Endorsement of multiple drugs among those who endorsed NMU of loperamide in the last 90 days was statistically significantly higher for lifetime and past 30 days NMU of prescription opioids, heroin, or any illicit drugs, compared to those who did not endorse NMU of loperamide in the last 90 days (Table 11.3.3.1). Of respondents who endorsed NMU of loperamide in the last 30 days, the proportion who also endorsed using opioids, heroin, and illicit drugs in the last 30 days were 30.3%, 7.1%, and 33.5% respectively.

11.1.2 Reasons and Routes for Non-Medical Use of Loperamide

If a survey respondent endorsed NMU of loperamide, they were also asked about the reason for NMU and route of administration for NMU. Answer choices regarding reason for NMU on the questionnaire include “To self-treat my pain”, “To treat a medical condition, other than pain”, “For enjoyment/to get high”, “To come down”, “To prevent or treat withdrawal symptoms”, and “Other reason”. Of these available options, the most commonly self-reported reason for NMU of loperamide was to “treat a medical condition other than pain” (56.6%), followed by to “self-treat pain” (39.0%) (Table 11.4.1.1). The survey did not inquire as to the specific medical condition treated. While this may have included diarrhea, the labeled indication, it may have included other medical conditions as well.

Answer choices regarding route of administration for NMU on the questionnaire include “Swallowed”, “Chewed and then swallowed”, “Dissolved in mouth (e.g. between cheek and gum, under tongue”, “Inhaled (snorted or smoked)”, “Injected (shot it up)”, and “Other route”. Of these available options, the most common routes of administration endorsed were “swallowing” (88.2%) followed by “chewing then swallowing” (12.2%). However, over 90% of respondents endorsing NMU of loperamide endorsed “swallowing” as their route of administration for self-treatment of pain as well as to treat medical conditions other than pain (Table 11.4.2.1). There

was insufficient data to present estimates for route of administration for “enjoyment or to get high”, “to come down”, “to prevent or treat withdrawal symptoms”, or other reasons.

11.1.3 Loperamide Misuse, Abuse, and Prevention or Treatment of Withdrawal Symptoms

Overall, these data estimate that in the general population, loperamide has been non-medically used for purposes of misuse by 2.3% of adults (95% CI: 2.1, 2.5), for purposes of abuse by 0.1% of adults (95% CI: 0.1, 0.2), and for purposes of preventing or treating withdrawal symptoms by 0.1% of adults (95% CI: 0.1, 0.2). Respondents could select more than one reason for non-medical use of loperamide. The overlap of these categories (e.g. adults who reported both misuse and abuse of loperamide) is presented in Figure 9.4.3.1. The largest overlap of reasons for NMU was observed between misuse and preventing or treating withdrawal (n=16 respondents). It is possible that respondents chose multiple reasons for NMU as a result of non-medical use of loperamide on multiple occasions for different reasons, or potentially seeking several effects from the drug from a single instance of NMU.

Similar risk factors were identified for misuse of loperamide compared to those who did not misuse loperamide as previously identified with any reason for NMU of loperamide (Table 11.5.1.1); however, endorsing use of heroin in the past 30 days was not statistically different between respondents who endorsed misuse and those who did not endorse misuse of loperamide (Table 11.5.2.1).

When examining risk factors for abuse of loperamide, those who endorsed abuse compared to those who did not were younger (average 34.4 years versus 46.6 years), more likely to score higher on the DAST-10 and less likely to be female; these groups were not statistically significantly different by census region, current or former military status, current student status, and current status as a healthcare professional (Table 11.5.3.1). Endorsement of multiple drugs among those who abuse loperamide was statistically significantly higher than those who did not endorse loperamide abuse. Among respondents who endorsed abuse of loperamide, the proportion of respondents who also endorsed using opioids, heroin, and illicit drugs in the past month were 42.1%, 20.6%, and 58.8% respectively (Table 11.5.4.1).

Respondents who endorsed NMU of loperamide to prevent or treat withdrawal symptoms were younger, more likely to score higher on the DAST-10, were less likely to be female, and to be current or former military, compared to those who did not report non-medical use of loperamide for this reason (Table 11.5.5.1). Similar to endorsing misuse of loperamide, endorsement of multiple drugs was significantly higher among respondents who endorsed NMU of loperamide to prevent or treat withdrawal symptoms than those who did not use loperamide to prevent or treat withdrawal symptoms, with the exception of past 30 day use of heroin (Table 11.5.6.1).

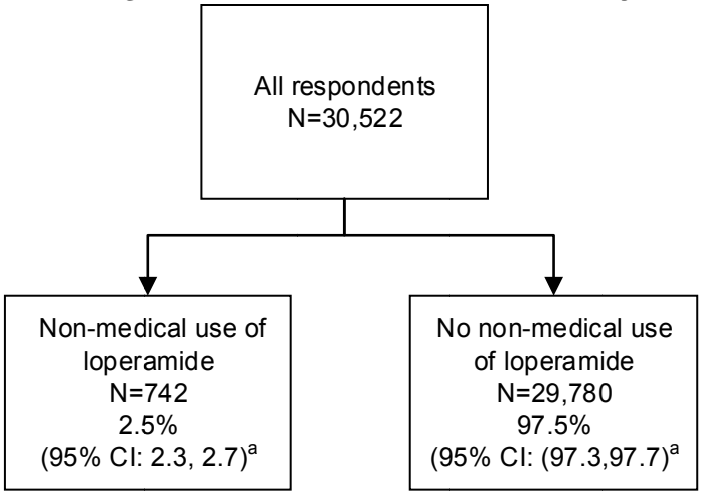
11.1.4 Rate of Recent Sales and Non-Medical Use of Loperamide

Overall, the rate of endorsements of NMU of loperamide in the last 90 days was 1.5/100 volume (95% CI: 1.3, 1.7), which equates to 1 endorsement for every 66.7 volume sold (e.g. tablets, soft gels, liquid equivalents, oral solutions, or oral suspensions) (Table 11.6.1.1).

11.2 Subject Disposition of Survey of Non-Medical Use of Prescription Drugs Program Respondents in the United States

11.2.1 Non-Medical Use of Loperamide

Figure 11.2.1.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program
Unweighted Subject Disposition Detailing Non-Medical Use of Loperamide
3rd Quarter 2016 United States Survey



[a] Prevalence estimates were weighted to reflect the distribution of United States adults by region, gender, and age

11.3 Respondent Characteristics and Behaviors by Non-Medical Use of Loperamide

11.3.1 Non-Medical Use of Loperamide

Table 11.3.1.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program
Characteristics of Respondents Endorsing Non-Medical Use (NMU) of Loperamide
3rd Quarter 2016 United States Survey

Characteristics	Total % (95% CI)[a]	NMU of Loperamide % (95% CI)[a]	No NMU of Loperamide % (95% CI)[a]	p-value[b]
Age, mean (SD), years	46.6 (46.4, 46.8)	42.7 (41.7, 43.8)	46.7 (46.5, 46.9)	<0.001
Female[c]	51.3 (50.7, 51.9)	53.2 (49.5, 56.9)	51.3 (50.7, 51.9)	0.319
Census region[c]				
Northeast	17.9 (17.4, 18.4)	15.1 (12.4, 17.9)	18.0 (17.5, 18.5)	<0.001
South	37.5 (36.9, 38.1)	43.1 (39.5, 46.8)	37.4 (36.8, 37.9)	
Midwest	21.1 (20.6, 21.6)	16.5 (13.8, 19.2)	21.2 (20.7, 21.7)	
West	23.5 (23.0, 24.0)	25.2 (21.9, 28.5)	23.4 (22.9, 24.0)	
Race				
White	83.9 (83.4, 84.4)	82.8 (80.0, 85.6)	83.9 (83.4, 84.4)	0.661
Black/African American	7.5 (7.2, 7.9)	7.0 (5.1, 8.9)	7.5 (7.2, 7.9)	
Asian	3.7 (3.5, 4.0)	3.8 (2.4, 5.1)	3.7 (3.5, 4.0)	
American Indian or Alaska Native	0.8 (0.7, 1.0)	1.5 (0.6, 2.3)	0.8 (0.7, 0.9)	
Native Hawaiian or Other Pacific Islander	0.3 (0.2, 0.3)	0.4 (0.0, 0.9)	0.3 (0.2, 0.3)	
Other	2.3 (2.1, 2.5)	3.1 (1.8, 4.5)	2.3 (2.1, 2.5)	
Did not provide	1.4 (1.2, 1.5)	1.5 (0.6, 2.3)	1.4 (1.2, 1.5)	

[a] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[b] Wald Chi-square test for categorical variables and t-test for continuous variables comparing NMU and no NMU of loperamide
[c] Gender and region distributions were incorporated into Survey of Non-Medical Use of Prescription Drugs Program quota sampling procedures

Characteristics	Total % (95% CI)[a]	Lifetime NMU of Loperamide % (95% CI)[a]	No lifetime NMU of Loperamide % (95% CI)[a]	p-value[b]
Ethnicity				
Hispanic	8.9 (8.5, 9.2)	14.7 (12.1, 17.3)	8.7 (8.4, 9.1)	<0.001
Non-Hispanic	90.1 (89.7, 90.5)	84.2 (81.5, 86.9)	90.3 (89.9, 90.7)	
Did not provide	1.0 (0.9, 1.1)	1.1 (0.4, 1.8)	1.0 (0.9, 1.1)	
Household income				
<$50,000	41.9 (41.3, 42.5)	36.1 (32.6, 39.7)	42.0 (41.4, 42.6)	<0.001
$50,000-$100,000	35.5 (34.9, 36.1)	41.4 (37.8, 45.1)	35.4 (34.8, 35.9)	
>$100,000	16.7 (16.2, 17.1)	19.6 (16.7, 22.5)	16.6 (16.2, 17.0)	
Did not provide	5.9 (5.6, 6.2)	2.8 (1.6, 4.0)	6.0 (5.7, 6.3)	
Current or former military service	10.6 (10.3, 10.9)	7.8 (5.9, 9.7)	10.7 (10.3, 11.0)	0.004
Current college student	11.1 (10.7, 11.6)	12.4 (9.7, 15.1)	11.1 (10.6, 11.5)	0.362
Current healthcare professional	5.1 (4.9, 5.4)	8.5 (6.4, 10.6)	5.0 (4.8, 5.3)	0.002
DAST-10 score				
0 None reported	49.1 (48.5, 49.8)	36.4 (32.9, 40.0)	49.5 (48.9, 50.2)	<0.001
1-2 Low level	39.2 (38.6, 39.9)	42.0 (38.3, 45.7)	39.1 (38.5, 39.8)	
3-5 Moderate level	6.8 (6.5, 7.2)	13.0 (10.4, 15.5)	6.6 (6.3, 7.0)	
6-8 Substantial level	3.0 (2.7, 3.2)	5.7 (3.9, 7.5)	2.9 (2.6, 3.1)	
9-10 Severe level	1.8 (1.7, 2.0)	2.9 (1.7, 4.2)	1.8 (1.6, 2.0)	
Lifetime illicit drug use	38.5 (37.9, 39.1)	49.4 (45.7, 53.2)	38.2 (37.6, 38.8)	<0.001

[a] Data were weighted to reflect the distribution of United States adults by region, gender, and age;
[b] Wald Chi-square test for categorical variables and t-test for continuous variables comparing NMU and no NMU of loperamide
[c] Gender and region distributions were incorporated into Survey of Non-Medical Use of Prescription Drugs Program quota sampling procedures

11.3.2 Recent Non-Medical Use of Loperamide

Table 11.3.2.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program
Characteristics of Respondents Endorsing Recent Non-Medical Use (NMU) of Loperamide
3rd Quarter 2016 United States Survey

Characteristics	Recent NMU of Loperamide				
	Last 7 days % (95% CI)[a]	Last 30 days % (95% CI)[a]	Last 90 days % (95% CI)[a]	No NMU in last 90 days % (95% CI)[a]	p-value[b]
Frequency of NMU, mean (SD), days	2.6 (2.2, 3.0)	5.2 (4.2, 6.3)	10.4 (8.2, 12.7)		
Frequency of NMU, median (IQR), days	1.6 (1.0, 2.8)	2.1 (1.0, 4.9)	4.3 (1.4, 9.7)		
Age, mean (SD), years	37.2 (34.5, 39.9)	37.9 (35.6, 40.2)	39.3 (37.3, 41.2)	46.7 (46.4, 46.9)	<0.001
Female[c]	33.0 (23.7, 42.3)	40.4 (32.3, 48.4)	43.2 (36.3, 50.2)	51.4 (50.8, 52.0)	0.027
Census region[c]					
Northeast	27.5 (17.6, 37.4)	22.1 (14.7, 29.6)	20.3 (14.3, 26.4)	17.9 (17.4, 18.4)	0.246
South	26.2 (17.3, 35.2)	33.2 (25.2, 41.1)	36.7 (29.8, 43.5)	37.5 (36.9, 38.1)	
Midwest	16.4 (8.8, 24.0)	15.9 (9.9, 22.0)	16.2 (11.0, 21.4)	21.1 (20.6, 21.6)	
West	29.9 (20.8, 38.9)	28.8 (21.4, 36.1)	26.8 (20.6, 33.0)	23.5 (23.0, 24.0)	
Race					
White	86.9 (80.2, 93.7)	83.9 (78.0, 89.9)	83.8 (78.7, 89.0)	83.9 (83.4, 84.4)	Not Reported[e]
Black/African American	1.9 (0.0, 4.6)	4.2 (0.9, 7.5)	4.7 (1.7, 7.7)	7.6 (7.2, 7.9)	
Asian	3.0 (0.0, 6.3)	4.3 (1.1, 7.5)	3.6 (1.1, 6.1)	3.7 (3.5, 4.0)	
American Indian or Alaska Native	3.0 (0.0, 6.3)	2.7 (0.1, 5.3)	2.4 (0.3, 4.4)	0.8 (0.7, 1.0)	
Native Hawaiian or Pacific Islander	-[d]	-[d]	-[d]	0.3 (0.2, 0.4)	
Other	5.2 (0.7, 9.7)	4.3 (0.9, 7.6)	4.6 (1.6, 7.6)	2.3 (2.1, 2.5)	
Did not provide	-[d]	0.6 (0.0, 1.9)	0.9 (0.0, 2.2)	1.4 (1.2, 1.5)	

[a] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[b] Wald Chi-square test for categorical variables and t-test for continuous variables comparing NMU of loperamide within the last 90 days to NMU of loperamide more than 90 days ago
[c] Gender and region distributions were incorporated into Survey of Non-Medical Use of Prescription Drugs program quota sampling procedures
[d] No survey respondents in stratum
[e] Insufficient data to calculate p-value

Characteristics	Recent NMU of Loperamide				
	Last 7 days % (95% CI)[a]	Last 30 days % (95% CI)[a]	Last 90 days % (95% CI)[a]	No NMU in Last 90 days % (95% CI)[a]	p-value[b]
Ethnicity					
Hispanic	23.7 (15.2, 32.2)	20.4 (13.9, 26.9)	20.1 (14.5, 25.7)	8.8 (8.4, 9.2)	0.001
Non-Hispanic	76.3 (67.8, 84.8)	79.0 (72.3, 85.6)	78.9 (73.2, 84.6)	90.2 (89.8, 90.6)	
Did not provide	-[d]	0.6 (0.0, 1.9)	1.1 (0.0, 2.5)	1.0 (0.9, 1.1)	
Household income					
<$50,000	18.3 (10.2, 26.4)	26.4 (19.0, 33.8)	29.8 (23.3, 36.2)	42.0 (41.4, 42.6)	<0.001
$50,000-$100,000	54.1 (43.8, 64.4)	48.5 (40.1, 57.0)	47.8 (40.6, 55.0)	35.4 (34.8, 36.0)	
>$100,000	26.7 (18.0, 35.3)	23.8 (17.0, 30.6)	21.5 (15.9, 27.1)	16.6 (16.2, 17.1)	
Did not provide	0.9 (0.0, 2.8)	1.3 (0.0, 3.0)	1.0 (0.0, 2.3)	6.0 (5.7, 6.3)	
Current or former military service	5.6 (1.4, 9.8)	4.9 (1.6, 8.2)	6.0 (2.9, 9.1)	10.6 (10.3, 11.0)	0.004
Current college student	20.7 (10.8, 30.6)	18.3 (10.8, 25.8)	17.3 (11.2, 23.4)	11.1 (10.6, 11.5)	0.054
Current healthcare professional	9.2 (3.7, 14.7)	8.1 (3.8, 12.4)	8.9 (5.0, 12.7)	5.1 (4.8, 5.4)	0.055
DAST-10 score					
0 None reported	17.6 (10.2, 25.0)	22.5 (15.8, 29.2)	27.2 (21.0, 33.3)	49.3 (48.7, 50.0)	<0.001
1-2 Low level	39.1 (29.2, 49.1)	44.4 (36.1, 52.7)	42.9 (35.9, 49.9)	39.2 (38.5, 39.9)	
3-5 Moderate level	21.3 (11.8, 30.9)	15.7 (8.8, 22.6)	15.4 (9.7, 21.1)	6.8 (6.4, 7.1)	
6-8 Substantial level	14.4 (7.1, 21.8)	12.4 (6.8, 18.0)	10.7 (6.2, 15.2)	2.9 (2.7, 3.1)	
9-10 Severe level	7.5 (2.5, 12.5)	5.0 (1.6, 8.5)	3.8 (1.2, 6.3)	1.8 (1.6, 2.0)	

[a] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[b] Wald Chi-square test for categorical variables and t-test for continuous variables comparing NMU of loperamide within the last 90 days to NMU of loperamide more than 90 days ago
[c] Gender and region distributions were incorporated into Survey of Non-Medical Use of Prescription Drugs Program quota sampling procedures
[d] No survey respondents in stratum
[e] Insufficient data to calculate p-value

11.3.3 Non-Medical Use of Loperamide and Drug Use

Table 11.3.3.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program
Drug Use of Respondents Endorsing Non-Medical Use (NMU) of Loperamide
3rd Quarter 2016 United States Survey

Drug of Interest	Timing of last NMU of Loperamide at time of survey				
	Last 7 days % (95% CI)[b]	Last 30 days % (95% CI)[b]	Last 90 days % (95% CI)[a]	No NMU in last 90 days % (95% CI)[a]	p-value[b]
Any prescription opioid					
Lifetime NMU	87.2 (80.7, 93.7)	85.9 (80.4, 91.4)	85.1 (80.2, 90.0)	62.8 (62.2, 63.4)	<0.001
Last 30 days NMU	36.0 (26.0, 45.9)	30.3 (22.4, 38.1)	25.0 (18.7, 31.4)	5.1 (4.8, 5.3)	<0.001
Heroin					
Lifetime use	20.7 (12.8, 28.6)	15.3 (9.5, 21.0)	13.3 (8.7, 17.9)	3.8 (3.6, 4.1)	<0.001
Last 30 day use	10.5 (4.6, 16.5)	7.1 (3.0, 11.2)	5.8 (2.6, 9.0)	1.4 (1.2, 1.5)	0.008
Any illicit drug					
Lifetime use	59.5 (49.5, 69.6)	55.8 (47.5, 64.1)	54.0 (46.9, 61.1)	38.4 (37.8, 39.0)	<0.001
Last 30 day use	40.5 (30.1, 50.9)	33.5 (25.3, 41.6)	28.5 (21.8, 35.2)	11.2 (10.8, 11.6)	<0.001

[a] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[b] Wald Chi-square test for categorical variables comparing NMU of loperamide within the last 90 days to NMU of loperamide more than 90 days ago

11.4 Reasons and Routes for Non-Medical Use of Loperamide

11.4.1 Reason and Route for Non-Medical Use of Loperamide

Table 11.4.1.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program
Reasons and Routes for Non-Medical Use (NMU) of Loperamide
3rd Quarter 2016 United States Survey

Respondent Endorsement	Lifetime NMU of Loperamide % (95% CI)[a]
Reason for NMU[b]	
To self-treat my pain	39.0 (35.4, 42.7)
To treat a medical condition, other than pain	56.6 (52.9, 60.3)
For enjoyment/to get high	5.9 (4.1, 7.7)
To come down	3.3 (1.9, 4.8)
To prevent or treat withdrawal symptoms	4.7 (3.1, 6.4)
Other reason	1.5 (0.6, 2.4)
Routes of administration for NMU[b]	
Swallowed	88.2 (85.8, 90.7)
Chewed and then swallowed	12.2 (9.6, 14.7)
Dissolved in mouth (e.g. between cheek and gum, under tongue)	7.1 (5.2, 9.0)
Inhaled (snorted or smoked)	5.2 (3.5, 6.9)
Injected (shot it up)	5.6 (3.9, 7.3)
Other route	5.7 (3.9, 7.4)

[a] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[b] Survey respondents may endorse multiple reasons and multiple routes, percentages will not sum to 100

11.4.2 Reason by Route for Non-Medical Use of Loperamide

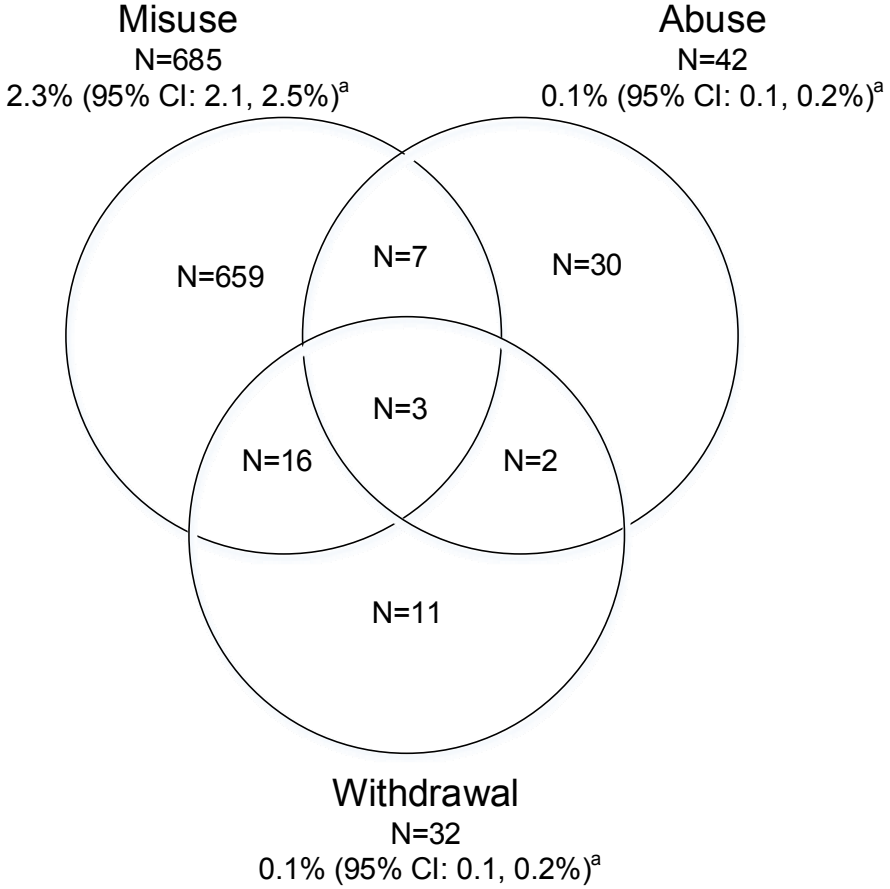
Table 11.4.2.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program Reasons for Non-Medical Use (NMU) of Loperamide by Route among Respondents 3rd Quarter 2016 United States Survey

Route of administration for NMU	Reasons for NMU[a,b]					
	To self-treat my pain % (95% CI)[c]	To treat a medical condition, other than pain % (95% CI)[c]	For enjoyment/ to get high % (95% CI)[c]	To come down % (95% CI)[c]	To prevent or treat withdrawal symptoms % (95% CI)[c]	Other reason % (95% CI)[c]
Swallowed	91.4 (87.7, 95.1)	90.7 (87.5, 93.9)	Not Reported[d]	Not Reported[d]	Not Reported[d]	Not Reported[d]
Chewed and then swallowed	11.5 (7.5, 15.6)	6.5 (3.7, 9.4)	Not Reported[d]	Not Reported[d]	Not Reported[d]	Not Reported[d]
Dissolved in mouth (e.g. between cheek and gum, under tongue)	6.3 (3.2, 9.4)	2.4 (0.8, 4.0)	Not Reported[d]	Not Reported[d]	Not Reported[d]	Not Reported[d]
Inhaled (snorted or smoked)	2.2 (0.2, 4.1)	0.8 (0.0, 1.7)	Not Reported[d]	Not Reported[d]	Not Reported[d]	Not Reported[d]
Injected (shot it up)	2.9 (0.7, 5.1)	1.0 (0.0, 2.1)	Not Reported[d]	Not Reported[d]	Not Reported[d]	Not Reported[d]
Other route	2.5 (0.5, 4.6)	1.4 (0.2, 2.7)	Not Reported[d]	Not Reported[d]	Not Reported[d]	Not Reported[d]

[a] Includes only respondents who endorse only one reason for NMU of loperamide (Unweighted N=677). Routes relate directly to the intended reason endorsed by respondents
[b] Survey respondents may endorse multiple routes, percentages will not sum to 100
[c] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[d] Reason and route combinations with less than 30 respondents in the denominator are excluded from the analysis

11.4.3 Reasons for Non-Medical Use of Loperamide

Figure 11.4.3.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program
Subject Disposition Detailing Reasons for Non-Medical Use of Loperamide
3rd Quarter 2016 United States Survey



[a] Prevalence estimates were weighted to reflect the distribution of United States adults by region, gender, and age
[b] The numbers in the circles represent the raw, unweighted number of respondents who reported reasons for non-medical use of loperamide in the survey. Respondents could select more than one reason for non-medical use of loperamide, hence the overlap between reported reasons.

11.5 Non-Medical Use of Loperamide for Misuse, Abuse, and Prevention or Treatment of Withdrawal Symptoms

11.5.1 Misuse of Loperamide

Table 11.5.1.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program Characteristics of Respondents Endorsing Misuse of Loperamide 3rd Quarter 2016 United States Survey

Characteristics	Total % (95% CI)[b]	Misuse[a] % (95% CI)[b]	No misuse[a] % (95% CI)[b]	p-value[c]
Age, mean (SD), years	46.6 (46.4, 46.8)	43.4 (42.2, 44.5)	46.7 (46.5, 46.9)	<0.001
Female[d]	51.3 (50.7, 51.9)	54.7 (50.8, 58.6)	51.2 (50.6, 51.8)	0.083
Census region[d]				
Northeast	17.9 (17.4, 18.4)	15.4 (12.5, 18.3)	18.0 (17.5, 18.5)	0.003
South	37.5 (36.9, 38.1)	43.3 (39.5, 47.2)	37.4 (36.8, 38.0)	
Midwest	21.1 (20.6, 21.6)	17.0 (14.1, 19.8)	21.2 (20.7, 21.7)	
West	23.5 (23.0, 24.0)	24.3 (20.9, 27.6)	23.5 (23.0, 24.0)	
Race				
White	83.9 (83.4, 84.4)	82.5 (79.6, 85.5)	83.9 (83.4, 84.4)	0.597
Black/African American	7.5 (7.2, 7.9)	6.8 (4.9, 8.7)	7.6 (7.2, 7.9)	
Asian	3.7 (3.5, 4.0)	4.1 (2.6, 5.6)	3.7 (3.5, 4.0)	
American Indian or Alaska Native	0.8 (0.7, 1.0)	1.4 (0.5, 2.3)	0.8 (0.7, 0.9)	
Native Hawaiian or Other Pacific Islander	0.3 (0.2, 0.3)	0.5 (0.0, 1.0)	0.3 (0.2, 0.3)	
Other	2.3 (2.1, 2.5)	3.3 (1.8, 4.7)	2.3 (2.1, 2.5)	
Did not provide	1.4 (1.2, 1.5)	1.4 (0.6, 2.3)	1.4 (1.2, 1.5)	

[a] Misuse is defined as non-medical use (NMU) of loperamide to self-treat pain or treat a medical condition other than pain
[b] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[c] Wald Chi-square test for categorical variables and t-test for continuous variables comparing misuse to no misuse of loperamide
[d] Gender and region distributions were incorporated into Survey of Non-Medical Use of Prescription Drugs Program quota sampling procedures

Characteristics	Total % (95% CI)[b]	Misuse[a] % (95% CI)[b]	No Misuse[a] % (95% CI)[b]	p-value[c]
Ethnicity				
Hispanic	8.9 (8.5, 9.2)	13.9 (11.2, 16.6)	8.8 (8.4, 9.1)	0.001
Non-Hispanic	90.1 (89.7, 90.5)	84.9 (82.2, 87.7)	90.2 (89.9, 90.6)	
Did not provide	1.0 (0.9, 1.1)	1.2 (0.4, 2.0)	1.0 (0.9, 1.1)	
Household income				
<$50,000	41.9 (41.3, 42.5)	38.0 (34.2, 41.8)	42.0 (41.4, 42.6)	<0.001
$50,000-$100,000	35.5 (34.9, 36.1)	40.7 (36.9, 44.5)	35.4 (34.8, 36.0)	
>$100,000	16.7 (16.2, 17.1)	18.3 (15.3, 21.2)	16.6 (16.2, 17.1)	
Did not provide	5.9 (5.6, 6.2)	3.0 (1.7, 4.4)	6.0 (5.7, 6.3)	
Current or former military service	10.6 (10.3, 10.9)	7.7 (5.8, 9.7)	10.7 (10.3, 11.0)	0.004
Current college student	11.1 (10.7, 11.6)	11.7 (8.9, 14.6)	11.1 (10.7, 11.6)	0.666
Current healthcare professional	5.1 (4.9, 5.4)	8.2 (6.0, 10.3)	5.0 (4.8, 5.3)	0.006
DAST-10 score				
0 None reported	49.1 (48.5, 49.8)	38.7 (34.9, 42.4)	49.4 (48.8, 50.1)	<0.001
1-2 Low level	39.2 (38.6, 39.9)	42.5 (38.6, 46.3)	39.1 (38.5, 39.8)	
3-5 Moderate level	6.8 96.5, 7.2)	11.4 (8.9, 14.0)	6.7 (6.4, 7.1)	
6-8 Substantial level	3.0 (2.7, 3.2)	5.1 (3.3, 7.0)	2.9 (2.7, 3.1)	
9-10 Severe level	1.8 (1.7, 2.0)	2.3 (1.1, 3.5)	1.8 (1.6, 2.0)	

[a] Misuse is defined as non-medical use (NMU) of loperamide to self-treat pain or treat a medical condition other than pain
[b] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[c] Wald Chi-square test for categorical variables and t-test for continuous variables comparing misuse to no misuse of loperamide
[d] Gender and region distributions were incorporated into Survey of Non-Medical Use of Prescription Drugs Program quota sampling procedures

11.5.2 Misuse of Loperamide and Drug Use

Table 11.5.2.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program
Drug Use of Respondents Endorsing Misuse of Loperamide
3rd Quarter 2016 United States Survey

Drug of Interest	Total % (95% CI)[b]	Misuse[a] % (95% CI)[b]	No misuse[a] % (95% CI)[b]	p-value[c]
Any prescription opioid				
Lifetime NMU	62.9 (62.3, 63.5)	83.4 (80.6, 86.3)	62.4 (61.9, 63.0)	<0.001
Last 30 days NMU	5.2 (4.9, 5.5)	10.4 (8.0, 12.9)	5.1 (4.8, 5.4)	<0.001
Heroin				
Lifetime use	3.9 (3.7, 4.1)	5.9 (4.1, 7.7)	3.8 (3.6, 4.1)	0.026
Last 30 day use	1.4 (1.3, 1.5)	1.9 (0.9, 2.9)	1.4 (1.2, 1.5)	0.340
Any illicit drug				
Lifetime use	38.5 (37.9, 39.1)	48.6 (44.7, 52.5)	38.3 (37.7, 38.9)	<0.001
Last 30 day use	11.3 (10.9, 11.7)	14.6 (11.6, 17.5)	11.2 (10.8, 11.6)	0.033

[a] Misuse is defined as non-medical use (NMU) of loperamide to self-treat pain or treat a medical condition other than pain
[b] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[c] Wald Chi-square test for categorical variables comparing misuse to no misuse of loperamide

11.5.3 Abuse of Loperamide

Table 11.5.3.1: RADARS® System Survey of Non-Medical use of Prescription Drugs Program Characteristics of Respondents Endorsing Abuse of Loperamide 3rd Quarter 2016 United States Survey

Characteristics	Total % (95% CI)[b]	Abuse[a] % (95% CI)[b]	No abuse[a] % (95% CI)[b]	p-value[c]
Age, mean (SD), years	46.6 (46.4, 46.8)	34.4 (31.9, 36.9)	46.6 (46.4, 46.8)	<0.001
Female[d]	51.3 (50.7, 51.9)	14.8 (4.4, 25.1)	51.4 (50.8, 52.0)	<0.001
Census region[d]				
Northeast	17.9 (17.4, 18.4)	21.7 (9.0, 34.5)	17.9 (17.4, 18.4)	0.208
South	37.5 (36.9, 38.1)	35.3 (20.1, 50.5)	37.5 (36.9, 38.1)	
Midwest	21.1 (20.6, 21.6)	11.2 (1.8, 20.6)	21.1 (20.6, 21.6)	
West	23.5 (23.0, 24.0)	31.9 (17.8, 46.0)	23.5 (23.0, 24.0)	
Race				
White	83.9 (83.4, 84.4)	87.9 (77.8, 97.9)	83.9 (83.4, 84.3)	Not Reported[f]
Black/African American	7.5 (7.2, 7.9)	12.1 (2.1, 22.2)	7.5 (7.2, 7.9)	
Asian	3.7 (3.5, 4.0)	-[e]	3.7 (3.5, 4.0)	
American Indian or Alaska Native	0.8 (0.7, 1.0)	-[e]	0.9 (0.7, 1.0)	
Native Hawaiian or Other Pacific Islander	0.3 (0.2, 0.3)	-[e]	0.3 (0.2, 0.3)	
Other	2.3 (2.1, 2.5)	-[e]	2.3 (2.1, 2.5)	
Did not provide	1.4 (1.2, 1.5)	-[e]	1.4 (1.2, 1.5)	

[a] Abuse is defined as non-medical use (NMU) of loperamide to get high
[b] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[c] Wald Chi-square test for categorical variables and t-test for continuous variables comparing abuse to no abuse of loperamide
[d] Gender and region distributions were incorporated into Survey of Non-Medical Use of Prescription Drugs Program quota sampling procedures
[e] No survey respondents in stratum
[f] Insufficient data to calculate p-value

Characteristics	Total % (95% CI)[b]	Abuse[a] % (95% CI)[b]	No abuse[a] % (95% CI)[b]	p-value[c]
Ethnicity				
Hispanic	8.9 (8.5, 9.2)	25.7 (12.4, 38.9)	8.8 (8.5, 9.2)	Not Reported[f]
Non-Hispanic	90.1 (89.7, 90.5)	74.3 (61.1, 87.6)	90.1 (89.8, 90.5)	
Did not provide	1.0 (0.9, 1.1)	-[e]	1.0 (0.9, 1.1)	
Household income				
<$50,000	41.9 (41.3, 42.5)	4.2 (0.0, 9.9)	42.0 (41.4, 42.5)	Not Reported[f]
$50,000-$100,000	35.5 (34.9, 36.1)	61.7 (46.9, 76.5)	35.5 (34.9, 36.0)	
>$100,000	16.7 (16.2, 17.1)	34.1 (19.7, 48.5)	16.7 (16.2, 17.1)	
Did not provide	5.9 (5.6, 6.2)	-[e]	5.9 (5.6, 6.2)	
Current or former military service	10.6 (10.3, 10.9)	15.5 (4.0, 27.0)	10.6 (10.3, 10.9)	0.411
Current college student	11.1 (10.7, 11.6)	17.0 (5.3, 28.6)	11.1 (10.7, 11.6)	0.331
Current healthcare professional	5.1 (4.9, 5.4)	14.7 (3.7, 25.8)	5.1 (4.8, 5.4)	0.101
DAST-10 score				
0 None reported	49.1 (48.5, 49.8)	2.3 (0.0, 6.9)	49.2 (48.6, 49.9)	<0.001
1-2 Low level	39.2 (38.6, 39.9)	38.5 (23.0, 54.0)	39.2 (38.6, 39.9)	
3-5 Moderate level	6.8 96.5, 7.2)	29.5 (15.7, 43.2)	6.8 (6.5, 7.1)	
6-8 Substantial level	3.0 (2.7, 3.2)	18.3 (6.7, 29.9)	2.9 (2.7, 3.2)	
9-10 Severe level	1.8 (1.7, 2.0)	11.3 (1.9, 20.8)	1.8 (1.6, 2.0)	

[a] Abuse is defined as non-medical use (NMU) of loperamide to get high
[b] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[c] Wald Chi-square test for categorical variables and t-test for continuous variables comparing abuse to no abuse of loperamide
[d] Gender and region distributions were incorporated into Survey of Non-Medical Use of Prescription Drugs Program quota sampling procedures;
[e] No survey respondents in stratum
[f] Insufficient data to calculate p-value

11.5.4 Abuse of Loperamide and Drug Use

Table 11.5.4.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program
Drug Use of Respondents Endorsing Abuse of Loperamide
3rd Quarter 2016 United States Survey

Drug of Interest	Total % (95% CI)[b]	Abuse[a] % (95% CI)[b]	No abuse[a] % (95% CI)[b]	p-value[c]
Any prescription opioid				
Lifetime NMU	62.9 (62.3, 63.5)	82.6 (70.8, 94.5)	62.9 (62.3, 63.5)	0.004
Last 30 days NMU	5.2 (4.9, 5.5)	42.1 (26.6, 57.6)	5.1 (4.9, 5.4)	<0.001
Heroin				
Lifetime use	3.9 (3.7, 4.1)	44.4 (29.1, 59.8)	3.8 (3.6, 4.1)	<0.001
Last 30 day use	1.4 (1.3, 1.5)	20.6 (8.5, 32.7)	1.4 (1.2, 1.5)	0.005
Any illicit drug				
Lifetime use	38.5 (37.9, 39.1)	67.7 (52.7, 82.6)	38.5 (37.9, 39.0)	0.001
Last 30 day use	11.3 (10.9, 11.7)	58.8 (43.4, 74.2)	11.3 (10.9, 11.6)	<0.001

[a] Abuse is defined as non-medical use (NMU) of loperamide to get high
[b] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[c] Wald Chi-square test for categorical variables comparing misuse to no misuse of loperamide

11.5.5 Non-Medical Use of Loperamide to Prevent or Treat Withdrawal Symptoms

Table 11.5.5.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program Characteristics of Respondents Endorsing Non-medical Use of Loperamide to Prevent or Treat Withdrawal Symptoms 3rd Quarter 2016 United States Survey

Characteristics	Total % (95% CI)[a]	To prevent or treat withdrawal symptoms % (95% CI)[a]	Not to prevent or treat withdrawal symptoms % (95% CI)[a]	p-value[b]
Age, mean (SD), years	46.6 (46.4, 46.8)	32.3 (28.8, 35.7)	46.6 (46.4, 46.8)	<0.001
Female[c]	51.3 (50.7, 51.9)	23.8 (8.9, 38.7)	51.4 (50.8, 52.0)	0.004
Census region[c]				
Northeast	17.9 (17.4, 18.4)	19.1 (6.0, 32.2)	17.9 (17.4, 18.4)	0.573
South	37.5 (36.9, 38.1)	47.4 (29.2, 65.6)	37.5 (36.9, 38.1)	
Midwest	21.1 (20.6, 21.6)	12.0 (0.0, 26.0)	21.1 (20.6, 21.6)	
West	23.5 (23.0, 24.0)	21.5 (7.1, 35.9)	23.5 (23.0, 24.0)	
Race				
White	83.9 (83.4, 84.4)	90.3 (79.7, 100.0)	83.9 (83.4, 84.3)	Not Reported[e]
Black/African American	7.5 (7.2, 7.9)	3.6 (0.0, 10.4)	7.5 (7.2, 7.9)	
Asian	3.7 (3.5, 4.0)	-[d]	3.7 (3.5, 4.0)	
American Indian or Alaska Native	0.8 (0.7, 1.0)	-[d]	0.8 (0.7, 1.0)	
Native Hawaiian or Other Pacific Islander	0.3 (0.2, 0.3)	-[d]	0.3 (0.2, 0.3)	
Other	2.3 (2.1, 2.5)	2.8 (0.0, 8.1)	2.3 (2.1, 2.5)	
Did not provide	1.4 (1.2, 1.5)	3.4 (0.0, 9.9)	1.4 (1.2, 1.5)	

[a] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[b] Wald Chi-square test for categorical variables and t-test for continuous variables comparing misuse to no misuse of loperamide among those who endorsed NMU of loperamide
[c] Gender and region distributions were incorporated into Survey of Non-Medical Use of Prescription Drugs Program quota sampling procedures
[d] No survey respondents in stratum
[e] Insufficient data to calculate p-value

Characteristics	Total % (95% CI)[a]	To prevent or treat withdrawal symptoms % (95% CI)[a]	Not to prevent or treat withdrawal symptoms % (95% CI)[a]	p-value[b]
Ethnicity				
Hispanic	8.9 (8.5, 9.2)	22.8 (8.4, 37.2)	8.9 (8.5, 9.2)	0.128
Non-Hispanic	90.1 (89.7, 90.5)	73.6 (58.3, 88.9)	90.1 (89.8, 90.5)	
Did not provide	1.0 (0.9, 1.1)	3.6 (0.0, 10.4)	1.0 (0.9, 1.1)	
Household income				
<$50,000	41.9 (41.3, 42.5)	28.6 (10.2, 46.9)	41.9 (41.3, 42.5)	Not Reported[e]
$50,000-$100,000	35.5 (34.9, 36.1)	39.8 (22.5, 57.1)	35.5 (34.9, 36.1)	
>$100,000	16.7 (16.2, 17.1)	31.6 (15.4, 47.8)	16.7 (16.2, 17.1)	
Did not provide	5.9 (5.6, 6.2)	-[d]	5.9 (5.6, 6.2)	
Current or former military service	10.6 (10.3, 10.9)	2.9 (0.0, 8.6)	10.6 (10.3, 11.0)	0.019
Current college student	11.1 (10.7, 11.6)	29.5 (11.0, 47.9)	11.1 (10.7, 11.6)	0.088
Current healthcare professional	5.1 (4.9, 5.4)	-[d]	5.1 (4.9, 5.4)	Not Reported[e]
DAST-10 score				
0 None reported	49.1 (48.5, 49.8)	16.4 (4.0, 28.8)	49.2 (48.5, 49.8)	0.006
1-2 Low level	39.2 (38.6, 39.9)	32.4 (16.0, 48.9)	39.2 (38.6, 39.9)	
3-5 Moderate level	6.8 96.5, 7.2)	20.4 (6.5, 34.2)	6.8 (6.5, 7.2)	
6-8 Substantial level	3.0 (2.7, 3.2)	19.7 (2.1, 37.3)	2.9 (2.7, 3.2)	
9-10 Severe level	1.8 (1.7, 2.0)	11.1 (0.7, 21.5)	1.8 (1.6, 2.0)	

[a] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[b] Wald Chi-square test for categorical variables and t-test for continuous variables comparing misuse to no misuse of loperamide among those who endorsed NMU of loperamide
[c] Gender and region distributions were incorporated into Survey of Non-Medical Use of Prescription Drugs Program quota sampling procedures
[d] No survey respondents in stratum
[e] Insufficient data to calculate p-value

11.5.6 Non-Medical Use of Loperamide to Prevent or Treat Withdrawal Symptoms and Drug Use

Table 11.5.6.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program
Drug Use of Respondents Endorsing Non-medical Use of Loperamide to Prevent or Treat Withdrawal Symptoms
3rd Quarter 2016 United States Survey

Drug of Interest	Total % (95% CI)[a]	To prevent or treat withdrawal symptoms % (95% CI)[a]	Not to prevent or treat withdrawal symptoms % (95% CI)[a]	p-value[b]
Any prescription opioid				
Lifetime NMU	62.9 (62.3, 63.5)	88.4 (77.5, 99.3)	62.9 (62.3, 63.5)	0.001
Last 30 days NMU	5.2 (4.9, 5.5)	48.4 (30.1, 66.6)	5.1 (4.9, 5.4)	0.001
Heroin				
Lifetime use	3.9 (3.7, 4.1)	29.5 (13.6, 45.4)	3.9 (3.6, 4.1)	0.005
Last 30 day use	1.4 (1.3, 1.5)	8.6 (0.0, 18.0)	1.4 (1.2, 1.5)	0.141
Any illicit drug				
Lifetime use	38.5 (37.9, 39.1)	69.4 (53.5, 85.3)	38.5 (37.9, 39.1)	0.003
Last 30 day use	11.3 (10.9, 11.7)	48.8 (30.6, 67.0)	11.3 (10.9, 11.7)	0.002

[a] Data were weighted to reflect the distribution of United States adults by region, gender, and age
[b] Wald Chi-square test for categorical variables comparing NMU to prevent or treat withdrawal symptoms to no NMU of loperamide to prevent or treat withdrawal symptoms

11.6 Rate of Recent Non-Medical Use of Loperamide Endorsements to Units Sold

11.6.1 Loperamide Non-Medical Use Endorsements and Sales Volume

Table 11.6.1.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program
Rate of Recent Loperamide Non-Medical Use Endorsements to Sales Volume
3rd Quarter 2016 United States Survey

Rate of last 90 day non-medical use (endorsements/100 sales volume[a])	95% Confidence Interval
1.5	(1.3, 1.7)

[a] Rate defined as number of endorsements of non-medical use in the past 90 days divided by the sales volume from 4th quarter 2015 (Oct. 5 – Dec. 27) and rescaled per 100 volume (e.g. tablets, soft gels, liquid equivalents, oral solutions, or oral suspensions).

12 Conclusions

12.1 Data Implications

Although the overall prevalence of NMU, misuse, abuse, and NMU of loperamide to prevent or treat withdrawal symptoms is low, these behaviors are risk factors for other behaviors that can be a high public health burden such as endorsement of multiple drugs (specifically, NMU of prescription opioids and use of heroin and any illicit drugs). The demographic characteristics and other risk factors identified that have been identified in this report can be used to target strategies for preventing NMU of loperamide.

Of respondents who endorsed NMU of loperamide, the majority reported misuse (to prevent or treat a medical condition other than pain or to self-treat pain) of loperamide. This report also identified that there are low proportions of respondents who endorse NMU of loperamide by unintended routes of administration. Public health interventions may be most effective by focusing on NMU of loperamide accomplished by routes that are recommended by the packaging (e.g. swallowing, and chewing and then swallowing).

12.2 Data Strengths

Some of the strengths of the data are the large sample size, which is weighted to represent the distribution of adults in the United States, and the richness of the data obtained in the Survey of Non-Medical Use of Prescription Drugs Program survey such as many possible risk factors, reason for use, and routes of administration of loperamide.

12.3 Data Limitations

Reason and route of proper medical use of loperamide is not collected; therefore, population estimates of proper use cannot be calculated using the survey data. Sales data denominators used in the rate of NMU of loperamide to sales volume should be treated as a proxy for drug utilization-based rates. Additionally, respondents in online panel surveys are a self-selected population and may not behave similarly to those who did not choose to complete the survey.

13 References

1. Skinner, H. A. “The Drug Abuse Screening Test.” *Addictive Behavior*, vol. 7, no. 4, 1982, pp 363–371.
2. “Methodology for the United States Population Estimates: Vintage 2015.” United States Census Bureau, http://www.census.gov/popest/methodology/2015-natstcopr-meth.pdf. Accessed November 2016.

1 National Poison Data System Summary of Loperamide-Containing Product Exposures

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SPONSOR CONTACT:	Leslie Shur, D.O., F.A.A.P. Director, OTC Global Medical Affairs Global Medical Affairs Leader—Analgesics
TARGET DRUG SUBSTANCES:	Loperamide
PROGRAMS:	National Poison Data System
REPORTING COUNTRIES:	United States
PRINCIPAL INVESTIGATORS:	**Jody L. Green, PhD, CCRP** Denver Health and Hospital Authority Rocky Mountain Poison & Drug Center 777 Bannock Street, Mail Code 0180 Denver, Colorado 80204 (United States)
REPORT DATE:	30 June 2017

2 Executive Summary

There have been reports of massive overdose of loperamide resulting in serious cardiovascular events. In particular, reports from poison centers have highlighted the association between loperamide abuse and cardiovascular toxicity.[1] These reports have primarily focused on the experience of only a single poison center, which may not reflect national trends. This report utilizes data from the National Poison Data System (NPDS), which is a national repository of all regional poison center data on pharmaceutical and non-pharmaceutical exposures. Loperamide-containing product data are summarized. This report also utilizes nationwide sales data to provide further context for loperamide-containing product availability and the association with reports of exposure.

Key findings:

- Over the 4-year study period (2012 to 2015), 4,856 exposures involving a loperamide-containing product were reported to the National Poison Data System (NPDS). The majority of these exposures involved unintentional reasons for exposure (exposure resulting from an unforeseen or unplanned event). Intentional abuse (n=185; intentional improper or incorrect use of a substance where 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) and intentional misuse (n=418; intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect) were reported infrequently (12.4% of all exposures).
- The rate of reported exposures in the context of sales of loperamide-containing products was low at 2.423 exposures per 1 million units sold or one case per 0.413 million units (i.e., tablets, gelcaps, liquid equivalents) sold, which didn't change significantly over the time period.
- Most exposures involved only the loperamide-containing product (n=3,619; 74.5%) and no other substances. A loperamide-containing product plus at least one other substance was reported in 25.5% (n=1,237).
- Exposures involved loperamide-containing products only in 3,619 (74.6%) of all exposures to loperamide-containing products. Intentional exposures to loperamide-containing products only involved mostly adults and children aged ≥12 years among intentional exposures (89.1%; n=599/672), while unintentional exposures involved mostly children aged <12 years (70.2%; n=1,911/2,723). Intentional exposures were referred for healthcare facility (HCF) care in 76.2% (n=512/672) of exposures and admitted to a HCF in 40.4% (n=207/512), and involved a remarkable medical outcome (moderate effect, major effect, or death) in 21.4% (n=144/672). Unintentional exposures were referred for HCF care in 26.3% (n=717/2,723) of exposures and admitted to a HCF in 11.3% (n=81/717), and involved a remarkable medical outcome in 1.0% (n=26/2,723).
    - A total of 125 (3.5%) exposures to loperamide-containing products only involved intentional abuse. Median age of patients among intentional abuse exposures to loperamide-containing products only was 26.0. Intentional abuse exposures were referred for HCF care in 92.0% (n=115) of exposures and admitted to a HCF in 57.4% (n=66) and involved a remarkable medical outcome in 43.2% (n=54). Average rate of intentional abuse of loperamide-containing products only was 0.061 exposures per 1 million units sold or one case per 16.393 million units (i.e., tablets, gelcaps, liquid equivalents) sold, which did not change over the study period.
    - A total of 353 exposures to loperamide-containing products only involved intentional misuse (9.8%). Median age of patients among intentional misuse

exposures of loperamide-containing products only was 46.0. Intentional misuse exposures were referred for HCF care in 62.9% (n=222) of exposures and admitted to a HCF in 22.5% (n=50) and involved a remarkable medical outcome in 12.5% (n=44). Average rate of intentional misuse of loperamide-containing products only was 0.173 exposures per 1 million units sold or one case per 5.780 million units (i.e., tablets, gelcaps, liquid equivalents) sold. This rate increased significantly over the study period (0.131 (CI 0.099, 0.173) in 2012 to 0.229 (CI 0.180, 0.290 in 2015).

  - Six fatalities involving loperamide-containing products only were reported between 2012 and 2014 (2012 n=2; 2013 n=1; 2014 n=3); no fatalities involving loperamide-containing products only were reported in 2015. Ages ranged from 21 to 29 years and the majority (83.3%; n=5) involved male patients. Intentional abuse was the reason for exposure in three cases (50.0%; n=3) and the remaining cases having either intentional unknown (33.3%, n=2) or unknown reason for exposure (16.7%; n=1). The loperamide-containing product was determined to be at least contributory to the fatality in all 6 cases.

- Exposures involved a loperamide-containing product plus another substance in 1,237 (25.5%) of all exposures to loperamide-containing products. Intentional exposures to loperamide-containing products plus another substance involved mostly adults (96.6%; n=600/621), while unintentional exposures primarily involved children aged ≥12 years (62.9%; n=327/520). Intentional exposures were referred for healthcare facility (HCF) care in 96.9% (n=602/621) of exposures and admitted to a HCF in 72.9% (n=439/602), and involved a remarkable medical outcome in 41.7% (n=259/621). Unintentional exposures were referred for HCF care in 48.7% (n=253/520) of exposures and admitted to a HCF in 21.3% (n=54/253), and involved a remarkable medical outcome in 4.8% (n=25/520).
  - A total of 60 exposures to a loperamide-containing product plus another substance involved intentional abuse (4.9%). Median age of patients among intentional abuse exposures to a loperamide-containing product plus another substance was 28.0. Intentional abuse exposures were referred for HCF care in 98.3% (n=59) of exposures and admitted to a HCF in 64.4% (n=38), and involved a remarkable medical outcome in 66.7% (n=40). The average rate of intentional abuse of loperamide-containing products plus another substance was 0.030 exposures per 1 million units sold or one case per 33.333 million units (i.e., tablets, gelcaps, liquid equivalents) sold, which did not change over the study period.
  - A total of 65 exposures to a loperamide-containing product plus another substance involved intentional misuse (5.3%). Median age of patients among intentional misuse exposures to a loperamide-containing product plus another substance was 31.0 (SD 19.73 years). Intentional misuse exposures were referred for HCF care in 81.5% (n=53) of exposures and admitted to a HCF in 47.2% (n=25), and involved a remarkable medical outcome in 32.3% (n=21). The average rate of intentional misuse of loperamide-containing products plus another substance was 0.032 exposures per 1 million units sold or one case per 31.250 million units (i.e., tablets, gelcaps, liquid equivalents) sold, which did not change over the study period.
  - Six fatalities involving a loperamide-containing product plus another substance were reported between 2013 and 2015 (2013 n=1; 2014 n=1; 2015 n=4); no fatalities involving loperamide-containing products plus another substance were reported in 2012. Ages ranged from 23 to 54 years and the majority (83.3%; n=5) were female. The reason for exposure was unknown in most (66.7%; n=4) cases,

with the remaining cases involving intentional suspected suicide (16.7%; n=1) and intentional abuse (16.7%; n=1). The exposure (including loperamide-containing products and non-loperamide containing products) was determined to be at least contributory to the fatality in 2 of the 6 cases.

3 Table of Contents

4 List of Tables

5 List of Figures

6 List of Acronyms

ADR	Adverse Drug Reaction
ALT	Alanine Aminotransferase
AMA	Against Medical Advice
AST	Aspartate Aminotransferase
CI	Confidence Interval
COMIRB	Colorado Multiple Institutional Review Board
CPK	Creatine Phosphokinase
CPR	Cardiopulmonary Resuscitation
CVA	Cerebrovascular Accident
ECG	Electrocardiography
ECMO	Extracorporeal Membrane Oxygenation
GI	Gastrointestinal
HCF	Healthcare Facility
IRI	Information Resources, Inc.®
IQR	Interquartile Range
IV	Intravenous
LFT	Liver Function Test
NAC	N-Acetyl Cysteine
NPDS	National Poison Data System
PO	Oral
PT	Prothrombin Time
RMPDC	Rocky Mountain Poison & Drug Center
SD	Standard Deviation
V fib	Ventricular Fibrillation
V tach	Ventricular Tachycardia

7 Glossary of Terms

95% Confidence Interval (CI)	A range that is estimated to contain the true population estimate (e.g., mean, percentage) in 95% of all samples.
Denominator	In a given analysis, the value representing the total population of interest.
Intentional Abuse	An exposure resulting from the intentional improper or incorrect use of a substance where 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.
Intentional Misuse	An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect.
Loperamide	Loperamide is an active pharmaceutical ingredient found in medications such as Imodium® that are approved for over-the-counter sales in the United States to help control symptoms of diarrhea.
Mean	The average; the sum of observed values divided by the number of observations.
Median	The middle value of all respondents, 50% of respondents fall above the median, and 50% of respondents fall below the median.
N	Sample size
Numerator	In a given analysis, the value representing the sub-set of interest in the population.
Opioids	Includes the active pharmaceutical ingredients buprenorphine fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, sufentanil, tramadol, or tapentadol.
p-value	The probability of obtaining a given result by chance alone. Generally, p-values that are less than 0.05 are treated as 'statistically significant' (less than a 5% probability that a given result is from chance alone).
Rate	The drug utilization measure used in this report is units (i.e., the number of tablets, gelcaps, liquid equivalents) of loperamide sold. The rate is calculated as the weighted number of non-medical use of loperamide endorsements (numerator) divided by the measure of drug utilization (denominator).
Remarkable medical outcome	Medical outcome of moderate effect, major effect, or death.
Standard deviation (SD)	A measure of variation or dispersion of data around the mean. A low standard deviation means there is little spread of values around the mean, whereas a high standard deviation means there is a wider range of values around the mean.
Statistical significance	Implies that the observed result was unlikely to have occurred by chance alone; usually based on a p-value less than 0.05.

8 Introduction

There have been reports of massive overdose of loperamide resulting in serious cardiovascular events. In particular, reports from poison centers have highlighted the association between loperamide abuse and cardiovascular toxicity.[1] These reports have primarily focused on the experience of only a single poison center, which may not reflect national trends. This report utilizes data from the National Poison Data System (NPDS), which is a national repository of all regional poison center data on pharmaceutical and non-pharmaceutical exposures. Loperamide-containing product data are summarized. This report also utilizes nationwide sales data to provide further context for loperamide-containing product availability and the association with reports of exposure.

9 Objectives

9.1 Loperamide-Containing Product Exposures by Intentional and Unintentional Reason for Exposures

The primary objective of this study is to describe loperamide-containing product exposures reported to the National Poison Data System (NPDS) by exposure reason type (intentional and unintentional). This description will include demographics, exposure characteristics, related outcomes (level of care, medical outcome), clinical effects, and therapies. This description will be stratified by intentional and unintentional exposures to both loperamide-containing products only and for exposures to loperamide-containing products plus another substance.

9.2 Intentional Abuse and Misuse of Loperamide-Containing Products

A secondary objective is to describe intentional abuse and intentional misuse of loperamide-containing products reported to the NPDS. These exposure reasons capture the intentional improper or incorrect use of a substance where 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 (intentional abuse) and the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect (intentional misuse). Intentional misuse would include the use of a loperamide-containing substance to treat symptoms of withdrawal from another substance. The description of intentional abuse and intentional misuse exposures will include demographics, exposure characteristics, and related outcomes (level of care, medical outcome), clinical effects, and therapies. This description will be performed for intentional abuse and intentional misuse exposures to loperamide-containing products only and for exposures to loperamide-containing products plus another substance.

9.3 Reported Rates of Exposure to Loperamide-Containing Products

Another secondary objective is to calculate an overall rate of reported loperamide-containing product exposure using national sales data as a measure of product availability. This rate analysis will also be calculated for intentional and unintentional exposures, as well as intentional abuse and intentional misuse exposures for both exposures to loperamide-containing products only and for exposures to loperamide-containing products plus another substance.

10 Methods

10.1 National Poison Data System

10.1.1 Overall Study Design and Plan

The National Poison Data System (NPDS) is the data repository for the regional poison centers of the American Association of Poison Control Centers (AAPCC). AAPCC member centers offer coverage for the entire United States, providing free medical management services to both healthcare professionals and the general public. Exposure information is collected using a standardized coding system and database. An exposure is defined as an actual or suspected contact with any substance, which has been ingested, inhaled, absorbed, applied to, or injected into the body, regardless of toxicity or clinical manifestation. For the purposes of this report, an exposure represents one unique case.

The NPDS was searched to identify human exposures from 2012 through 2015 to loperamide-containing products with or without any other pharmaceutical or non-pharmaceutical substance. Cases that were confirmed later to be non-exposures and non-human exposures were excluded. All loperamide-containing products were selected, which includes loperamide single ingredient products and loperamide multiple ingredient products.

10.1.2 Fatality Review and Reporting

Every fatality reported to the NPDS is systematically reviewed by the regional poison center that provided the medical management services. Each fatality record is then reviewed by a team of medical and clinical toxicologists (the Fatality Review Team). The Fatality Review Team reviews all fatalities for relatedness of the exposure to the fatality using a standardized ranking system of relative contribution. The categories of relative contribution to fatality (RCF) are:

1 – Undoubtedly responsible
2 – Probably responsible
3 – Contributory
4 – Probably not responsible
5 – Clearly not responsible
6 – Unknown

The definitions of relatedness are presented in Appendix B. For each fatality determined to have a RCF of 1 to 3 (at least contributory), cause rank is also reported. Cause rank provides an assessment of the contribution of each substance to the fatality. Detailed information regarding the methodology of the AAPCC Fatality Review Team is published in the 2008 Annual Report of the AAPCC's NPDS.[2]

Fatalities are reported to the NPDS directly and indirectly. Indirect deaths are fatality reports that do not involve an inquiry to the poison center for management of the exposure and usually come from the media or a medical examiner. The methodology for recording indirect deaths varies by poison center and the details for these cases are not collected in the same manner of direct fatality reports. For purposes of this report, all loperamide-containing fatality abstracts reported directly to the NPDS from 2012 to 2015 were collected. Indirect deaths were excluded.

10.2 Other Data Sources – Information Resources, Inc. ® (IRI)

Total loperamide multi-outlet sales (consisting of sales from sources such as grocery, drug, military, and chain stores) in the form of unit sales (i.e., the number of tablets, gelcaps, liquid equivalents) data were obtained from IRI (Information Resources, Inc., Chicago, IL). IRI uses a proprietary projection methodology to extrapolate from the observed data to national estimated multi-outlet sales in the US. Sales data from 2012 to 2015 were obtained per Table 10.2.1.

Table 10.1.2.1: Unit Sales of All Loperamide-Containing Products

Year	Unit Sales in Millions
2012	523.1
2013	496.5
2014	478.7
2015	506.4

10.3 Data Analysis and Reporting

10.3.1 Variables of Interest

The NPDS database consists of categorical variables, which capture patient demographics, exposure details including exposure reason, chronicity, products involved, medical outcome, clinical effects, and therapies. The NPDS definitions associated with these variables are outlined in Appendix A. Clinical effects are recorded by their relationship to the exposure. Similarly, therapies are recorded by whether they were recommended and/or performed as a treatment. For purposes of this analysis, only related clinical effects and therapies that were performed were included. In addition, the frequency of cardiovascular-related clinical effects were also summarized (Appendix A).

Reported quantity was also evaluated by exposure reason and by the report of severe cardiovascular-related clinical effects among acute exposures. Exposures with severe cardiovascular-related clinical effects were defined as the report of one or more cardiovascular-related clinical effect (Appendix A) with a medical outcome of major effect or death. Acute exposures only were included due to limitations in the way quantity is documented in NPDS for chronic exposures.

10.3.2 Descriptive and Statistical Analysis

Descriptive statistics were used to describe the variables of interest by intentional and unintentional reason for exposure. The frequency of exposures involving patients aged <12 years (pediatric) and ≥12 years (adults and children) were described in alignment with loperamide labeling, along with the estimated NPDS age category (unknown child (≤19 years), unknown adult (>19 years), and unknown age as these exposures could not be categorized by the 12 year of age cutoff. Additional subanalyses were performed for intentional abuse and intentional misuse reasons for exposure. The data were stratified by exposures to loperamide-containing products only (no other substance) and exposures to loperamide-containing products plus another substance. Evaluation of exposures to a single substance is a common practice employed by the NPDS[3] and allows for closer examination of the role of the substance (loperamide-containing products) and outcomes in the absence of concomitant medications. Other substances reported among exposures involving a loperamide-containing product plus another substance were summarized by the AAPCC generic code, which is the grouping of

similar products that may differ by characteristics like formulation or brand. The frequency of cases reporting an opioid-containing product was also summarized.

The full dataset was summarized in aggregate. Sales data (IRI, Scan Data, Multi-Outlet) were used to calculate reported exposure rates per million units (i.e., tablets, gelcaps, liquid equivalents) sold. Predicted exposure rates and corresponding 95% confidence intervals were calculated utilizing a log-linear Poisson regression model with an adjustment incorporated for product sales. All calculations and analyses were done in SAS, version 9.4 (SAS Institute, Cary, NC, USA).

10.3.3 Fatality Data Summarization

Fatalities for direct deaths are summarized in aggregate and on a case level. Each direct death fatality abstract was evaluated and summarized on a case-level for year, age, gender, reason for exposure, substances involved, relative contribution of the loperamide-containing product to the fatality (Appendix B), cause rank of each substance (if applicable), autopsy results, and other relative details reported in the case record narratives. Relevant narrative details included exposure details like dose and reason for exposure, as well as contributory history like a history of reported drug abuse.

10.3.4 Institutional Review Board / Ethics Committee

The study protocol was reviewed and approved as Non-Human Subject Research.by the Colorado Multiple Institutional Review Board (COMIRB) on 09 December 2016

10.3.5 Investigators and Study Personnel

The principal investigator of this study is Jody L. Green, PhD, CCRP.

11 Results

11.1 All Exposures to Loperamide-Containing Products

A total of 4,856 exposures involving loperamide-containing products were reported to the National Poison Data System (NPDS) from 01 January 2012 to 31 December 2015. The rate of reported exposures to loperamide-containing products during this period was 2.423 exposures per 1 million units sold (CI 2.325, 2.524). This equates to one case per 0.413 million units (i.e., tablets, gelcaps, liquid equivalents) sold. Exposures to loperamide-containing products only (no non-loperamide-containing substances) were reported in 3,619 (74.5%), while exposures to a loperamide-containing product plus another substance were reported in 1,237 (25.5%; Figure 12.1.1.1).

The median age of patients among all loperamide-containing product exposures was 12.0 years. Just over one-half (53.5%) of patients were female (Table 12.2.1.1). Exposure characteristics showed that most (93.9%) exposures occurred in the patient's own residence, involved ingestion (99.5%) of the product, and involved an acute exposure (85.1%). The mean number of substances reported per case was 1.7 (SD 1.82), with 74.3% of exposures involving a single product, 10.5% involving two products, 5.8% involving three products, and 9.3% involving four or more products (Table 12.2.1.1). Unintentional exposures occurred in 66.8% of exposures, while intentional exposures occurred in 26.6%, adverse reactions occurred in 5.3% of exposures, and other or unknown reasons for exposure occurred in 1.3% (Figure 12.1.1.1;

Table 12.2.1.1). Intentional abuse and misuse occurred in 12.4% of all loperamide-containing product exposures (3.8% intentional abuse, 8.6%intentional misuse).

11.2 Exposures to Loperamide-Containing Products Only

Exposures to loperamide-containing products occurred in 3,619 (74.5%) of exposures (Figure 12.1.1.1). The overall rate of reported exposures to loperamide-containing products only was 1.805 exposure per 1 million units sold (CI 1.726, 1.889). This equates to one exposure per every 0.554 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The rate of reported exposures increased from 1.747 per million units (CI 1.630, 1.871) in 2012 to a peak rate of 1.866 per million units (CI 1.743, 1.998) in 2015 (Table 12.2.1.2).

The median age of patients exposed to loperamide-containing products only was 4.0 years, with more than half (53.8%)of exposures occurring in children <12 years of age. The slight majority (52.6%) of patients were female. Exposure characteristics showed that most (94.4%) exposures occurred in the patient's own residence. Route of exposures was primarily (99.6%) via ingestion. The majority (87.4%) of exposures involved an acute exposure. Nine exposures (0.2%) involved exposure to two loperamide-containing products and no exposures involved more than two loperamide-containing products (Table 12.2.1.1).

Reason for exposure was intentional in 18.6% (n=672) and unintentional in 75.1% (n=2,723; Figure 12.1.1.1; Table 12.2.1.1).

11.2.1 Intentional Exposures to Loperamide-Containing Products Only

Among exposures involving loperamide-containing products only, 672 (18.6%) involved an intentional exposure reason (Figure 12.1.1.1). The overall rate of reported intentional exposures to loperamide-containing products only from 2012 to 2015 was 0.335 per million units (CI 0.254, 0.442). This equates to one case per 2.985 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The rate of reported exposures decreased annually from 0.352 per million units (CI 0.267, 0.465) in 2012 to 0.318 per million units (CI 0.241, 0.419) in 2015 (Table 12.2.2.1).

Median age of patients among intentional exposures to loperamide-containing products only was 33.0 years, with 89.1% involving adults and children aged ≥12 years. The slight majority (52.1%) of patients were female. Exposure site was primarily (91.5%) the patient's own residence. Ingestion of the loperamide-containing product was the most common (99.7%) route of exposure. An acute exposure was most commonly reported (67.0%). Three of the intentional exposures to loperamide-containing products only (0.4%) involved two loperamide-containing products and no exposures involved more than two loperamide-containing products (Table 12.2.2.2).

Most (76.2%) intentional exposures to loperamide-containing products only were recommended to or received care in a healthcare facility (HCF). Of those that received care in a HCF, 32.0% were treated without being admitted, while 40.4% were admitted, (admitted to a critical care unit (20.3%), admitted to non-critical care unit (12.5%), admitted to psychiatric care facility (7.6%); Table 12.2.2.3). The majority of exposures (64.3%) were followed to a known outcome, most of which involved no or an unrelated effect (26.2% of all intentional exposures involving loperamide-containing products only), minor effect (16.7% of all intentional exposures involving loperamide-containing products only), or moderate effect (15.8% of all intentional exposures

involving loperamide-containing products only). Five deaths (0.7%) were reported (Table 12.2.2.4).

Among intentional exposures to loperamide-containing products only, the most common related clinical effects reported were drowsiness/lethargy (14.3%), nausea (6.3%), and abdominal pain (6.1%; Table 12.2.2.5). Among exposures resulting in at least moderate effect (n=144; moderate effect, major effect or death), the most common related clinical effects reported were drowsiness/lethargy (37.5%), respiratory depression (23.6%), and tachycardia (15.3%; Table 12.2.2.6). Cardiovascular-related clinical effects were reported in 72 exposures (10.7%). Among intentional exposures to loperamide-containing products only, 417 (62.1%) did not receive any therapy. The most common therapies performed to treat clinical effects included fluids, IV (19.2%), oxygen (9.4%), naloxone (7.7%), and benzodiazepines (5.7%; Table 12.2.2.7).

Among intentional exposures to loperamide-containing products only, intentional abuse was reported in 125 exposures (18.6% of intentional exposures) and intentional misuse was reported in 353 (52.5% of intentional exposures; Figure 12.1.1.1; Table 12.2.1.1).

11.2.1.1 Intentional Abuse Exposures to Loperamide-Containing Products Only

Intentional abuse was the reason for exposure in 125 of exposures involving loperamide-containing products only (18.6% of intentional exposures to loperamide-containing products only). The overall rate of these exposures from 2012 to 2015 was 0.061 exposures per 1 million units (CI 0.046, 0.081). This equates to one case per every 16.393 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The rate of reported exposures increased from 0.046 (CI 0.032, 0.066) in 2012 to a peak rate of 0.081 (CI 0.058, 0.112) in 2015 (Table 12.2.3.1).

Median age of patients among intentional abuse exposures involving loperamide-containing products only was 26.0 years, with 92.8% involving adults and children aged ≥12 years. The majority (80.0%) of patients were male and most (91.2%) exposures occurred in the patient's own residence. Ingestion of the loperamide-containing product was the most common (97.6%) route of exposure and most exposures were acute (48.0%). One exposure (0.8%) involved two loperamide-containing products and no exposures involved more than two loperamide-containing products (Table 12.2.3.2).

Almost all (92.0%) of the intentional abuse exposures to loperamide-containing products only were recommended to or received care in a healthcare facility (HCF). Among those who received HCF care, 24.3% were treated/evaluated and released without admission. A total of 57.3% of patients were admitted (admitted to critical care unit (37.4%), admitted to non-critical care unit (11.3%), and admitted to a psychiatric care facility (8.7%); Table 12.2.3.3). Most of these exposures (80.0%) were followed to a known outcome, with a remarkable medical outcome reported in 43.2% (moderate effect 27.2%, major effect 13.6%, or death 2.4%; Table 12.2.3.4).

Among intentional abuse exposures to loperamide-containing products only, the most common related clinical effects reported were drowsiness/lethargy (24.0%), respiratory depression (13.6%), and agitated/irritable (10.4%; Table 12.2.3.5). Among exposures resulting in at least moderate effect (n=54; moderate effect, major effect, or death), the most common related clinical effects reported were drowsiness/lethargy (38.9%), respiratory depression (31.5%), coma (20.4%), and conduction disturbance (20.4%; Table 12.2.3.6). Cardiovascular-related

clinical effects were reported in 26 exposures (20.8%). The most common therapies performed to treat clinical effects included fluids, IV (35.2%), oxygen (22.4%), and naloxone (18.4%; Table 12.2.3.7). Among intentional abuse exposures to loperamide-containing products only, 57 (45.6%) did not have any reported therapies performed.

11.2.1.2 Intentional Misuse Exposures to Loperamide-Containing Products Only

Intentional misuse was the reason for exposure in 353 of exposures involving loperamide-containing products only (52.5% of intentional exposures to loperamide-containing products only; Figure 12.1.1.1; Table 12.2.1.1). The overall rate of these exposures from 2012 to 2015 was 0.173 exposures per 1 million units (CI 0.146, 0.205). This equates to one case per every 5.780 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The rate of reported intentional misuse exposures to loperamide-containing products only increased from 0.131 per million units (CI 0.099, 0.173) in 2012 to a peak rate of 0.229 per million units (CI 0.180, 0.290) in 2015 (Table 12.2.3.1).

Median age of patients among intentional misuse exposures to loperamide-containing products only was 46.0 years, with 86.4% of exposure occurring in adults and children aged ≥12 years. The majority (58.1%) of patients were female and most (93.2%) exposures occurred in the patient's own residence. All (100%) of intentional misuse exposures involved ingestion and the majority (64.0%) of exposures were acute. One exposure involved two loperamide-containing products (0.3%) and no exposures involved more than two loperamide-containing products (Table 12.2.3.2).

Most (62.9%) intentional misuse exposures involving loperamide-containing products only were recommended to receive or received healthcare facility (HCF) care. Most (40.1%) of these exposures were treated/evaluated or released, with admission to a healthcare facility occurring in 22.5% (admitted to a critical care unit (9.0%), admitted to a non-critical care unit (12.2%), admitted to a psychiatric facility (1.4%); Table 12.2.3.3). Approximately half (53.8%) of these exposures were followed to a known outcome, with exposures most commonly not followed because minimal clinical effects were expected (28.9%) or involving no or an unrelated effect (25.5%). A remarkable medical outcome was reported in 12.4% (moderate effect 10.8%, major effect 1.7%). No deaths were reported (Table 12.2.3.4).

Among intentional misuse exposures to loperamide-containing products only, the most common related clinical effects reported were drowsiness/lethargy (8.5%), abdominal pain (8.5%), and other (unspecified; 5.4%; Table 12.2.3.5). Among exposures resulting in at least moderate effect (n=44; moderate effect, major effect or death), the most common related clinical effects reported were drowsiness/lethargy (31.8%), confusion (25.0%), abdominal pain (15.9%), dizziness/vertigo (15.9%), and vomiting (15.9%; Table 12.2.3.6). Cardiovascular-related clinical effects were reported in 22 exposures (6.2%). The most common therapies performed to treat clinical effects included fluids, IV (12.7%), other (unspecified; 10.2%), and dilute/irrigate/wash (6.8%; Table 12.2.3.7). Among intentional misuse exposures to loperamide-containing products only, 244 (69.1%) did not have any reported therapies performed.

11.2.2 Unintentional Exposures to Loperamide-Containing Products Only

Among exposures involving loperamide-containing products only, 2,723 (75.2%) involved an unintentional exposure reason (Figure 12.1.1.1). The overall rate of reported unintentional exposures to loperamide-containing products only from 2012 to 2015 was 1.357 per million units (CI 1.343, 1.370). This equates to one case per 0.737 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The rate of reported exposures decreased significantly from 1.428 per million units (CI 1.405, 1.452) in 2012 to 1.288 per million units (CI 1.266, 1.311) in 2015 (Table 12.2.2.1).

Median age of patients among unintentional exposures to loperamide-containing products only was 2.0 years, with the majority (70.2%) of exposures occurring in children <12 years of age. The slight majority of exposures (52.4%) involved female patients. Nearly all exposures occurred in the patient's own residence (95.1%), involved an oral ingestion (99.6%), and involved an acute exposure (93.7%). Six of the unintentional exposures to loperamide-containing products only (0.2%) involved two loperamide-containing products (Table 12.2.2.2).

Most unintentional exposures to only loperamide-containing products (72.2%) were managed outside of a healthcare facility (recommended to or received healthcare facility (HCF) care – No). Of those that were managed in a HCF, 63.0% were treated/evaluated and released without admission (Table 12.2.2.3). Approximately half of exposures (50.9%) were not followed to a known outcome, with most of those exposures not followed because minimal clinical effects were expected (38.1% of all unintentional exposures to a loperamide-containing product only). Of exposures followed to a known outcome, most (41.9% of unintentional exposures to a loperamide-containing product only) resulted in no or an unrelated effect. Remarkable medical outcomes were reported in 1.0% of unintentional exposures to loperamide-containing products only, with 0.9% involving moderate effect, <0.1% involving major effect, and no deaths reported (Table 12.2.2.4).

Among all unintentional exposures to loperamide-containing products only, the most common clinical effects reported were drowsiness/lethargy (3.1%), abdominal pain (1.2%), vomiting (1.1%), and nausea (1.0%; Table 12.2.2.5). Within exposures involving moderate or greater level of effect (moderate effect, major effect, or death), drowsiness/lethargy (34.6%), hypotension (19.2%), and miosis (15.4%) were the most common clinical effects reported (Table 12.2.2.6). Cardiovascular-related clinical effects were reported in nine exposures (0.3%). Among unintentional exposures to loperamide-containing products only, 1,832 (67.3%) did not receive any therapy. The most common therapies performed to treat clinical effects included dilute/irrigate/wash (23.9%), food/snack (8.3%), other (unspecified; 3.3%), and single dose charcoal (3.0%; Table 12.2.2.7).

11.2.3 Summary of Fatalities Involving Loperamide-Containing Products Only

Six fatalities involving loperamide-containing products only were reported between 2012 and 2014 (2012 n=2; 2013 n=1; 2014 n=3). No fatalities were reported in 2015.

Ages ranged from 21 to 29 years and the majority (83.3%; n=5) involved male patients. Intentional abuse was the reason for exposure in three cases (50.0%), with a fourth case providing evidence of loperamide abuse reported in the case narrative though the case was

categorized as unknown reason for exposure. The product involved was confirmed to be a single-ingredient loperamide product in five cases (83.3%), with no history of ingestion in the fifth case and no details regarding the products reported. In two cases (33.3%) additional substances were observed upon toxicology screening, but no history of ingestion was reported and these substances were not recorded in the case. The exposure was determined to be undoubtedly responsible for the fatality in two cases (33.3%), probably responsible in two cases (33.3%), and contributory in two cases (33.3%). Because these fatalities involved only the loperamide product, the cause rank for loperamide was one in each of these fatalities (Table 12.2.4.1).

11.2.4 Reported Quantity Summary by Exposure Reason and Severe Cardiovascular-Related Clinical Effect

Among 3,164 acute exposures to loperamide-containing products only, 2,475 (78.2%) reported quantity information. When quantity was evaluated by exposure reason, the mean quantity was highest among intentional abuse cases (131.6; SD 97.84), followed by all other intentional exposures (90.0; SD 122.4) and intentional misuse (57.8; SD 89.87;Table 12.2.5.1).

A severe cardiovascular-related clinical effect was reported in 82 (2.6%) of acute exposures, of which 8 (9.8%) reported quantity information. Analysis of quantity by report of severe cardiovascular-related clinical effect showed that mean quantity among cases with a severe cardiovascular-related clinical effect was nearly 20 times that of cases without a severe cardiovascular-related clinical effect (severe cardiovascular-related clinical effect 356.8 (SD 282.76); no severe cardiovascular-related clinical effect 17.9 (SD 50.85)). Median quantity followed a similar pattern (severe cardiovascular-related clinical effect 294.0 (IQR 168.0, 560.0); no severe cardiovascular-related clinical effect 4.0 (IQR 2.0, 12.0)).

11.3 Exposures to a Loperamide-Containing Product Plus Another Substance

Exposures to a loperamide-containing product plus another substance occurred in 1,237 (25.5%) of exposures (Figure 12.1.1.1). The overall rate of reported exposures to a loperamide-containing product plus another substance between 2012 to 2015 was 0.617 exposure per 1 million units (CI 0.571, 0.667). This equates to one case per every 1.621 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The rate of reported exposures increased from 0.597 (CI 0.544, 0.655) in 2012 to a peak rate of 0.638 (0.582, 0.700) in 2015 (Table 12.2.1.2).

The median age of patients among exposures to loperamide-containing product plus another substance was 22.0 years, with more than half (69.2%) of exposures occurring in adults and children aged ≥12 years of age. The majority (56.3%) of patients were female. Exposure characteristics showed that most (92.2%) exposures to a loperamide-containing product plus another substance occurred in the patient's own residence. Route of exposure was primarily (99.4%) via ingestion and most (78.4%) cases involved an acute exposure. Exposures most commonly (40.6%) involved two products/substances total (loperamide-containing product plus one other substance). Three total products/substances (1 loperamide-containing product plus two other substances) was reported in 22.8% of exposures and four or more total products/substances (one loperamide-containing product plus three or more other products/substances) was reported in 36.6% (Table 12.2.1.2). The other substances most commonly reported were ibuprofen (n=169; 13.7%), benzodiazepines (n=159; 12.9%), and non-

cough/cold antihistamines (n=142; 11.5%). Opioid or opioid-containing products were reported in 10.3% of exposures (n=128).

Reason for exposure was unintentional in 42.0% (n=520) and intentional in 50.2% (n=621; Figure 12.1.1.1; Table 12.2.1.1).

11.3.1 Intentional Exposures to a Loperamide-Containing Product Plus Another Substance

Among exposures to loperamide-containing products plus another substance, 621 (50.2%) involved intentional reasons for exposure. The overall rate of reported intentional exposures to a loperamide-containing product plus another substance from 2012 to 2015 was 0.309 per million units (CI 0.269, 0.357). This equates to one case per 3.236 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The rate of reported intentional exposures to a loperamide-containing product plus another substance increased from 0.285 per million units (CI 0.233, 0.349) in 2012 to a peak rate of 0.336 per million units (CI 0.277, 0.409) in 2015 (Table 12.2.5.1).

Median age of patients among intentional exposures to loperamide-containing products plus another substance was 26.0 years, with 96.6% involving adults and children aged ≥12 years. The majority (58.5%) of patients were female. Exposure site was primarily (92.4%) the patient's own residence. Ingestion of a loperamide-containing product plus another substance was the most common (99.2%) route of exposure. The majority (72.8%) of exposures involved an acute exposure. Exposures most commonly (44.9%) involved four or more total products/substances (loperamide-containing product plus three or more other substances; Table 12.2.5.2). The other substances most commonly reported included benzodiazepines (n=108; 17.4%), ethanol beverage (n=98; 15.8%), ibuprofen (n=82; 13.2%), and non-cough/cold antihistamines (n=79; 12.7%). Opioid or opioid-containing products were reported in 13.7%.

Most intentional exposures to a loperamide-containing product plus another substance (96.9%) were recommended to or received care in a healthcare facility (HCF). Of those that received care in a HCF, 17.9% were treated without being admitted (treated/evaluated and released), while 72.9% were admitted (admitted to a critical care unit (36.0%), admitted to non-critical care unit (17.8%), admitted to psychiatric care facility (19.1%); Table 12.2.5.3). The majority of exposures (87.4%) were followed to a known outcome. The most common (30.6%) medical outcome was moderate effect, with a remarkable medical outcome reported in 41.7% (moderate effect 30.6%, major effect 10.8%, death (0.3%). Two deaths (0.3%) were reported (Table 12.2.5.4).

Among intentional exposures to a loperamide-containing product plus another substance, the most common related clinical effects reported were drowsiness/lethargy (36.2%), tachycardia (22.1%), and vomiting (12.1%; Table 12.2.5.5). Among exposures resulting in at least moderate effect (n=259; moderate effect, major effect or death), the most common related clinical effects reported were drowsiness/lethargy (53.3%), tachycardia (40.2%), coma (18.9%), conduction disturbance (18.5%), and hypotension (18.5%; Table 12.2.5.6). Cardiovascular-related clinical effects were reported in 228 exposures (36.7%). The most common therapies performed to treat clinical effects included fluids, IV (44.8%), oxygen (17.9%), other (unspecified; 14.3%), and charcoal, single dose (13.5%; Table 12.2.5.7). Among intentional exposures to a loperamide-containing product plus another product, 211 (34.0%) did not have any reported therapies performed.

Among intentional exposures to a loperamide-containing product plus another substance, intentional abuse was reported in 60 exposures (9.7% of intentional exposures) and intentional misuse was reported in 65 (10.5% of intentional exposures; Figure 12.1.1.1; Table 12.2.1.1).

11.3.1.1 Intentional Abuse Exposures to a Loperamide-Containing Product Plus Another Substance

Intentional abuse was the reason for exposure in 60 of exposures to a loperamide-containing products plus another substance (9.7% of intentional exposures). The overall rate of these exposures from 2012 to 2015 was 0.030 exposures per 1 million units (CI 0.023, 0.038). This equates to one case per every 33.333 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The rate of reported intentional abuse exposures to a loperamide-containing product plus another substance increased from 0.024 per million units (CI 0.016, 0.034) in 2012 to a peak rate of 0.037 per million units (0.026, 0.052) in 2015 (Table 12.2.6.1).

Median age of patients among intentional abuse exposures involving a loperamide-containing product plus another substance was 28.0 years, with all (100%) exposures involving adults and children aged ≥12 years. The majority (78.3%) of patients were male., Most exposures (88.3%) occurred in the patient's own residence. Ingestion of a loperamide-containing product plus another substance was the most common (95.0%) route of exposure and the majority (66.7%) were acute exposures. Most (58.3%) exposures involved exposure to two total products/substances (a loperamide-containing product plus one other substance; Table 12.2.6.2). The most common other substances reported included benzodiazepines (n=14; 23.3%), ethanol beverage (n=9; 15.0%), heroin (n=7; 11.7%), and diphenhydramine (n=6; 10.0%). Opioid or opioid-containing products were reported in 20.0% of exposures (n=12).

Almost all (98.3%) of the intentional abuse exposures involving a loperamide-containing product plus another substance were recommended to or received care in a healthcare facility (HCF). Among those who received HCF care, 25.4% were treated/evaluated and released without admission. A total of 64.4% of patients were admitted (admitted to critical care unit (42.4%), admitted to non-critical care unit (18.6%), and admitted to a psychiatric care facility (3.4%); Table 12.2.6.3). Most (88.3%) of these exposures were followed to a known outcome, with cases with a remarkable medical outcome reported in 66.7% (moderate effect 40.0%, major effect 25.0%, death 1.7%). One death (1.7%) death was reported (Table 12.2.6.4).

Among intentional abuse exposures to a loperamide-containing product plus another substance, the most common related clinical effects reported were drowsiness/lethargy (48.3%), tachycardia (31.7%), respiratory depression (20.0%), confusion (16.7%), and hypertension (16.7%; Table 12.2.6.5). Among exposures resulting in at least moderate effect (n=40; moderate effect, major effect or death), the most common related clinical effects reported were drowsiness/lethargy (55.0%), tachycardia (42.5%), respiratory depression (27.5%), hypertension (25.0%), and confusion (25.0%; Table 12.2.6.6). Cardiovascular-related clinical effects were reported in 30 exposures (50.0%). The most common therapies performed to treat clinical effects a included fluids, IV (50.0%), naloxone (35%), oxygen (35.0%), and other (unspecified; 25.0%; Table 12.2.6.7). Among intentional abuse exposures to a loperamide-containing product plus another substance, 14 (23.3%) did not have any reported therapies performed.

11.3.1.2 Intentional Misuse Exposures to a Loperamide-Containing Product Plus Another Substance

Intentional misuse was the reason for exposure in 65 of exposures to a loperamide-containing product plus another substance (10.5% of intentional exposures). The overall rate of these exposures from 2012 to 2015 was 0.032 exposures per 1 million units (CI 0.025, 0.041). This equates to one case per every 31.250 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The rate of reported intentional misuse exposures to a loperamide-containing product plus another substance increased from 0.026 per million units (CI 0.018, 0.037) in 2012 to 0.040 per million units (0.029, 0.056) in 2015 (Table 12.2.6.1).

Median age of patients among intentional misuse exposures involving a loperamide-containing product plus another substance was 31.0 years, with 86.2% of exposures occurring in adults and children aged ≥12 years. Thirty-three (33; 50.8%) exposures involved a male patient and most (93.8%) exposures occurred in the patient's own residence. Ingestion of a loperamide-containing product plus another substance was the most common (98.5%) route of exposure and most (66.2%) were acute exposures. The majority (64.6%) of exposures involved two total substances (a loperamide-containing product plus one other substance; Table 12.2.6.2). Cardiovascular-related clinical effects were reported in 19 exposures (29.2%).The most common other substances reported included salicylate-containing antacids (n=7; 10.8%) and laxative (n=7; 10.8%). Opioid or opioid-containing products were reported in 12.3% of exposures (n=8).

The majority of intentional misuse exposures (81.5%) involving a loperamide-containing product plus another substance were recommended to receive or received healthcare facility (HCF) care. Among those who received HCF care, 30.2% were treated/evaluated and released without admission. A total of 47.2% of patients were admitted (admitted to a critical care unit (24.5%), admitted to a non-critical care unit (15.1%), admitted to a psychiatric facility (7.5%); Table 12.2.6.3). The majority of exposures (67.7%) were followed to a known outcome, with cases with a remarkable medical outcome reported in 32.3% (moderate effect 23.1%, major effect 9.2%). No deaths were reported (Table 12.2.6.4)

Among intentional misuse exposures to a loperamide-containing product plus another substance, the most common related clinical effects reported were tachycardia (21.5%), drowsiness/lethargy (16.9%), and other (unspecified; 15.4%; Table 12.2.6.5). Among exposures resulting in at least moderate effect (n=21; moderate effect, major effect or death), the most common related clinical effects reported were tachycardia (52.4%), drowsiness/lethargy (42.9%), other (unspecified; 28.6%), confusion (23.8%), conduction disturbance (23.8%), and hypertension (23.8%; Table 12.2.6.6). Among intentional misuse exposures to a loperamide-containing product plus another substance, 31 (47.7%) did not receive any therapy. The most common therapies performed to treat clinical effects included fluids, IV (26.2%), other (unspecified; 15.4%), and benzodiazepines (12.3%; Table 12.2.6.7).

11.3.2 Unintentional Exposures to a Loperamide-Containing Product Plus Another Substance

Among the exposures to a loperamide-containing product plus another product, 520 (42.0%) involved an unintentional exposure reason (Figure 12.1.1.1). The overall rate of reported unintentional exposures to a loperamide-containing product plus another substance from 2012 to 2015 was 0.259 per million units (CI 0.222, 0.303). This equates to one case per 3.861 million

units (i.e., tablets, gelcaps, liquid equivalents) sold. The rate of reported exposures decreased from 0.238 per million units (CI 0.193, 0.295) in 2012 to 0.282 per million units (CI 0.229, 0.346) in 2015 (Table 12.2.5.1).

Median age of patients among unintentional exposures to a loperamide-containing product plus another substance was 3.0 years, with the majority (62.9%) of exposures occurring in children <12 years of age. The slight majority (53.1%) of exposures involved female patients. Nearly all exposures occurred in the patient's own residence (92.9%), involved an oral ingestion (99.8%), and involved an acute exposure (88.5%). Most commonly (48.7%), exposures involved two total products (a loperamide-containing product plus another substance) (Table 12.2.5.2). The most common other substances reported were ibuprofen (n=81; 15.6%) and non-cough/cold antihistamines (n=53; 10.2%). Opioid-containing products were reported in 6.0% of exposures (n=31).

Approximately half (48.7%) of unintentional exposures to a loperamide-containing product plus another substance were recommended to receive or received healthcare facility (HCF) care. Most of the exposures that were managed in a HCF were treated/evaluated and released (66.4%), with admission to a HCF occurring in 21.3% (admitted to a critical care unit (9.9%), admitted to a non-critical care unit (9.1%), admitted to a psychiatric facility (2.4%); Table 12.2.5.3). The majority (63.3%) of exposures were followed to a known outcome, most of which involved no or an unrelated effect (49.0% of all unintentional exposures involving a loperamide-containing product plus another substance). Remarkable medical outcomes were reported in 4.8% of exposures (moderate effect 4.0%, major effect 0.8%). No deaths were reported (Table 12.2.5.4).

Among all unintentional exposures to a loperamide-containing product plus another substance, the most common clinical effects reported were drowsiness/lethargy (7.5%), vomiting (3.7%), and nausea (2.9%; Table 12.2.5.5). Within exposures involving moderate or greater level of effect (moderate effect, major effect, or death), drowsiness/lethargy (52.0%), bradycardia (24%), confusion (16.0%), vomiting (16.0%), and respiratory depression (16.0%) were the most common clinical effects reported (Table 12.2.5.6). Cardiovascular-related clinical effects were reported in 12 exposures (2.3%). The most common therapies performed to treat clinical effects were dilute/irrigate/wash (19.2%), food/snack (10.0%), charcoal, single dose (6.5%), and other (unspecified; 6.3%; Table 12.2.5.7). Among unintentional exposures to a loperamide-containing product plus another substance, 311 (59.8%) did not have any reported therapies performed.

11.3.3 Summary of Fatalities Involving a Loperamide-Containing Product Plus Another Substance

Six fatalities involving a loperamide-containing product plus another substance were reported between 2013 and 2015 (2013 n=1; 2014 n=1, 2015 n=4); no fatalities involving a loperamide-containing product plus another substance were reported in 2012. Ages ranged from 23 to 54 years and the majority (83.3%; n=5) were female. The reason for exposure was unknown in most (66.7%; n=4) cases, with the remaining cases involving intentional suspected suicide (16.7%; n=1) and intentional abuse (16.7%; n=1). Single-ingredient loperamide products were confirmed in five cases (83.3%). The remaining case (16.7%) involved an unknown loperamide-containing product as no history of ingestion was reported. A range of other substances were reported among these cases including benzodiazepines in three cases (50.0%) and opioids in three cases (50.0%; Table 12.2.7.1).

The exposure was determined to be probably responsible for the fatality in one case (16.7%) and undoubtedly responsible in one case (16.7%). Among the remaining cases, the exposure was determined to be probably not responsible for the fatality in two cases (33.3%) and the relatedness was unknown in another two (33.3%). Among the cases that the exposure was determined to be at least probably related to the fatality, loperamide was assigned a cause-rank of 1 (primary substance) in both cases (Table 12.2.7.1).

11.3.4 Reported Quantity Summary by Exposure Reason and Severe Cardiovascular-Related Clinical Effect for Exposures to a Loperamide-Containing Product Plus Another Substance

Among 970 acute exposures to a loperamide-containing product plus another substance, 532 (54.8%) reported quantity information. When quantity was evaluated by exposure reason, the mean quantity was highest among intentional abuse cases (300.3; SD 395.14), followed by all other intentional (58.2; SD 120.91) and intentional misuse (29.5; SD 68.96; Table 12.2.9.1). Median quantity by exposure reason followed a similar pattern.

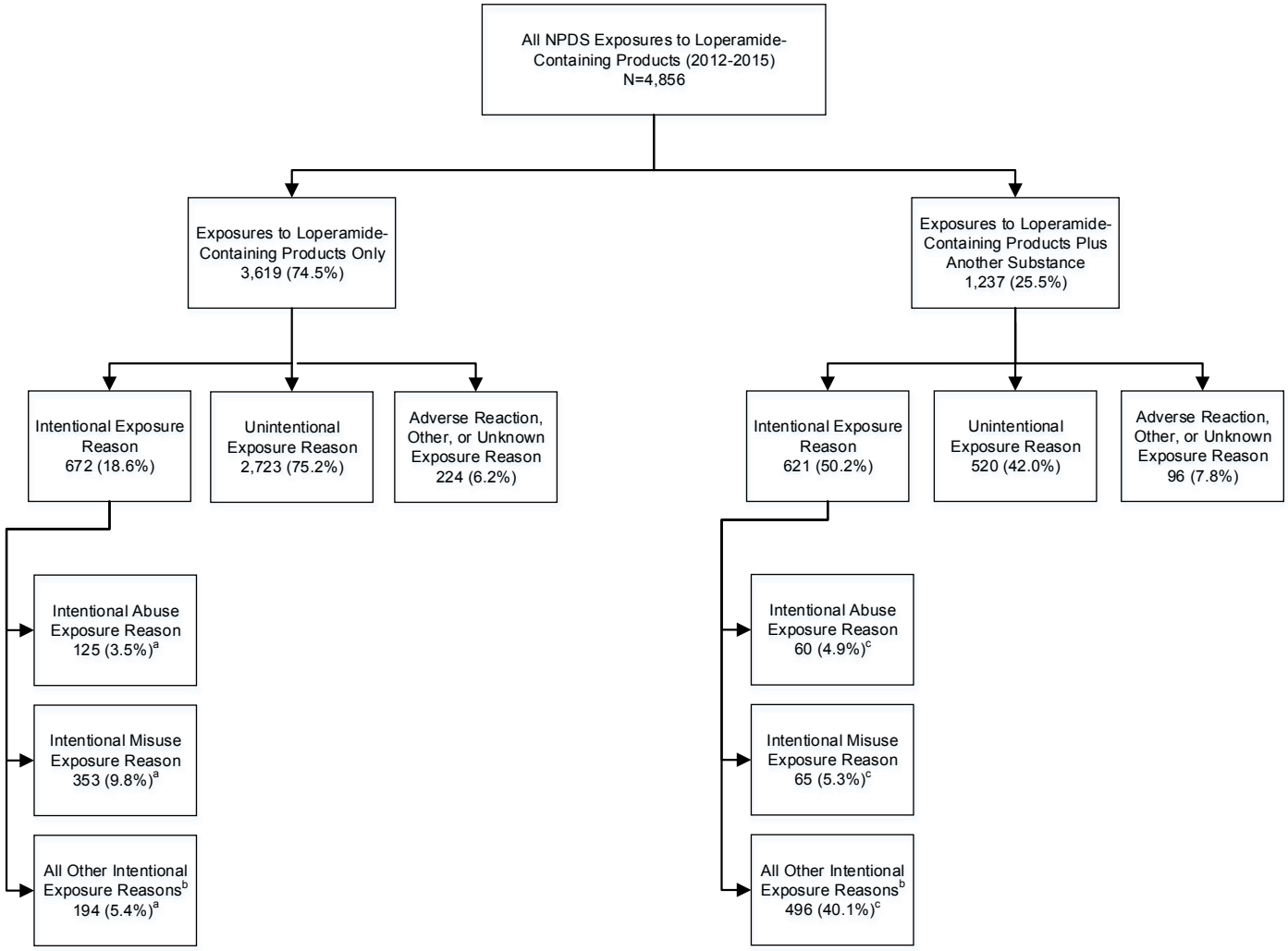
A severe cardiovascular-related clinical effect was reported in 248 (25.6%) of acute exposures, of which 13 (5.2%) reported quantity information. Analysis of quantity by report of severe cardiovascular-related clinical effect showed that mean quantity among cases with a severe cardiovascular-related clinical effect was nearly 11 times that of cases without a severe cardiovascular-related clinical effect (severe cardiovascular-related clinical effect 325.1 (SD 396.77); no severe cardiovascular-related clinical effect 30.8 (SD 104.56)). Median quantity among cases with severe cardiovascular-related clinical effect was nearly 35 times that of cases without a severe cardiovascular-related effect (severe cardiovascular-related clinical effect 140.0 (IQR 30.0, 544.0); no severe cardiovascular-related clinical effect 4.0 (IQR 2.0, 20.0)).

12 Figures and Tables

12.1 Figures

12.1.1 All Loperamide-Containing Product Exposures

Figure 12.1.1.1: Disposition of All Loperamide-Containing Product Exposures Reported to the National Poison Data System (NPDS), 2012 to 2015



[a]*Percentage of exposures to a loperamide-containing product only.*
[b]*All other intentional exposure reasons includes suspected suicide and intentional unknown.*
[c]*Percentage of exposures to a loperamide-containing product plus another substance.*

12.2 Tables

12.2.1 All Loperamide-Containing Product Exposures

Table 12.2.1.1: Demographics and Exposure Characteristics of All Loperamide-Containing Product Exposures by Number of Substances

Characteristics	Exposures to Loperamide-Containing Products Only (N=3,619)	Exposures to a Loperamide-Containing Product Plus Another Substance (N=1,237)	All Exposures to Loperamide-Containing Products (N=4,856)
Age			
Median, years	4.0	22.0	12.0
Mean (SD), years	22.0 (27.09)	27.1 (23.23)	23.3 (26.24)
Age (categorical)			
Pediatric (<12 years)	1,948 (53.8%)	340 (27.5%)	2,288 (47.1%)
Adults and Children (≥12 years)	1,473 (40.7%)	856 (69.2%)	2,329 (48.0%)
Unknown child (≤19 years)	2 (0.1%)	0 (0.0%)	2 (<0.1%)
Unknown adult (>19 years)	174 (4.8%)	36 (2.9%)	210 (4.3%)
Unknown age	22 (0.6%)	5 (0.4%)	27 (0.6%)
Female	1,903 (52.6%)	697 (56.3%)	2,600 (53.5%)
Exposure Site			
Own Residence	3,418 (94.4%)	1,141 (92.2%)	4,559 (93.9%)
Other Residence	109 (3.0%)	30 (2.4%)	139 (2.9%)
Workplace	8 (0.2%)	3 (0.2%)	11 (0.2%)
Health Care Facility	9 (0.2%)	5 (0.4%)	14 (0.3%)
School	7 (0.2%)	7 (0.6%)	14 (0.3%)
Other	49 (1.4%)	35 (2.8%)	84 (1.7%)
Unknown	19 (0.5%)	16 (1.3%)	35 (0.7%)
Route of Exposure[a]			
Ingestions	3,605 (99.6%)	1,229 (99.4%)	4,834 (99.5%)
Inhalation/nasal	6 (0.2%)	13 (1.1%)	19 (0.4%)
Ocular	7 (0.2%)	1 (0.1%)	8 (0.2%)

Characteristics	Exposures to Loperamide-Containing Products Only (N=3,619)	Exposures to a Loperamide-Containing Product Plus Another Substance (N=1,237)	All Exposures to Loperamide-Containing Products (N=4,856)
Dermal	7 (0.2%)	4 (0.3%)	11 (0.2%)
Parenteral	2 (0.1%)	15 (1.2%)	17 (0.4%)
Other	1 (<0.1%)	0 (0.0%)	1 (<0.1%)
Unknown	4 (0.1%)	4 (0.3%)	8 (0.2%)
Chronicity			
Acute	3,164 (87.4%)	970 (78.4%)	4,134 (85.1%)
Acute-on-Chronic	207 (5.7%)	172 (13.9%)	379 (7.8%)
Chronic	213 (5.9%)	39 (3.2%)	252 (5.2%)
Unknown	35 (1.0%)	56 (4.5%)	91 (1.9%)
Number of Substances			
Mean (SD)	1.0 (0.05)	3.8 (2.70)	1.7 (1.82)
Median	1.0	3.0	1.0
Range	(1.0, 2.0)	(2.0, 28.0)	(1.0, 28.0)
Number of Substances (Categories)			
1 Product/Substance	3,610 (99.8%)	0 (0.0%)	3,610 (74.3%)
2 Products/Substances	9 (0.2%)	502 (40.6%)	511 (10.5%)
3 Products/Substances	0 (0.0%)	282 (22.8%)	282 (5.8%)
4+ Products/Substances	0 (0.0%)	453 (36.6%)	453 (9.3%)
Reason for Exposure			
Unintentional - Therapeutic error	693 (19.1%)	123 (9.9%)	816 (16.8%)
Unintentional – General	1,933 (53.4%)	375 (30.3%)	2,308 (47.5%)
Unintentional – Misuse	91 (2.5%)	15 (1.2%)	106 (2.2%)
Unintentional – Other	6 (0.2%)	7 (0.6%)	13 (0.3%)
Intentional – Misuse	353 (9.8%)	65 (5.3%)	418 (8.6%)
Intentional – Abuse	125 (3.5%)	60 (4.9%)	185 (3.8%)
Intentional – Suspected suicide	153 (4.2%)	465 (37.6%)	618 (12.7%)
Intentional – Unknown	41 (1.1%)	31 (2.5%)	72 (1.5%)

Characteristics	Exposures to Loperamide-Containing Products Only (N=3,619)	Exposures to a Loperamide-Containing Product Plus Another Substance (N=1,237)	All Exposures to Loperamide-Containing Products (N=4,856)
Adverse reaction – Drug	181 (5.0%)	66 (5.3%)	247 (5.1%)
Adverse reaction – Other	6 (0.2%)	2 (0.2%)	8 (0.2%)
Other	11 (0.3%)	3 (0.2%)	14 (0.3%)
Unknown reason	26 (0.7%)	25 (2.0%)	51 (1.1%)

[a]*A single exposure may involve more than one route.*

Table 12.2.1.2: Predicted Rates of Exposure to All Loperamide-Containing Products by Number of Substances

Year	Exposures to Loperamide-Containing Products Only Rate per 1 Million Units (95% CI)	Exposures to a Loperamide-Containing Product Plus Another Substance Rate per 1 Million Units (95% CI)	All Exposures to Loperamide-Containing Products Rate per 1 Million Units (95% CI)
2012	1.747 (1.630, 1.871)	0.597 (0.544, 0.655)	2.344 (2.188, 2.510)
2013	1.786 (1.701, 1.874)	0.610 (0.564, 0.660)	2.396 (2.290, 2.506)
2014	1.825 (1.740, 1.915)	0.624 (0.577, 0.675)	2.449 (2.342, 2.562)
2015	1.866 (1.743, 1.998)	0.638 (0.582, 0.700)	2.504 (2.340, 2.680)
Total	**1.805 (1.726, 1.889)**	**0.617 (0.571, 0.667)**	**2.423 (2.325, 2.524)**

12.2.2 Exposures to Loperamide-Containing Products Only

Table 12.2.2.1: Predicted Rates of Exposure to Loperamide-Containing Products Only by Intentional or Unintentional Reason for Exposure

Year	Intentional Exposure Reason Rate per 1 Million Units (95% CI)	Unintentional Exposure Reason Rate per 1 Million Units (95% CI)
2012	0.352 (0.267, 0.465)	1.428 (1.405, 1.452)
2013	0.341 (0.258, 0.449)	1.380 (1.365, 1.395)
2014	0.329 (0.249, 0.434)	1.333 (1.318, 1.349)
2015	0.318 (0.241, 0.419)	1.288 (1.266, 1.311)
Total	**0.335 (0.254, 0.442)**	**1.357 (1.343, 1.370)**

Table 12.2.2.2: Demographics and Exposure Characteristics of Exposures to Loperamide-Containing Products Only by Intentional or Unintentional Reason for Exposure

Characteristics	Intentional Exposure Reason (N=672)	Unintentional Exposure Reason (N=2,723)
Age		
Median, years	33.0	2.0
Mean (SD), years	39.7 (20.26)	16.3 (25.79)
Age (categorical)		
Pediatric (<12 years)	13 (1.9%)	1,911 (70.2%)
Adults and Children (≥12 years)	599 (89.1%)	711 (26.1%)
Unknown child (≤19 years)	0 (0.0%)	2 (0.1%)
Unknown adult (>19 years)	55 (8.2%)	85 (3.1%)
Unknown age	5 (0.7%)	14 (0.5%)
Female	350 (52.1%)	1,426 (52.4%)
Exposure Site		
Own Residence	615 (91.5%)	2,590 (95.1%)
Other Residence	20 (3.0%)	86 (3.2%)
Workplace	3 (0.4%)	4 (0.1%)
Health Care Facility	4 (0.6%)	5 (0.2%)
School	1 (0.1%)	6 (0.2%)
Other	19 (2.8%)	26 (1.0%)
Unknown	10 (1.5%)	6 (0.2%)
Route of Exposure[a]		
Ingestions	670 (99.7%)	2,711 (99.6%)
Inhalation/nasal	1 (0.1%)	5 (0.2%)
Ocular	0 (0.0%)	7 (0.3%)
Dermal	0 (0.0%)	7 (0.3%)
Parenteral	1 (0.1%)	1 (<0.1%)
Other	0 (0.0%)	1 (<0.1%)
Unknown	1 (0.1%)	3 (0.1%)
Chronicity		
Acute	450 (67.0%)	2,551 (93.7%)
Acute-on-Chronic	84 (12.5%)	99 (3.6%)
Chronic	120 (17.9%)	67 (2.5%)
Unknown	18 (2.7%)	6 (0.2%)
Number of Substances		
Mean (SD)	1.0 (0.07)	1.0 (0.05)
Median	1.0	1.0
Range	(1.0, 2.0)	(1.0, 2.0)
Number of Substances (Categories)		
1 Product/Substance	669 (99.6%)	2,717 (99.8%)
2 Products/Substances	3 (0.4%)	6 (0.2%)
3 Products/Substances	0 (0.0%)	0 (0.0%)
4+ Products/Substances	0 (0.0%)	0 (0.0%)

[a] *A single exposure may involve more than one route.*

Table 12.2.2.3: Level of Healthcare Facility (HCF) Care of Exposures to Loperamide-Containing Products Only by Intentional or Unintentional Reason for Exposure

Characteristics	Intentional Exposure Reason (N=672)	Unintentional Exposure Reason (N=2,723)
Recommended to or Received Healthcare Facility Care (HCF)		
Yes	512 (76.2%)	717 (26.3%)
No	138 (20.5%)	1,966 (72.2%)
Unknown	22 (3.3%)	40 (1.5%)
Level of Care[a]		
Treated/evaluated and released	164 (32.0%)	452 (63.0%)
Admitted to non-critical care unit	64 (12.5%)	52 (7.3%)
Admitted to critical care unit	104 (20.3%)	26 (3.6%)
Admitted to psychiatric care facility	39 (7.6%)	3 (0.4%)
Patient refused referral/did not arrive at HCF	36 (7.0%)	75 (10.5%)
Patient lost to follow-up/left AMA	105 (20.5%)	109 (15.2%)

[a]*Denominator is the number of exposures that were recommended to or received healthcare facility care.*

Table 12.2.2.4: Medical Outcome of Exposures to Loperamide-Containing Products Only by Intentional or Unintentional Reason for Exposure

Medical Outcome	Intentional Exposure Reason (N=672)	Unintentional Exposure Reason (N=2,723)
Followed to a Known Outcome	432 (64.3%)	1,336 (49.1%)
Death	5 (0.7%)	0 (0.0%)
Major Effect	33 (4.9%)	1 (<0.1%)
Moderate Effect	106 (15.8%)	25 (0.9%)
Minor Effect	112 (16.7%)	169 (6.2%)
No Effect or Unrelated Effect	176 (26.2%)	1,141 (41.9%)
Not Followed to Known Outcome	240 (35.7%)	1,387 (50.9%)
Unable to follow, potentially toxic	102 (15.2%)	127 (4.7%)
Not followed, Non-toxic	12 (1.8%)	223 (8.2%)
Not followed, minimal clinical effects expected	126 (18.8%)	1,037 (38.1%)

Table 12.2.2.5: Related Clinical Effects Among Exposures to Loperamide-Containing Products Only by Intentional or Unintentional Reason for Exposure

Clinical Effect	Intentional Exposure Reason (N=672)	Unintentional Exposure Reason (N=2,723)
Drowsiness/lethargy	96 (14.3%)	84 (3.1%)
Abdominal Pain	41 (6.1%)	32 (1.2%)
Nausea	42 (6.3%)	27 (1.0%)
Vomiting	32 (4.8%)	31 (1.1%)
Other	35 (5.2%)	17 (0.6%)
Respiratory depression	34 (5.1%)	2 (0.1%)
Dizziness/vertigo	25 (3.7%)	10 (0.4%)
Miosis	20 (3.0%)	7 (0.3%)
Tachycardia	25 (3.7%)	2 (0.1%)
Constipation	13 (1.9%)	11 (0.4%)
Hypotension	19 (2.8%)	5 (0.2%)
Coma	21 (3.1%)	0 (0.0%)
Agitated/irritable	19 (2.8%)	1 (<0.1%)
Confusion	19 (2.8%)	1 (<0.1%)
Bradycardia	16 (2.4%)	2 (0.1%)
Conduction disturbance	18 (2.7%)	0 (0.0%)
Syncope	13 (1.9%)	0 (0.0%)
Diarrhea	6 (0.9%)	6 (0.2%)
Dysrhythmia (v tach/v fib)	10 (1.5%)	0 (0.0%)
Electrolyte abnormality	10 (1.5%)	0 (0.0%)
Cough/choke	2 (0.3%)	7 (0.3%)
ECG change (other)	9 (1.3%)	0 (0.0%)
Headache	6 (0.9%)	3 (0.1%)
Ataxia	6 (0.9%)	2 (0.1%)
Tremor	8 (1.2%)	0 (0.0%)
Diaphoresis	6 (0.9%)	1 (<0.1%)
Acidosis	6 (0.9%)	0 (0.0%)
Blurred vision	5 (0.7%)	1 (<0.1%)
CPK elevated	6 (0.9%)	0 (0.0%)
Chest pain (including noncardiac)	5 (0.7%)	1 (<0.1%)
Dysrhythmia (other)	6 (0.9%)	0 (0.0%)
Hypertension	6 (0.9%)	0 (0.0%)
Slurred speech	3 (0.4%)	3 (0.1%)

Clinical Effect	Intentional Exposure Reason (N=672)	Unintentional Exposure Reason (N=2,723)
Throat irritation	0 (0.0%)	6 (0.2%)
X-ray findings(+)	5 (0.7%)	1 (<0.1%)
Fever/hyperthermia	5 (0.7%)	0 (0.0%)
Mydriasis	4 (0.6%)	1 (<0.1%)
Respiratory arrest	5 (0.7%)	0 (0.0%)
Urinary retention	4 (0.6%)	1 (<0.1%)
ADR to treatment	3 (0.4%)	1 (<0.1%)
Dyspnea	4 (0.6%)	0 (0.0%)
Dystonia	3 (0.4%)	1 (<0.1%)
Ileus/no bowel sounds	3 (0.4%)	1 (<0.1%)
Rhabdomyolysis	4 (0.6%)	0 (0.0%)
Seizure (single)	4 (0.6%)	0 (0.0%)
Cardiac arrest	3 (0.4%)	0 (0.0%)
Edema	1 (0.1%)	2 (0.1%)
Muscle weakness	2 (0.3%)	1 (<0.1%)
Ocular - Irritation/pain	0 (0.0%)	3 (0.1%)
Pneumonitis	3 (0.4%)	0 (0.0%)
AST, ALT>100<=1,000	2 (0.3%)	0 (0.0%)
Anion gap increased	2 (0.3%)	0 (0.0%)
Asystole	2 (0.3%)	0 (0.0%)
Creatinine increased	2 (0.3%)	0 (0.0%)
Cyanosis	2 (0.3%)	0 (0.0%)
Dehydration	1 (0.1%)	1 (<0.1%)
Hallucinations/delusions	2 (0.3%)	0 (0.0%)
Hyperglycemia	2 (0.3%)	0 (0.0%)
Hyperventilation/tachypnea	2 (0.3%)	0 (0.0%)
Hypothermia	2 (0.3%)	0 (0.0%)
Oral irritation	0 (0.0%)	2 (0.1%)
Pain (not dermal, GI, ocular)	2 (0.3%)	0 (0.0%)
Pallor	2 (0.3%)	0 (0.0%)
Pupil(s) nonreactive	2 (0.3%)	0 (0.0%)
Red eye/conjunctivitis	0 (0.0%)	2 (0.1%)
Renal failure	2 (0.3%)	0 (0.0%)
Anorexia	0 (0.0%)	1 (<0.1%)
Bullae	1 (0.1%)	0 (0.0%)

Clinical Effect	Intentional Exposure Reason (N=672)	Unintentional Exposure Reason (N=2,723)
Erythema/flushed	1 (0.1%)	0 (0.0%)
Fecal incontinence	1 (0.1%)	0 (0.0%)
Hives/welts	0 (0.0%)	1 (<0.1%)
Oliguria/anuria	1 (0.1%)	0 (0.0%)
Pruritus	0 (0.0%)	1 (<0.1%)
Seizures (multi/discrete)	1 (0.1%)	0 (0.0%)

Table 12.2.2.6: Related Clinical Effects Among Exposures to Loperamide-Containing Products Only with Moderate Effect, Major Effect, or Death Medical Outcome by Intentional or Unintentional Reason for Exposure

Clinical Effect	Intentional Exposure Reason (N=144)	Unintentional Exposure Reason (N=26)
Drowsiness/lethargy	54 (37.5%)	9 (34.6%)
Respiratory depression	34 (23.6%)	2 (7.7%)
Hypotension	19 (13.2%)	5 (19.2%)
Tachycardia	22 (15.3%)	1 (3.8%)
Miosis	18 (12.5%)	4 (15.4%)
Coma	20 (13.9%)	0 (0.0%)
Conduction disturbance	18 (12.5%)	0 (0.0%)
Vomiting	17 (11.8%)	1 (3.8%)
Bradycardia	15 (10.4%)	2 (7.7%)
Nausea	16 (11.1%)	1 (3.8%)
Agitated/irritable	16 (11.1%)	0 (0.0%)
Confusion	15 (10.4%)	1 (3.8%)
Other	12 (8.3%)	2 (7.7%)
Syncope	13 (9.0%)	0 (0.0%)
Dizziness/vertigo	12 (8.3%)	0 (0.0%)
Dysrhythmia (v tach/v fib)	10 (6.9%)	0 (0.0%)
Electrolyte abnormality	10 (6.9%)	0 (0.0%)
Abdominal Pain	7 (4.9%)	2 (7.7%)
ECG change (other)	9 (6.3%)	0 (0.0%)
Tremor	8 (5.6%)	0 (0.0%)
Acidosis	6 (4.2%)	0 (0.0%)
CPK elevated	6 (4.2%)	0 (0.0%)
Diaphoresis	5 (3.5%)	1 (3.8%)
Dysrhythmia (other)	6 (4.2%)	0 (0.0%)
Hypertension	6 (4.2%)	0 (0.0%)
X-ray findings(+)	5 (3.5%)	1 (3.8%)
Ataxia	4 (2.8%)	1 (3.8%)
Constipation	5 (3.5%)	0 (0.0%)
Fever/hyperthermia	5 (3.5%)	0 (0.0%)
Respiratory arrest	5 (3.5%)	0 (0.0%)
Blurred vision	3 (2.1%)	1 (3.8%)
Chest pain (including noncardiac)	4 (2.8%)	0 (0.0%)

Clinical Effect	Intentional Exposure Reason (N=144)	Unintentional Exposure Reason (N=26)
Dyspnea	4 (2.8%)	0 (0.0%)
Headache	4 (2.8%)	0 (0.0%)
Rhabdomyolysis	4 (2.8%)	0 (0.0%)
Seizure (single)	4 (2.8%)	0 (0.0%)
Slurred speech	3 (2.1%)	1 (3.8%)
Urinary retention	3 (2.1%)	1 (3.8%)
Cardiac arrest	3 (2.1%)	0 (0.0%)
Diarrhea	2 (1.4%)	1 (3.8%)
Dystonia	2 (1.4%)	1 (3.8%)
Pneumonitis	3 (2.1%)	0 (0.0%)
ADR to treatment	2 (1.4%)	0 (0.0%)
AST, ALT>100<=1,000	2 (1.4%)	0 (0.0%)
Anion gap increased	2 (1.4%)	0 (0.0%)
Asystole	2 (1.4%)	0 (0.0%)
Cough/choke	2 (1.4%)	0 (0.0%)
Creatinine increased	2 (1.4%)	0 (0.0%)
Cyanosis	2 (1.4%)	0 (0.0%)
Dehydration	1 (0.7%)	1 (3.8%)
Edema	1 (0.7%)	1 (3.8%)
Hallucinations/delusions	2 (1.4%)	0 (0.0%)
Hyperglycemia	2 (1.4%)	0 (0.0%)
Hyperventilation/tachypnea	2 (1.4%)	0 (0.0%)
Hypothermia	2 (1.4%)	0 (0.0%)
Ileus/no bowel sounds	2 (1.4%)	0 (0.0%)
Pallor	2 (1.4%)	0 (0.0%)
Pupil(s) nonreactive	2 (1.4%)	0 (0.0%)
Renal failure	2 (1.4%)	0 (0.0%)
Bullae	1 (0.7%)	0 (0.0%)
Fecal incontinence	1 (0.7%)	0 (0.0%)
Hives/welts	0 (0.0%)	1 (3.8%)
Muscle weakness	1 (0.7%)	0 (0.0%)
Mydriasis	1 (0.7%)	0 (0.0%)
Oliguria/anuria	1 (0.7%)	0 (0.0%)
Pain (not dermal, GI, ocular)	1 (0.7%)	0 (0.0%)
Seizures (multi/discrete)	1 (0.7%)	0 (0.0%)

Table 12.2.2.7: Therapies Performed Among Exposures to Loperamide-Containing Products Only by Intentional or Unintentional Reason for Exposure

Therapy	Intentional Exposure Reason (N=672)	Unintentional Exposure Reason (N=2,723)
Dilute/irrigate/wash	30 (4.5%)	652 (23.9%)
Food/snack	13 (1.9%)	225 (8.3%)
Fluids, IV	129 (19.2%)	33 (1.2%)
Other	71 (10.6%)	90 (3.3%)
Charcoal, single dose	21 (3.1%)	81 (3.0%)
Oxygen	63 (9.4%)	6 (0.2%)
Naloxone	52 (7.7%)	5 (0.2%)
Benzodiazepines	38 (5.7%)	4 (0.1%)
Intubation	30 (4.5%)	2 (0.1%)
Vasopressors	26 (3.9%)	2 (0.1%)
Ventilator	25 (3.7%)	2 (0.1%)
Antiemetics	16 (2.4%)	6 (0.2%)
Alkalinization	20 (3.0%)	1 (<0.1%)
Antibiotics	17 (2.5%)	2 (0.1%)
Sedation (other)	19 (2.8%)	0 (0.0%)
Antiarrhythmic	17 (2.5%)	0 (0.0%)
Other emetic	0 (0.0%)	17 (0.6%)
CPR	12 (1.8%)	1 (<0.1%)
Cathartic	8 (1.2%)	5 (0.2%)
Cardioversion	8 (1.2%)	0 (0.0%)
Antihistamines	5 (0.7%)	2 (0.1%)
Pacemaker	5 (0.7%)	0 (0.0%)
Antihypertensives	3 (0.4%)	1 (<0.1%)
Atropine	4 (0.6%)	0 (0.0%)
Calcium	4 (0.6%)	0 (0.0%)
Hemodialysis	1 (0.1%)	3 (0.1%)
Insulin	4 (0.6%)	0 (0.0%)
Steroids	3 (0.4%)	1 (<0.1%)
Bronchodilators	3 (0.4%)	0 (0.0%)
Glucose, > 5%	3 (0.4%)	0 (0.0%)
Flumazenil	2 (0.3%)	0 (0.0%)
NAC, IV	2 (0.3%)	0 (0.0%)
Anticonvulsants	1 (0.1%)	0 (0.0%)

Therapy	Intentional Exposure Reason (N=672)	Unintentional Exposure Reason (N=2,723)
ECMO	1 (0.1%)	0 (0.0%)
Fresh air	0 (0.0%)	1 (<0.1%)
Lavage	1 (0.1%)	0 (0.0%)
NAC, PO	1 (0.1%)	0 (0.0%)

12.2.3 Exposures to Loperamide-Containing Products Only by Intentional Abuse or Intentional Misuse Reason for Exposure

Table 12.2.3.1: Predicted Rates of Exposure to Loperamide-Containing Products Only by Intentional Abuse or Intentional Misuse Reason for Exposure

Year	Intentional Abuse Exposure Rate per 1 Million Units (95% CI)	Intentional Misuse Exposure Rate per 1 Million Units (95% CI)
2012	0.046 (0.032, 0.066)	0.131 (0.099, 0.173)
2013	0.056 (0.041, 0.075)	0.157 (0.130, 0.191)
2014	0.067 (0.050, 0.089)	0.190 (0.160, 0.225)
2015	0.081 (0.058, 0.112)	0.229 (0.180, 0.290)
Total	**0.061 (0.046, 0.081)**	**0.173 (0.146, 0.205)**

Table 12.2.3.2: Demographics and Exposure Characteristics of Exposures to Loperamide-Containing Products Only by Intentional Abuse or Intentional Misuse Reason for Exposure

Characteristics	Intentional Abuse Exposure (N=125)	Intentional Misuse Exposure (N=353)
Age, years		
Median	26.0	46.0
Mean (SD)	27.9 (10.28)	47.0 (20.48)
Age (categorical)		
Pediatric (<12 years)	0 (0.0%)	10 (2.8%)
Adults and Children (≥12 years)	116 (92.8%)	305 (86.4%)
Unknown child (≤19 years)	0 (0.0%)	0 (0.0%)
Unknown adult (>19 years)	8 (6.4%)	36 (10.2%)
Unknown age	1 (0.8%)	2 (0.6%)
Female	25 (20.0%)	205 (58.1%)
Exposure Site		
Own Residence	114 (91.2%)	329 (93.2%)
Other Residence	2 (1.6%)	12 (3.4%)
Workplace	0 (0.0%)	2 (0.6%)
Health Care Facility	1 (0.8%)	2 (0.6%)
School	0 (0.0%)	0 (0.0%)
Other	2 (1.6%)	6 (1.7%)
Unknown	6 (4.8%)	2 (0.6%)
Route of Exposure[a]		
Ingestions	122 (97.6%)	353 (100.0%)
Inhalation/nasal	1 (0.8%)	0 (0.0%)
Ocular	0 (0.0%)	0 (0.0%)
Dermal	0 (0.0%)	0 (0.0%)
Parenteral	1 (0.8%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)
Unknown	1 (0.8%)	0 (0.0%)
Chronicity		
Acute	60 (48.0%)	226 (64.0%)
Acute-on-Chronic	20 (16.0%)	50 (14.2%)
Chronic	38 (30.4%)	72 (20.4%)
Unknown	7 (5.6%)	5 (1.4%)
Number of Substances		

Characteristics	Intentional Abuse Exposure (N=125)	Intentional Misuse Exposure (N=353)
Mean (SD)	1.0 (0.09)	1.0 (0.05)
Median	1.0	1.0
Range	(1.0, 2.0)	(1.0, 2.0)
Number of Substances (Categorical)		
1 Product/Substance	124 (99.2%)	352 (99.7%)
2 Products/Substances	1 (0.8%)	1 (0.3%)
3 Products/Substances	0 (0.0%)	0 (0.0%)
4+ Products/Substances	0 (0.0%)	0 (0.0%)

[a]*A single exposure may involve more than one route.*

Table 12.2.3.3: Level of Healthcare Facility (HCF) Care of Exposures to Loperamide-Containing Products Only by Intentional Abuse or Intentional Misuse Reason for Exposure

Characteristics	Intentional Abuse Exposure (N=125)	Intentional Misuse Exposure (N=353)
Recommended to or Received Healthcare Facility Care (HCF)		
Yes	115 (92.0%)	222 (62.9%)
No	9 (7.2%)	114 (32.3%)
Unknown	1 (0.8%)	17 (4.8%)
Level of HCF Care[a]		
Treated/evaluated and released	28 (24.3%)	89 (40.1%)
Admitted to non-critical care unit	13 (11.3%)	27 (12.2%)
Admitted to critical care unit	43 (37.4%)	20 (9.0%)
Admitted to psychiatric care facility	10 (8.7%)	3 (1.4%)
Patient refused referral/did not arrive at HCF	6 (5.2%)	15 (6.8%)
Patient lost to follow-up/left AMA	15 (13.0%)	68 (30.6%)

[a]*Denominator is the number that were recommended to or received healthcare facility care.*

Table 12.2.3.4: Medical Outcome of Exposures to Loperamide-Containing Products Only by Intentional Abuse or Intentional Misuse Reason for Exposure

Medical Outcome	Intentional Abuse Exposure (N=125)	Intentional Misuse Exposure (N=353)
Followed to a Known Outcome	100 (80.0%)	190 (53.8%)
Death	3 (2.4%)	0 (0.0%)
Major Effect	17 (13.6%)	6 (1.7%)
Moderate Effect	34 (27.2%)	38 (10.8%)
Minor Effect	25 (20.0%)	56 (15.9%)
No Effect or Unrelated Effect	21 (16.8%)	90 (25.5%)
Not Followed to Known Outcome	25 (20.0%)	163 (46.2%)
Unable to follow, potentially toxic	15 (12.0%)	51 (14.4%)
Not followed, Non-toxic	0 (0.0%)	10 (2.8%)
Not followed, minimal clinical effects expected	10 (8.0%)	102 (28.9%)

Table 12.2.3.5: Related Clinical Effects of Exposures to Loperamide-Containing Products Only by Intentional Abuse or Intentional Misuse Reason for Exposure

Clinical Effect	Intentional Abuse Exposure (N=125)	Intentional Misuse Exposure (N=353)
Drowsiness/lethargy	30 (24.0%)	30 (8.5%)
Abdominal Pain	6 (4.8%)	30 (8.5%)
Other	11 (8.8%)	19 (5.4%)
Nausea	12 (9.6%)	16 (4.5%)
Vomiting	10 (8.0%)	15 (4.2%)
Dizziness/vertigo	4 (3.2%)	17 (4.8%)
Respiratory depression	17 (13.6%)	4 (1.1%)
Agitated/irritable	13 (10.4%)	5 (1.4%)
Confusion	2 (1.6%)	14 (4.0%)
Conduction disturbance	11 (8.8%)	4 (1.1%)
Tachycardia	9 (7.2%)	5 (1.4%)
Bradycardia	8 (6.4%)	5 (1.4%)
Miosis	6 (4.8%)	7 (2.0%)
Coma	11 (8.8%)	1 (0.3%)
Hypotension	6 (4.8%)	6 (1.7%)
Constipation	2 (1.6%)	9 (2.5%)
Syncope	9 (7.2%)	2 (0.6%)
Dysrhythmia (v tach/v fib)	7 (5.6%)	1 (0.3%)
Tremor	3 (2.4%)	4 (1.1%)
Ataxia	2 (1.6%)	4 (1.1%)
Diaphoresis	4 (3.2%)	2 (0.6%)
Dysrhythmia (other)	5 (4.0%)	1 (0.3%)
ECG change (other)	3 (2.4%)	3 (0.8%)
Electrolyte abnormality	5 (4.0%)	1 (0.3%)
CPK elevated	4 (3.2%)	1 (0.3%)
Diarrhea	2 (1.6%)	3 (0.8%)
Acidosis	2 (1.6%)	2 (0.6%)
Blurred vision	1 (0.8%)	3 (0.8%)
Chest pain (including noncardiac)	2 (1.6%)	2 (0.6%)
Headache	2 (1.6%)	2 (0.6%)
Mydriasis	4 (3.2%)	0 (0.0%)
Seizure (single)	3 (2.4%)	1 (0.3%)
Urinary retention	2 (1.6%)	2 (0.6%)

Clinical Effect	Intentional Abuse Exposure (N=125)	Intentional Misuse Exposure (N=353)
Fever/hyperthermia	3 (2.4%)	0 (0.0%)
Hypertension	2 (1.6%)	1 (0.3%)
Respiratory arrest	3 (2.4%)	0 (0.0%)
Rhabdomyolysis	2 (1.6%)	1 (0.3%)
ADR to treatment	2 (1.6%)	0 (0.0%)
Anion gap increased	1 (0.8%)	1 (0.3%)
Cardiac arrest	2 (1.6%)	0 (0.0%)
Cough/choke	2 (1.6%)	0 (0.0%)
Dyspnea	1 (0.8%)	1 (0.3%)
Hallucinations/delusions	1 (0.8%)	1 (0.3%)
Hyperglycemia	2 (1.6%)	0 (0.0%)
Hypothermia	2 (1.6%)	0 (0.0%)
Pain (not dermal, GI, ocular)	1 (0.8%)	1 (0.3%)
Pallor	1 (0.8%)	1 (0.3%)
Slurred speech	1 (0.8%)	1 (0.3%)
X-ray findings(+)	2 (1.6%)	0 (0.0%)
AST, ALT>100<=1,000	0 (0.0%)	1 (0.3%)
Asystole	1 (0.8%)	0 (0.0%)
Creatinine increased	0 (0.0%)	1 (0.3%)
Cyanosis	1 (0.8%)	0 (0.0%)
Dehydration	1 (0.8%)	0 (0.0%)
Dystonia	0 (0.0%)	1 (0.3%)
Edema	0 (0.0%)	1 (0.3%)
Erythema/flushed	1 (0.8%)	0 (0.0%)
Fecal incontinence	0 (0.0%)	1 (0.3%)
Ileus/no bowel sounds	0 (0.0%)	1 (0.3%)
Muscle weakness	1 (0.8%)	0 (0.0%)
Oliguria/anuria	0 (0.0%)	1 (0.3%)
Pneumonitis	1 (0.8%)	0 (0.0%)
Pupil(s) nonreactive	0 (0.0%)	1 (0.3%)
Renal failure	0 (0.0%)	1 (0.3%)
Seizures (multi/discrete)	0 (0.0%)	1 (0.3%)

Table 12.2.3.6: Related Clinical Effects Among Exposures to Loperamide-Containing Products Only with Moderate Effect, Major Effect, or Death Medical Outcome by Intentional Abuse or Intentional Misuse Reason for Exposure

Clinical Effect	Intentional Abuse Exposure (N=54)	Intentional Misuse Exposure (N=44)
Drowsiness/lethargy	21 (38.9%)	14 (31.8%)
Respiratory depression	17 (31.5%)	4 (9.1%)
Agitated/irritable	10 (18.5%)	5 (11.4%)
Conduction disturbance	11 (20.4%)	4 (9.1%)
Vomiting	7 (13.0%)	7 (15.9%)
Confusion	2 (3.7%)	11 (25.0%)
Bradycardia	8 (14.8%)	4 (9.1%)
Coma	11 (20.4%)	1 (2.3%)
Hypotension	6 (11.1%)	6 (13.6%)
Miosis	6 (11.1%)	6 (13.6%)
Tachycardia	9 (16.7%)	3 (6.8%)
Nausea	6 (11.1%)	5 (11.4%)
Syncope	9 (16.7%)	2 (4.5%)
Dizziness/vertigo	3 (5.6%)	7 (15.9%)
Other	6 (11.1%)	3 (6.8%)
Dysrhythmia (v tach/v fib)	7 (13.0%)	1 (2.3%)
Abdominal Pain	0 (0.0%)	7 (15.9%)
Tremor	3 (5.6%)	4 (9.1%)
Dysrhythmia (other)	5 (9.3%)	1 (2.3%)
ECG change (other)	3 (5.6%)	3 (6.8%)
Electrolyte abnormality	5 (9.3%)	1 (2.3%)
CPK elevated	4 (7.4%)	1 (2.3%)
Diaphoresis	3 (5.6%)	2 (4.5%)
Acidosis	2 (3.7%)	2 (4.5%)
Ataxia	2 (3.7%)	2 (4.5%)
Seizure (single)	3 (5.6%)	1 (2.3%)
Chest pain (including noncardiac)	2 (3.7%)	1 (2.3%)
Constipation	1 (1.9%)	2 (4.5%)
Fever/hyperthermia	3 (5.6%)	0 (0.0%)
Hypertension	2 (3.7%)	1 (2.3%)
Respiratory arrest	3 (5.6%)	0 (0.0%)
Rhabdomyolysis	2 (3.7%)	1 (2.3%)

Clinical Effect	Intentional Abuse Exposure (N=54)	Intentional Misuse Exposure (N=44)
Urinary retention	2 (3.7%)	1 (2.3%)
ADR to treatment	2 (3.7%)	0 (0.0%)
Anion gap increased	1 (1.9%)	1 (2.3%)
Blurred vision	1 (1.9%)	1 (2.3%)
Cardiac arrest	2 (3.7%)	0 (0.0%)
Cough/choke	2 (3.7%)	0 (0.0%)
Dyspnea	1 (1.9%)	1 (2.3%)
Hallucinations/delusions	1 (1.9%)	1 (2.3%)
Headache	1 (1.9%)	1 (2.3%)
Hyperglycemia	2 (3.7%)	0 (0.0%)
Hypothermia	2 (3.7%)	0 (0.0%)
Pallor	1 (1.9%)	1 (2.3%)
Slurred speech	1 (1.9%)	1 (2.3%)
X-ray findings(+)	2 (3.7%)	0 (0.0%)
AST, ALT>100<=1,000	0 (0.0%)	1 (2.3%)
Asystole	1 (1.9%)	0 (0.0%)
Creatinine increased	0 (0.0%)	1 (2.3%)
Cyanosis	1 (1.9%)	0 (0.0%)
Dehydration	1 (1.9%)	0 (0.0%)
Diarrhea	0 (0.0%)	1 (2.3%)
Dystonia	0 (0.0%)	1 (2.3%)
Edema	0 (0.0%)	1 (2.3%)
Fecal incontinence	0 (0.0%)	1 (2.3%)
Muscle weakness	1 (1.9%)	0 (0.0%)
Mydriasis	1 (1.9%)	0 (0.0%)
Oliguria/anuria	0 (0.0%)	1 (2.3%)
Pain (not dermal, GI, ocular)	1 (1.9%)	0 (0.0%)
Pneumonitis	1 (1.9%)	0 (0.0%)
Pupil(s) nonreactive	0 (0.0%)	1 (2.3%)
Renal failure	0 (0.0%)	1 (2.3%)
Seizures (multi/discrete)	0 (0.0%)	1 (2.3%)

Table 12.2.3.7: Therapies Performed Among Exposures to Loperamide-Containing Products Only by Intentional Abuse and Intentional Misuse Reason for Exposure

Therapy	Intentional Abuse Exposure (N=125)	Intentional Misuse Exposure (N=353)
Fluids, IV	44 (35.2%)	45 (12.7%)
Other	21 (16.8%)	36 (10.2%)
Oxygen	28 (22.4%)	14 (4.0%)
Naloxone	23 (18.4%)	11 (3.1%)
Benzodiazepines	21 (16.8%)	12 (3.4%)
Dilute/irrigate/wash	2 (1.6%)	24 (6.8%)
Intubation	15 (12.0%)	4 (1.1%)
Antiarrhythmic	14 (11.2%)	3 (0.8%)
Ventilator	13 (10.4%)	4 (1.1%)
Vasopressors	10 (8.0%)	6 (1.7%)
Alkalinization	8 (6.4%)	6 (1.7%)
Sedation (other)	10 (8.0%)	4 (1.1%)
Antibiotics	10 (8.0%)	1 (0.3%)
Antiemetics	7 (5.6%)	4 (1.1%)
Food/snack	1 (0.8%)	10 (2.8%)
CPR	7 (5.6%)	2 (0.6%)
Cardioversion	6 (4.8%)	1 (0.3%)
Calcium	4 (3.2%)	0 (0.0%)
Pacemaker	4 (3.2%)	0 (0.0%)
Antihistamines	2 (1.6%)	1 (0.3%)
Atropine	2 (1.6%)	1 (0.3%)
Charcoal, single dose	1 (0.8%)	2 (0.6%)
Insulin	2 (1.6%)	1 (0.3%)
Antihypertensives	1 (0.8%)	1 (0.3%)
Bronchodilators	1 (0.8%)	1 (0.3%)
Cathartic	0 (0.0%)	2 (0.6%)
Flumazenil	2 (1.6%)	0 (0.0%)
Glucose, > 5%	2 (1.6%)	0 (0.0%)
Steroids	1 (0.8%)	1 (0.3%)
Anticonvulsants	1 (0.8%)	0 (0.0%)
ECMO	1 (0.8%)	0 (0.0%)
Hemodialysis	0 (0.0%)	1 (0.3%)
Lavage	1 (0.8%)	0 (0.0%)

Therapy	Intentional Abuse Exposure (N=125)	Intentional Misuse Exposure (N=353)
NAC, IV	1 (0.8%)	0 (0.0%)

12.2.4 Fatalities Involving Loperamide-Containing Products Only

Table 12.2.4.1: Case Characteristics of Fatalities Involving Loperamide-Containing Products Only

Year	Age, Gender	Exposure Reason	Chronicity	Products or Substances Involved (Cause Rank, if applicable)	Relative Contribution of Exposure to Fatality	Autopsy Findings (if applicable) and Other Details Reported	Additional Information Reported in Case Notes
2012	21 Years, Male	Intentional Abuse	Chronic	**Loperamide-Containing Product:** Single-ingredient loperamide (1)	Contributory	*Autopsy not performed* **Loperamide Levels:** Not reported	• Patient reportedly trying to detox from heroin • Reportedly used ~200 tablets of loperamide over 5 days
2012	26 Years, Male	Unknown Reason	Unknown	**Loperamide-Containing Product:** Single-ingredient loperamide (1) **Other Products/ Substances**: Digoxin[a,b] Nicotine/cotinine [a,b] Phenobarbital [a,b]	Contributory	**Cause of death:** Cardiac dysrhythmia (Brugada syndrome) and chronic loperamide abuse evidenced by history and toxicology results **Manner of death:** Natural **Loperamide Levels:** Postmortem - 19 ng/mL (source not specified)	• Evidence of loperamide abuse to detoxify himself

Year	Age, Gender	Exposure Reason	Chronicity	Products or Substances Involved (Cause Rank, if applicable)	Relative Contribution of Exposure to Fatality	Autopsy Findings (if applicable) and Other Details Reported	Additional Information Reported in Case Notes
2013	29 Years, Male	Intentional Unknown	Acute	**Loperamide-Containing Product:** Single-ingredient loperamide (1)	Probably responsible	**Cause of death:** Unknown **Manner of death:** Not reported **Loperamide Levels:** All lab toxicology results were negative	• Found with 3 empty boxes of loperamide product
2014	25 Years, Female	Intentional Abuse	Unknown	**Loperamide-Containing Product:** Single-ingredient loperamide (1)	Undoubtedly responsible	**Case of death:** Complications of loperamide intoxication **Manner of death:** Accident **Loperamide Levels:** Antemortem (upon last admission) - 35 ng/mL (blood)	• Patient admitted to taking 30-60 tablets of loperamide at a time for 2 years for its opiate-like effects to help with withdrawal from oxycodone with acetaminophen History of 3 admissions in the 3.5 months prior with loperamide concentration of 35 ng/mL detected on last admission

Year	Age, Gender	Exposure Reason	Chronicity	Products or Substances Involved (Cause Rank, if applicable)	Relative Contribution of Exposure to Fatality	Autopsy Findings (if applicable) and Other Details Reported	Additional Information Reported in Case Notes
2014	25 Years, Male	Intentional Abuse	Acute	**Loperamide-Containing Product:** Single-ingredient loperamide (1)	Probably responsible	*Autopsy not performed* **Loperamide Levels:** Not reported	• Patient's girlfriend reported the patient had been taking 200 tablets of loperamide per day because it made him feel like he was on hydrocodone
2014	27 Years, Male	Intentional Unknown	Unknown	**Loperamide-Containing Product:** Unknown loperamide-containing product (1)[a] **Other Products/ Substances**: THC [a,b]	Undoubtedly responsible	**Case of death:** Loperamide toxicity **Manner of death:** Accidental **Loperamide Levels:** Antemortem (14 hours post admission) - 0.013 mg/L (blood), 1.4 mg/kg (liver)	• History of narcotic drug use

[a]*Substance observed upon toxicology screen only (no history of ingestion).*
[b]*Case categorized as an exposure to a loperamide-containing product only as other product/substance was not systematically reported in the case.*

12.2.5 Reported Quantity by Exposure Reason and Severe Cardiovascular Effect for Exposures to Loperamide-Containing Products Only

Table 12.2.5.1: Reported Quantity by Exposure Reason for Exposures to Loperamide-Containing Products Only

	Intentional Abuse	Intentional Misuse	All Other Intentional	Unintentional	Adverse Reaction	Other or Unknown
Mean (SD)	131.6 (97.84)	57.8 (89.87)	90.0 (122.44)	8.0 (30.28)	4.6 (3.91)	41.5 (79.17)
Median	110.0	24.0	42.0	4.0	4.0	10.0
Range	(10.0, 400.0)	(0.3, 760.0)	(2.0, 800.0)	(0.0, 1200.0)	(0.3, 20.0)	(1.0, 288.0)
IQR	(50.0, 192.0)	(20.0, 100.0)	(20.0, 100.0)	(2.0, 8.0)	(2.0, 4.0)	(3.0, 40.0)
N	52	189	138	1,970	113	13

Table 12.2.5.2: Reported Quantity by Severe Cardiovascular Effect for Exposures to Loperamide-Containing Products Only

Statistic	Severe Cardiovascular-Related Clinical Effect	No Severe Cardiovascular-Related Clinical Effect
Mean (SD)	356.8 (282.76)	17.9 (50.85)
Median	294.0	4.0
Range	(10.0, 800.0)	(0.0, 1200)
IQR	(168.0, 560.0)	(2.0, 12.0)
N	8	2,467

12.2.6 Exposures to a Loperamide-Containing Product Plus Another Substances

Table 12.2.6.1: Predicted Rates of Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional or Unintentional Reason for Exposure

Year	Intentional Exposure Reason Rate per 1 Million Units (95% CI)	Unintentional Exposure Reason Rate per 1 Million Units (95% CI)
2012	0.285 (0.233, 0.349)	0.238 (0.193, 0.295)
2013	0.301 (0.259, 0.350)	0.252 (0.214, 0.297)
2014	0.318 (0.274, 0.369)	0.266 (0.227, 0.313)
2015	0.336 (0.277, 0.409)	0.282 (0.229, 0.346)
Total	**0.309 (0.269, 0.357)**	**0.259 (0.222, 0.303)**

Table 12.2.6.2: Demographics and Exposure Characteristics of Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional or Unintentional Reason for Exposure

Characteristics	Intentional Exposure Reason (N=621)	Unintentional Exposure Reason (N=520)
Age, years		
Median	26.0	3.0
Mean (SD)	30.8 (16.89)	19.9 (27.87)
Age (categorical)		
Pediatric (<12 years)	10 (1.6%)	327 (62.9%)
Adults and Children (≥12 years)	600 (96.6%)	174 (33.5%)
Unknown child (≤19 years)	0 (0.0%)	0 (0.0%)
Unknown adult (>19 years)	10 (1.6%)	18 (3.5%)
Unknown age	1 (0.2%)	1 (0.2%)
Female	363 (58.5%)	276 (53.1%)
Exposure Site		
Own Residence	574 (92.4%)	483 (92.9%)
Other Residence	7 (1.1%)	21 (4.0%)
Workplace	0 (0.0%)	2 (0.4%)
Health Care Facility	0 (0.0%)	4 (0.8%)
School	7 (1.1%)	0 (0.0%)
Other	21 (3.4%)	9 (1.7%)
Unknown	12 (1.9%)	1 (0.2%)
Route of Exposure[a]		
Ingestions	616 (99.2%)	519 (99.8%)
Inhalation/nasal	8 (1.3%)	4 (0.8%)
Ocular	0 (0.0%)	1 (0.2%)
Dermal	3 (0.5%)	1 (0.2%)
Parenteral	12 (1.9%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)
Unknown	2 (0.3%)	1 (0.2%)
Chronicity		
Acute	452 (72.8%)	460 (88.5%)
Acute-on-Chronic	113 (18.2%)	46 (8.8%)
Chronic	21 (3.4%)	7 (1.3%)
Unknown	35 (5.6%)	7 (1.3%)
Number of Substances		
Mean (SD)	4.1 (2.99)	3.4 (2.31)
Median	3.0	3.0
Range	(2.0, 28.0)	(2.0, 25.0)
Number of Substances (Categories)		
1 Product/Substance	0 (0.0%)	0 (0.0%)
2 Products/Substances	193 (31.1%)	253 (48.7%)
3 Products/Substances	149 (24.0%)	117 (22.5%)
4+ Products/Substances	279 (44.9%)	150 (28.8%)

[a] *A single exposure may involve more than one route.*

Table 12.2.6.3: Level of Healthcare Facility (HCF) Care of Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional or Unintentional Reason for Exposure

Characteristics	Intentional Exposure Reason (N=621)	Unintentional Exposure Reason (N=520)
Recommended to or Received Healthcare Facility Care (HCF)		
Yes	602 (96.9%)	253 (48.7%)
No	14 (2.3%)	260 (50.0%)
Unknown	5 (0.8%)	7 (1.3%)
Level of Care[a]		
Treated/evaluated and released	108 (17.9%)	168 (66.4%)
Admitted to non-critical care unit	107 (17.8%)	23 (9.1%)
Admitted to critical care unit	217 (36.0%)	25 (9.9%)
Admitted to psychiatric care facility	115 (19.1%)	6 (2.4%)
Patient refused referral/did not arrive at HCF	14 (2.3%)	11 (4.3%)
Patient lost to follow-up/left AMA	41 (6.8%)	20 (7.9%)

[a]*Denominator is the number that were recommended to or received healthcare facility care.*

Table 12.2.6.4: Medical Outcome of Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional or Unintentional Reason for Exposure

Medical Outcome	Intentional Exposure Reason (N=621)	Unintentional Exposure Reason (N=520)
Followed to a Known Outcome	543 (87.4%)	329 (63.3%)
Death	2 (0.3%)	0 (0.0%)
Major Effect	67 (10.8%)	4 (0.8%)
Moderate Effect	190 (30.6%)	21 (4.0%)
Minor Effect	167 (26.9%)	49 (9.4%)
No Effect or Unrelated Effect	117 (18.8%)	255 (49.0%)
Not Followed to Known Outcome	78 (12.6%)	191 (36.7%)
Unable to follow, potentially toxic	52 (8.4%)	23 (4.4%)
Not followed, Non-toxic	0 (0.0%)	20 (3.8%)
Not followed, minimal clinical effects expected	26 (4.2%)	148 (28.5%)

Table 12.2.6.5: Related Clinical Effects Among Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional or Unintentional Reason for Exposure

Clinical Effect	Intentional Exposure Reason (N=621)	Unintentional Exposure Reason (N=520)
Drowsiness/lethargy	225 (36.2%)	39 (7.5%)
Tachycardia	137 (22.1%)	3 (0.6%)
Vomiting	75 (12.1%)	19 (3.7%)
Nausea	51 (8.2%)	15 (2.9%)
Agitated/irritable	58 (9.3%)	5 (1.0%)
Confusion	52 (8.4%)	6 (1.2%)
Other	52 (8.4%)	4 (0.8%)
Hypotension	52 (8.4%)	2 (0.4%)
Coma	51 (8.2%)	1 (0.2%)
Conduction disturbance	50 (8.1%)	1 (0.2%)
Hypertension	46 (7.4%)	0 (0.0%)
Respiratory depression	42 (6.8%)	4 (0.8%)
Abdominal Pain	24 (3.9%)	8 (1.5%)
Bradycardia	26 (4.2%)	6 (1.2%)
Dizziness/vertigo	21 (3.4%)	10 (1.9%)
Electrolyte abnormality	29 (4.7%)	1 (0.2%)
Mydriasis	24 (3.9%)	3 (0.6%)
Acidosis	19 (3.1%)	1 (0.2%)
Slurred speech	19 (3.1%)	1 (0.2%)
Miosis	17 (2.7%)	2 (0.4%)
CPK elevated	18 (2.9%)	0 (0.0%)
Ataxia	13 (2.1%)	4 (0.8%)
Hallucinations/delusions	16 (2.6%)	1 (0.2%)
Diarrhea	5 (0.8%)	10 (1.9%)
Fever/hyperthermia	15 (2.4%)	0 (0.0%)
ECG change (other)	13 (2.1%)	1 (0.2%)
Tremor	12 (1.9%)	2 (0.4%)
Diaphoresis	13 (2.1%)	0 (0.0%)
Hyperventilation/tachypnea	11 (1.8%)	1 (0.2%)
Creatinine increased	11 (1.8%)	0 (0.0%)
Hypoglycemia	8 (1.3%)	1 (0.2%)
X-ray findings(+)	9 (1.4%)	0 (0.0%)

Clinical Effect	Intentional Exposure Reason (N=621)	Unintentional Exposure Reason (N=520)
ADR to treatment	8 (1.3%)	0 (0.0%)
Dysrhythmia (v tach/v fib)	8 (1.3%)	0 (0.0%)
Headache	7 (1.1%)	1 (0.2%)
Seizure (single)	6 (1.0%)	2 (0.4%)
AST, ALT>100<=1,000	7 (1.1%)	0 (0.0%)
Pneumonitis	7 (1.1%)	0 (0.0%)
Urinary retention	7 (1.1%)	0 (0.0%)
Cardiac arrest	6 (1.0%)	0 (0.0%)
Rhabdomyolysis	6 (1.0%)	0 (0.0%)
Anion gap increased	5 (0.8%)	0 (0.0%)
Blurred vision	5 (0.8%)	0 (0.0%)
Dyspnea	3 (0.5%)	2 (0.4%)
Erythema/flushed	4 (0.6%)	1 (0.2%)
Numbness	4 (0.6%)	1 (0.2%)
Nystagmus	3 (0.5%)	2 (0.4%)
Pallor	3 (0.5%)	2 (0.4%)
Respiratory arrest	5 (0.8%)	0 (0.0%)
Syncope	5 (0.8%)	0 (0.0%)
Tinnitus	5 (0.8%)	0 (0.0%)
Constipation	4 (0.6%)	0 (0.0%)
Dysrhythmia (other)	4 (0.6%)	0 (0.0%)
Hypothermia	3 (0.5%)	1 (0.2%)
Cough/choke	2 (0.3%)	1 (0.2%)
Muscle rigidity	3 (0.5%)	0 (0.0%)
Muscle weakness	2 (0.3%)	1 (0.2%)
Pupil(s) nonreactive	3 (0.5%)	0 (0.0%)
Seizures (multi/discrete)	3 (0.5%)	0 (0.0%)
Urinary incontinence	3 (0.5%)	0 (0.0%)
Alkalosis	2 (0.3%)	0 (0.0%)
Chest pain (including noncardiac)	2 (0.3%)	0 (0.0%)
Cyanosis	2 (0.3%)	0 (0.0%)
Dermal - Irritation/pain	2 (0.3%)	0 (0.0%)
Dystonia	2 (0.3%)	0 (0.0%)
Edema	2 (0.3%)	0 (0.0%)
Excess secretions	1 (0.2%)	1 (0.2%)

Clinical Effect	Intentional Exposure Reason (N=621)	Unintentional Exposure Reason (N=520)
Hyperglycemia	2 (0.3%)	0 (0.0%)
Ileus/no bowel sounds	2 (0.3%)	0 (0.0%)
Oliguria/anuria	2 (0.3%)	0 (0.0%)
PT prolonged	2 (0.3%)	0 (0.0%)
Polyuria	1 (0.2%)	1 (0.2%)
Pruritus	2 (0.3%)	0 (0.0%)
Urine color change	2 (0.3%)	0 (0.0%)
AST, ALT>1,000	1 (0.2%)	0 (0.0%)
Asystole	1 (0.2%)	0 (0.0%)
Bleeding (other)	1 (0.2%)	0 (0.0%)
Bronchospasm	1 (0.2%)	0 (0.0%)
CVA	1 (0.2%)	0 (0.0%)
Dehydration	1 (0.2%)	0 (0.0%)
Hemo/myoglobinuria	1 (0.2%)	0 (0.0%)
Multiple Chemical Sensitivities	1 (0.2%)	0 (0.0%)
Ocular - Irritation/pain	0 (0.0%)	1 (0.2%)
Other LFT abnormality	1 (0.2%)	0 (0.0%)
Other coagulopathy	1 (0.2%)	0 (0.0%)
Pain (not dermal, GI, ocular)	1 (0.2%)	0 (0.0%)
Red eye/conjunctivitis	1 (0.2%)	0 (0.0%)
Renal failure	1 (0.2%)	0 (0.0%)
Throat irritation	0 (0.0%)	1 (0.2%)
Visual defect	1 (0.2%)	0 (0.0%)

Table 12.2.6.6: Related Clinical Effects Among Exposures to a Loperamide-Containing Product Plus Another Substance with Moderate Effect, Major Effect, or Death Medical Outcome by Intentional or Unintentional Reason for Exposure

Clinical Effect	Intentional Exposure Reason (N=259)	Unintentional Exposure Reason (N=25)
Drowsiness/lethargy	138 (53.3%)	13 (52.0%)
Tachycardia	104 (40.2%)	2 (8.0%)
Coma	49 (18.9%)	1 (4.0%)
Conduction disturbance	48 (18.5%)	1 (4.0%)
Hypotension	48 (18.5%)	1 (4.0%)
Confusion	44 (17.0%)	4 (16.0%)
Vomiting	43 (16.6%)	4 (16.0%)
Hypertension	45 (17.4%)	0 (0.0%)
Respiratory depression	41 (15.8%)	4 (16.0%)
Agitated/irritable	34 (13.1%)	2 (8.0%)
Other	35 (13.5%)	1 (4.0%)
Bradycardia	24 (9.3%)	6 (24.0%)
Electrolyte abnormality	28 (10.8%)	1 (4.0%)
Nausea	25 (9.7%)	3 (12.0%)
Acidosis	19 (7.3%)	1 (4.0%)
CPK elevated	17 (6.6%)	0 (0.0%)
Hallucinations/delusions	16 (6.2%)	1 (4.0%)
Mydriasis	16 (6.2%)	1 (4.0%)
Miosis	14 (5.4%)	1 (4.0%)
ECG change (other)	13 (5.0%)	1 (4.0%)
Fever/hyperthermia	13 (5.0%)	0 (0.0%)
Slurred speech	13 (5.0%)	0 (0.0%)
Tremor	12 (4.6%)	1 (4.0%)
Ataxia	9 (3.5%)	3 (12.0%)
Creatinine increased	11 (4.2%)	0 (0.0%)
Diaphoresis	11 (4.2%)	0 (0.0%)
Dizziness/vertigo	9 (3.5%)	2 (8.0%)
Hyperventilation/tachypnea	9 (3.5%)	1 (4.0%)
Abdominal Pain	8 (3.1%)	1 (4.0%)
Hypoglycemia	8 (3.1%)	1 (4.0%)
X-ray findings(+)	9 (3.5%)	0 (0.0%)
Dysrhythmia (v tach/v fib)	8 (3.1%)	0 (0.0%)

Clinical Effect	Intentional Exposure Reason (N=259)	Unintentional Exposure Reason (N=25)
Seizure (single)	6 (2.3%)	2 (8.0%)
AST, ALT>100<=1,000	7 (2.7%)	0 (0.0%)
Pneumonitis	7 (2.7%)	0 (0.0%)
ADR to treatment	6 (2.3%)	0 (0.0%)
Cardiac arrest	6 (2.3%)	0 (0.0%)
Rhabdomyolysis	6 (2.3%)	0 (0.0%)
Anion gap increased	5 (1.9%)	0 (0.0%)
Respiratory arrest	5 (1.9%)	0 (0.0%)
Syncope	5 (1.9%)	0 (0.0%)
Urinary retention	5 (1.9%)	0 (0.0%)
Dysrhythmia (other)	4 (1.5%)	0 (0.0%)
Nystagmus	3 (1.2%)	1 (4.0%)
Tinnitus	4 (1.5%)	0 (0.0%)
Blurred vision	3 (1.2%)	0 (0.0%)
Dyspnea	2 (0.8%)	1 (4.0%)
Headache	3 (1.2%)	0 (0.0%)
Hypothermia	3 (1.2%)	0 (0.0%)
Muscle rigidity	3 (1.2%)	0 (0.0%)
Muscle weakness	2 (0.8%)	1 (4.0%)
Numbness	2 (0.8%)	1 (4.0%)
Pallor	2 (0.8%)	1 (4.0%)
Pupil(s) nonreactive	3 (1.2%)	0 (0.0%)
Seizures (multi/discrete)	3 (1.2%)	0 (0.0%)
Urinary incontinence	3 (1.2%)	0 (0.0%)
Alkalosis	2 (0.8%)	0 (0.0%)
Chest pain (including noncardiac)	2 (0.8%)	0 (0.0%)
Constipation	2 (0.8%)	0 (0.0%)
Cough/choke	1 (0.4%)	1 (4.0%)
Cyanosis	2 (0.8%)	0 (0.0%)
Dystonia	2 (0.8%)	0 (0.0%)
Hyperglycemia	2 (0.8%)	0 (0.0%)
Ileus/no bowel sounds	2 (0.8%)	0 (0.0%)
Oliguria/anuria	2 (0.8%)	0 (0.0%)
PT prolonged	2 (0.8%)	0 (0.0%)
Urine color change	2 (0.8%)	0 (0.0%)

Clinical Effect	Intentional Exposure Reason (N=259)	Unintentional Exposure Reason (N=25)
AST, ALT>1,000	1 (0.4%)	0 (0.0%)
Asystole	1 (0.4%)	0 (0.0%)
Bleeding (other)	1 (0.4%)	0 (0.0%)
Bronchospasm	1 (0.4%)	0 (0.0%)
CVA	1 (0.4%)	0 (0.0%)
Dehydration	1 (0.4%)	0 (0.0%)
Diarrhea	1 (0.4%)	0 (0.0%)
Edema	1 (0.4%)	0 (0.0%)
Erythema/flushed	1 (0.4%)	0 (0.0%)
Hemo/myoglobinuria	1 (0.4%)	0 (0.0%)
Multiple Chemical Sensitivities	1 (0.4%)	0 (0.0%)
Ocular - Irritation/pain	0 (0.0%)	1 (4.0%)
Other LFT abnormality	1 (0.4%)	0 (0.0%)
Other coagulopathy	1 (0.4%)	0 (0.0%)
Pain (not dermal, GI, ocular)	1 (0.4%)	0 (0.0%)
Polyuria	1 (0.4%)	0 (0.0%)
Renal failure	1 (0.4%)	0 (0.0%)
Visual defect	1 (0.4%)	0 (0.0%)

Table 12.2.6.7: Therapies Performed Among Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional or Unintentional Reason for Exposure

Therapy	Intentional Exposure Reason (N=621)	Unintentional Exposure Reason (N=520)
Fluids, IV	278 (44.8%)	30 (5.8%)
Other	89 (14.3%)	33 (6.3%)
Oxygen	111 (17.9%)	8 (1.5%)
Charcoal, single dose	84 (13.5%)	34 (6.5%)
Dilute/irrigate/wash	15 (2.4%)	100 (19.2%)
Benzodiazepines	70 (11.3%)	7 (1.3%)
Naloxone	64 (10.3%)	6 (1.2%)
Intubation	64 (10.3%)	4 (0.8%)
Ventilator	59 (9.5%)	4 (0.8%)
Food/snack	6 (1.0%)	52 (10.0%)
NAC, IV	57 (9.2%)	0 (0.0%)
Sedation (other)	47 (7.6%)	5 (1.0%)
Alkalinization	37 (6.0%)	0 (0.0%)
Antiemetics	33 (5.3%)	3 (0.6%)
Cathartic	20 (3.2%)	7 (1.3%)
Vasopressors	23 (3.7%)	0 (0.0%)
Antibiotics	21 (3.4%)	0 (0.0%)
Other emetic	2 (0.3%)	10 (1.9%)
Glucose, > 5%	10 (1.6%)	1 (0.2%)
Calcium	8 (1.3%)	0 (0.0%)
Antiarrhythmic	7 (1.1%)	0 (0.0%)
Antihistamines	5 (0.8%)	2 (0.4%)
Antihypertensives	6 (1.0%)	1 (0.2%)
Neuromuscular blocker	7 (1.1%)	0 (0.0%)
NAC, PO	6 (1.0%)	0 (0.0%)
Flumazenil	5 (0.8%)	0 (0.0%)
Lavage	4 (0.6%)	1 (0.2%)
CPR	4 (0.6%)	0 (0.0%)
Atropine	1 (0.2%)	2 (0.4%)
Glucagon	2 (0.3%)	1 (0.2%)
Anticonvulsants	2 (0.3%)	0 (0.0%)
Bronchodilators	1 (0.2%)	1 (0.2%)

Therapy	Intentional Exposure Reason (N=621)	Unintentional Exposure Reason (N=520)
Cardioversion	2 (0.3%)	0 (0.0%)
Charcoal, multiple doses	2 (0.3%)	0 (0.0%)
Octreotide	2 (0.3%)	0 (0.0%)
Steroids	2 (0.3%)	0 (0.0%)
Folate	1 (0.2%)	0 (0.0%)
Fresh air	0 (0.0%)	1 (0.2%)
Hemodialysis	1 (0.2%)	0 (0.0%)
Insulin	1 (0.2%)	0 (0.0%)
Pacemaker	1 (0.2%)	0 (0.0%)
Pyridoxine	1 (0.2%)	0 (0.0%)

12.2.7 Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional Abuse or Intentional Misuse Reason for Exposure

Table 12.2.7.1: Predicted Rates of Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional Abuse or Intentional Misuse Reason for Exposure

Year	Intentional Abuse Exposure Rate per 1 Million Units (95% CI)	Intentional Misuse Exposure Rate per 1 Million Units (95% CI)
2012	0.024 (0.016, 0.034)	0.026 (0.018, 0.037)
2013	0.027 (0.021, 0.036)	0.030 (0.023, 0.039)
2014	0.032 (0.024, 0.042)	0.035 (0.027, 0.045)
2015	0.037 (0.026, 0.052)	0.040 (0.029, 0.056)
Total	**0.030 (0.023, 0.038)**	**0.032 (0.025, 0.041)**

Table 12.2.7.2: Demographics and Exposure Characteristics of Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional Abuse or Intentional Misuse Reason for Exposure

Characteristics	Intentional Abuse Exposure (N=60)	Intentional Misuse Exposure (N=65)
Age, years		
Median	28.0	31.0
Mean (SD)	29.9 (10.07)	36.4 (19.73)
Age (categorical)		
Pediatric (<12 years)	0 (0.0%)	4 (6.2%)
Adults and Children (≥12 years)	60 (100%)	56 (86.2%)
Unknown child (≤19 years)	0 (0.0%)	0 (0.0%)
Unknown adult (>19 years)	0 (0.0%)	5 (7.7%)
Unknown age	0 (0.0%)	0 (0.0%)
Female	13 (21.7%)	32 (49.2%)
Exposure Site		
Own Residence	53 (88.3%)	61 (93.8%)
Other Residence	2 (3.3%)	1 (1.5%)
Workplace	0 (0.0%)	0 (0.0%)
Health Care Facility	0 (0.0%)	0 (0.0%)
School	0 (0.0%)	0 (0.0%)
Other	2 (3.3%)	3 (4.6%)
Unknown	3 (5.0%)	0 (0.0%)
Route of Exposure[a]		
Ingestions	57 (95.0%)	64 (98.5%)
Inhalation/nasal	4 (6.7%)	0 (0.0%)
Ocular	0 (0.0%)	0 (0.0%)
Dermal	0 (0.0%)	2 (3.1%)
Parenteral	5 (8.3%)	1 (1.5%)
Other	0 (0.0%)	0 (0.0%)
Unknown	0 (0.0%)	0 (0.0%)
Chronicity		
Acute	40 (66.7%)	43 (66.2%)
Acute-on-Chronic	7 (11.7%)	11 (16.9%)
Chronic	8 (13.3%)	9 (13.8%)
Unknown	5 (8.3%)	2 (3.1%)
Number of Substances		

Characteristics	Intentional Abuse Exposure (N=60)	Intentional Misuse Exposure (N=65)
Mean (SD)	2.7 (1.09)	2.6 (1.11)
Median	2.0	2.0
Range	(2.0, 7.0)	(2.0, 8.0)
Number of Substances (Categories)		
1 Product/Substance	0 (0.0%)	0 (0.0%)
2 Products/Substances	35 (58.3%)	42 (64.6%)
3 Products/Substances	14 (23.3%)	13 (20.0%)
4+ Products/Substances	11 (18.3%)	10 (15.4%)

[a]*A single exposure may involve more than one route.*

Table 12.2.7.3: Level of Healthcare Facility (HCF) Care of Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional Abuse or Intentional Misuse Reason for Exposure

Characteristics	Intentional Abuse Exposure (N=60)	Intentional Misuse Exposure (N=65)
Recommended to or Received Healthcare Facility Care (HCF)		
Yes	59 (98.3%)	53 (81.5%)
No	1 (1.7%)	11 (16.9%)
Unknown	0 (0.0%)	1 (1.5%)
Level of Care[a]		
Treated/evaluated and released	15 (25.4%)	16 (30.2%)
Admitted to non-critical care unit	11 (18.6%)	8 (15.1%)
Admitted to critical care unit	25 (42.4%)	13 (24.5%)
Admitted to psychiatric care facility	2 (3.4%)	4 (7.5%)
Patient refused referral/did not arrive at HCF	1 (1.7%)	5 (9.4%)
Patient lost to follow-up/left AMA	5 (8.5%)	7 (13.2%)

[a]*Denominator is the number of exposures that were recommended to or received healthcare facility care.*

Table 12.2.7.4: Medical Outcome of Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional Abuse or Intentional Misuse Reason for Exposure

Medical Outcome	Intentional Abuse Exposure (N=60)	Intentional Misuse Exposure (N=65)
Followed to a Known Outcome	53 (88.3%)	44 (67.7%)
Death	1 (1.7%)	0 (0.0%)
Major Effect	15 (25.0%)	6 (9.2%)
Moderate Effect	24 (40.0%)	15 (23.1%)
Minor Effect	11 (18.3%)	11 (16.9%)
No Effect or Unrelated Effect	2 (3.3%)	12 (18.5%)
Not Followed to Known Outcome	7 (11.7%)	21 (32.3%)
Unable to follow, potentially toxic	6 (10.0%)	11 (16.9%)
Not followed, Non-toxic	0 (0.0%)	0 (0.0%)
Not followed, minimal clinical effects expected	1 (1.7%)	10 (15.4%)

Table 12.2.7.5: Related Clinical Effects Among Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional Abuse or Intentional Misuse Reason for Exposure

Clinical Effect	Intentional Abuse Exposure (N=60)	Intentional Misuse Exposure (N=65)
Drowsiness/lethargy	29 (48.3%)	11 (16.9%)
Tachycardia	19 (31.7%)	14 (21.5%)
Confusion	10 (16.7%)	6 (9.2%)
Other	6 (10.0%)	10 (15.4%)
Agitated/irritable	9 (15.0%)	6 (9.2%)
Hypertension	10 (16.7%)	5 (7.7%)
Conduction disturbance	9 (15.0%)	5 (7.7%)
Respiratory depression	12 (20.0%)	2 (3.1%)
Nausea	6 (10.0%)	5 (7.7%)
Diaphoresis	5 (8.3%)	4 (6.2%)
Hypotension	5 (8.3%)	4 (6.2%)
Vomiting	6 (10.0%)	3 (4.6%)
Abdominal Pain	4 (6.7%)	4 (6.2%)
Coma	7 (11.7%)	1 (1.5%)
Miosis	6 (10.0%)	2 (3.1%)
Bradycardia	4 (6.7%)	2 (3.1%)
CPK elevated	4 (6.7%)	2 (3.1%)
ECG change (other)	4 (6.7%)	2 (3.1%)
Fever/hyperthermia	4 (6.7%)	2 (3.1%)
Tremor	3 (5.0%)	2 (3.1%)
Ataxia	4 (6.7%)	0 (0.0%)
Creatinine increased	2 (3.3%)	2 (3.1%)
Dysrhythmia (v tach/v fib)	2 (3.3%)	2 (3.1%)
Electrolyte abnormality	3 (5.0%)	1 (1.5%)
Hallucinations/delusions	2 (3.3%)	2 (3.1%)
Mydriasis	3 (5.0%)	1 (1.5%)
Syncope	3 (5.0%)	1 (1.5%)
Urinary retention	4 (6.7%)	0 (0.0%)
Acidosis	1 (1.7%)	2 (3.1%)
Cardiac arrest	2 (3.3%)	1 (1.5%)
Diarrhea	1 (1.7%)	2 (3.1%)
Dizziness/vertigo	1 (1.7%)	2 (3.1%)

Clinical Effect	Intentional Abuse Exposure (N=60)	Intentional Misuse Exposure (N=65)
Muscle rigidity	2 (3.3%)	1 (1.5%)
Pneumonitis	3 (5.0%)	0 (0.0%)
Respiratory arrest	2 (3.3%)	1 (1.5%)
X-ray findings(+)	3 (5.0%)	0 (0.0%)
AST, ALT>100<=1,000	0 (0.0%)	2 (3.1%)
Constipation	0 (0.0%)	2 (3.1%)
Cough/choke	1 (1.7%)	1 (1.5%)
Cyanosis	1 (1.7%)	1 (1.5%)
Erythema/flushed	1 (1.7%)	1 (1.5%)
Muscle weakness	1 (1.7%)	1 (1.5%)
Pallor	2 (3.3%)	0 (0.0%)
Pruritus	0 (0.0%)	2 (3.1%)
Rhabdomyolysis	2 (3.3%)	0 (0.0%)
Slurred speech	2 (3.3%)	0 (0.0%)
Tinnitus	0 (0.0%)	2 (3.1%)
ADR to treatment	0 (0.0%)	1 (1.5%)
Alkalosis	1 (1.7%)	0 (0.0%)
Anion gap increased	0 (0.0%)	1 (1.5%)
Asystole	1 (1.7%)	0 (0.0%)
Blurred vision	1 (1.7%)	0 (0.0%)
Bronchospasm	1 (1.7%)	0 (0.0%)
CVA	0 (0.0%)	1 (1.5%)
Dehydration	1 (1.7%)	0 (0.0%)
Dermal - Irritation/pain	0 (0.0%)	1 (1.5%)
Dysrhythmia (other)	1 (1.7%)	0 (0.0%)
Edema	0 (0.0%)	1 (1.5%)
Excess secretions	1 (1.7%)	0 (0.0%)
Headache	0 (0.0%)	1 (1.5%)
Hyperglycemia	0 (0.0%)	1 (1.5%)
Hypoglycemia	0 (0.0%)	1 (1.5%)
Multiple Chemical Sensitivities	0 (0.0%)	1 (1.5%)
Numbness	0 (0.0%)	1 (1.5%)
Nystagmus	1 (1.7%)	0 (0.0%)
Other LFT abnormality	1 (1.7%)	0 (0.0%)
Pain (not dermal, GI, ocular)	1 (1.7%)	0 (0.0%)

Clinical Effect	Intentional Abuse Exposure (N=60)	Intentional Misuse Exposure (N=65)
Seizure (single)	1 (1.7%)	0 (0.0%)
Seizures (multi/discrete)	1 (1.7%)	0 (0.0%)
Urinary incontinence	1 (1.7%)	0 (0.0%)
Visual defect	1 (1.7%)	0 (0.0%)

Table 12.2.7.6: Related Clinical Effects Among Exposures to a Loperamide-Containing Product Plus Another Substance with Moderate Effect, Major Effect, or Death Medical Outcome by Intentional Abuse or Intentional Misuse Reason for Exposure

Clinical Effect	Intentional Abuse Exposure (N=40)	Intentional Misuse Exposure (N=21)
Drowsiness/lethargy	22 (55.0%)	9 (42.9%)
Tachycardia	17 (42.5%)	11 (52.4%)
Confusion	10 (25.0%)	5 (23.8%)
Hypertension	10 (25.0%)	5 (23.8%)
Conduction disturbance	9 (22.5%)	5 (23.8%)
Respiratory depression	11 (27.5%)	2 (9.5%)
Agitated/irritable	7 (17.5%)	4 (19.0%)
Other	5 (12.5%)	6 (28.6%)
Hypotension	5 (12.5%)	4 (19.0%)
Diaphoresis	5 (12.5%)	3 (14.3%)
Nausea	6 (15.0%)	2 (9.5%)
Vomiting	6 (15.0%)	2 (9.5%)
Coma	6 (15.0%)	1 (4.8%)
Miosis	5 (12.5%)	2 (9.5%)
CPK elevated	4 (10.0%)	2 (9.5%)
ECG change (other)	4 (10.0%)	2 (9.5%)
Bradycardia	3 (7.5%)	2 (9.5%)
Fever/hyperthermia	4 (10.0%)	1 (4.8%)
Tremor	3 (7.5%)	2 (9.5%)
Abdominal Pain	3 (7.5%)	1 (4.8%)
Ataxia	4 (10.0%)	0 (0.0%)
Creatinine increased	2 (5.0%)	2 (9.5%)
Dysrhythmia (v tach/v fib)	2 (5.0%)	2 (9.5%)
Electrolyte abnormality	3 (7.5%)	1 (4.8%)
Hallucinations/delusions	2 (5.0%)	2 (9.5%)
Syncope	3 (7.5%)	1 (4.8%)
Urinary retention	4 (10.0%)	0 (0.0%)
Acidosis	1 (2.5%)	2 (9.5%)
Cardiac arrest	2 (5.0%)	1 (4.8%)
Muscle rigidity	2 (5.0%)	1 (4.8%)
Mydriasis	3 (7.5%)	0 (0.0%)
Pneumonitis	3 (7.5%)	0 (0.0%)

Clinical Effect	Intentional Abuse Exposure (N=40)	Intentional Misuse Exposure (N=21)
Respiratory arrest	2 (5.0%)	1 (4.8%)
X-ray findings(+)	3 (7.5%)	0 (0.0%)
AST, ALT>100<=1,000	0 (0.0%)	2 (9.5%)
Cyanosis	1 (2.5%)	1 (4.8%)
Muscle weakness	1 (2.5%)	1 (4.8%)
Rhabdomyolysis	2 (5.0%)	0 (0.0%)
ADR to treatment	0 (0.0%)	1 (4.8%)
Alkalosis	1 (2.5%)	0 (0.0%)
Anion gap increased	0 (0.0%)	1 (4.8%)
Asystole	1 (2.5%)	0 (0.0%)
Blurred vision	1 (2.5%)	0 (0.0%)
Bronchospasm	1 (2.5%)	0 (0.0%)
CVA	0 (0.0%)	1 (4.8%)
Constipation	0 (0.0%)	1 (4.8%)
Cough/choke	1 (2.5%)	0 (0.0%)
Dehydration	1 (2.5%)	0 (0.0%)
Dysrhythmia (other)	1 (2.5%)	0 (0.0%)
Erythema/flushed	1 (2.5%)	0 (0.0%)
Hyperglycemia	0 (0.0%)	1 (4.8%)
Hypoglycemia	0 (0.0%)	1 (4.8%)
Multiple Chemical Sensitivities	0 (0.0%)	1 (4.8%)
Numbness	0 (0.0%)	1 (4.8%)
Nystagmus	1 (2.5%)	0 (0.0%)
Other LFT abnormality	1 (2.5%)	0 (0.0%)
Pain (not dermal, GI, ocular)	1 (2.5%)	0 (0.0%)
Pallor	1 (2.5%)	0 (0.0%)
Seizure (single)	1 (2.5%)	0 (0.0%)
Seizures (multi/discrete)	1 (2.5%)	0 (0.0%)
Slurred speech	1 (2.5%)	0 (0.0%)
Tinnitus	0 (0.0%)	1 (4.8%)
Urinary incontinence	1 (2.5%)	0 (0.0%)
Visual defect	1 (2.5%)	0 (0.0%)

Table 12.2.7.7: Therapies Performed Among Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional Abuse and Intentional Misuse Exposure Reason

Therapy	Intentional Abuse Exposure (N=60)	Intentional Misuse Exposure (N=65)
Fluids, IV	30 (50.0%)	17 (26.2%)
Oxygen	21 (35.0%)	7 (10.8%)
Other	15 (25.0%)	10 (15.4%)
Naloxone	21 (35.0%)	3 (4.6%)
Benzodiazepines	13 (21.7%)	8 (12.3%)
Alkalinization	8 (13.3%)	5 (7.7%)
Intubation	9 (15.0%)	3 (4.6%)
Ventilator	8 (13.3%)	3 (4.6%)
Sedation (other)	8 (13.3%)	2 (3.1%)
Antibiotics	8 (13.3%)	1 (1.5%)
Dilute/irrigate/wash	1 (1.7%)	5 (7.7%)
Antiarrhythmic	4 (6.7%)	1 (1.5%)
Antiemetics	3 (5.0%)	2 (3.1%)
Charcoal, single dose	4 (6.7%)	0 (0.0%)
Neuromuscular blocker	3 (5.0%)	1 (1.5%)
Vasopressors	3 (5.0%)	1 (1.5%)
CPR	3 (5.0%)	0 (0.0%)
Calcium	2 (3.3%)	1 (1.5%)
Food/snack	1 (1.7%)	2 (3.1%)
Antihistamines	1 (1.7%)	1 (1.5%)
Cardioversion	1 (1.7%)	1 (1.5%)
NAC, IV	2 (3.3%)	0 (0.0%)
Antihypertensives	1 (1.7%)	0 (0.0%)
Bronchodilators	1 (1.7%)	0 (0.0%)
Cathartic	1 (1.7%)	0 (0.0%)
NAC, PO	1 (1.7%)	0 (0.0%)
Other emetic	0 (0.0%)	1 (1.5%)
Pacemaker	1 (1.7%)	0 (0.0%)
Steroids	1 (1.7%)	0 (0.0%)

12.2.8 Fatalities Involving a Loperamide-Containing Product Plus Another Substance

Table 12.2.8.1: Case Characteristics of Fatalities Involving a Loperamide-Containing Product Plus Another Substance

Year	Age, Gender	Exposure Reason	Chronicity	Products or Substances Involved (Cause Rank, if applicable[a])	Relative Contribution of Exposure to Fatality	Autopsy Findings (if applicable) and Other Details Reported	Additional Information Reported in Case Notes
2013	37 Years, Female	Intentional Suspected Suicide	Acute	**Loperamide-Containing Product:** Single-ingredient loperamide (1) **Other Products/Substances**: Escitalopram (2) Meloxicam (3)	Probably responsible	**Cause of death:** Prescription medication toxicity **Manner of death:** Not reported **Loperamide Levels:** Not reported	• Patient found with 2 mg loperamide (10 caplets missing), 20 mg escitalopram (20 tablets missing), 15 mg meloxicam (13 tablets missing)
2014	43 Years, Female	Unknown Reason	Unknown	**Loperamide-Containing Product:** Single-ingredient loperamide **Other Products/Substances**: Naproxen Ativan Cetirizine Hydrocodone with acetaminophen	Probably not responsible	*Autopsy findings not available* **Loperamide Levels:** Not reported	• Patient found unresponsive after motor vehicle accident with all reported products in her purse (no history of ingestion)

Year	Age, Gender	Exposure Reason	Chronicity	Products or Substances Involved (Cause Rank, if applicable[a])	Relative Contribution of Exposure to Fatality	Autopsy Findings (if applicable) and Other Details Reported	Additional Information Reported in Case Notes
2015	23 Years, Male	Intentional Abuse	Acute	**Loperamide-Containing Product:** Single-ingredient loperamide (1) **Other Products/Substances**: Clonazepam[b] (2) Buprenorphine[b,c]	Undoubtedly responsible	**Cause of death:** Complications of mixed drug intoxication **Manner of death:** Accidental **Loperamide Levels:** Postmortem – 77 ng/mL (heart blood)	• Found with 6 empty bottles of 2 mg loperamide tablets • History of substance abuse; recent ER visit for opioids
2015	28 Years, Female	Unknown Reason	Unknown	**Loperamide-Containing Product:** Unknown loperamide-containing product* **Other Products/Substances**: Amitriptyline Benzonatate Orphenadrine Alprazolam[b] Dextromethorphan[b] Doxylamine[b]	Unknown	**Cause of death:** Unknown[#] **Manner of death:** Unknown [#]*Autopsy results were unremarkable with the exception of acute pulmonary congestions with edema along with acute visceral congestion.* **Loperamide Levels:** Not reported	• Found with amitriptyline, orphenadrine, and benzonatate in her immediate area • History of bipolar disorder; lamotrigine prescribed for patient but not detected in toxicological testing

Year	Age, Gender	Exposure Reason	Chronicity	Products or Substances Involved (Cause Rank, if applicable[a])	Relative Contribution of Exposure to Fatality	Autopsy Findings (if applicable) and Other Details Reported	Additional Information Reported in Case Notes
2015	54 Years, Female	Unknown Reason	Acute-on-chronic	**Loperamide-Containing Product:** Single-ingredient loperamide **Other Products/Substances**: Diphenhydramine Multi-ingredient cough/cold medication Lamotrogine Methadone[b] Opioids[b]	Probably not responsible	*Autopsy not performed* **Loperamide Levels:** Not reported	• History of drug abuse • The patient's boyfriend reported a 2 day history of chills, vomiting, diarrhea, and dyspnea for which the patient was taking single-ingredient loperamide, diphenhydramine, and a multi-ingredient cough/cold medication
2015	Unknown, Female	Unknown Reason	Unknown	**Loperamide-Containing Product:** Single-ingredient loperamide **Other Products/Substances**: Amlodipine Cetirizine Diphenhydramine Hydrocodone with acetaminophen Levitiracetam	Unknown	*Autopsy information unavailable* **Loperamide Levels:** Not reported	• Female found dead with bottles of the listed products and substances

[a] *Cause rank is only reported when the exposure is at least probably related to the fatality.*
[b] *Substance observed upon toxicology screen only (no history of ingestion).*
[c] *Not listed as a substance in the case because the toxicology screen determined level was therapeutic.*

12.2.9 Reported Quantity by Exposure Reason and Severe Cardiovascular-Related Clinical Effect for Exposures to a Loperamide-Containing Product Plus Another Substance

Table 12.2.9.1: Reported Quantity by Exposure Reason for Exposures to a Loperamide-Containing Product Plus Another Substance

	Intentional Abuse	Intentional Misuse	All Other Intentional	Unintentional	Adverse Reaction	Other or Unknown
Mean (SD)	300.3 (395.14)	29.5 (68.96)	58.2 (120.91)	6.2 (13.31)	7.3 (16.81)	9.0 (9.54)
Median	142.0	12.0	20.0	2.0	2.0	4.0
Range	(4.0, 1,656.0)	(2.0, 400.0)	(2.0, 820.0)	(0.2, 144.0)	(0.5, 100.0)	(3.0, 20.0)
IQR	(32.0, 400.0)	(4.0, 32.0)	(10.0, 44.0)	(2.0, 4.0)	(2.0, 6.0)	(3.0, 20.0)
N	26	33	163	269	38	3

Table 12.2.9.2: Reported Quantity by Severe Cardiovascular-Related Clinical Effect for Exposures to a Loperamide-Containing Product Plus Another Substance

Statistic	Severe Cardiovascular-Related Clinical Effect	No Severe Cardiovascular-Related Clinical Effect
Mean (SD)	325.1 (396.77)	30.8 (104.56)
Median	140.0	4.0
Range	(6.0, 1200)	(0.2, 1656)
IQR	(30.0, 544.0)	(2.0, 20.0)
N	13	519

13 Conclusions

13.1 Data Implications

The majority of exposures to loperamide-containing products reported to the National Poison Data System (NPDS) involve loperamide-containing products only (no other substance). One loperamide-containing product exposure is reported for every 0.413 million units (i.e., tablets, gelcaps, liquid equivalents) sold, with the rate of reported exposures three times higher among exposures involving loperamide-containing products only compared to exposures involving a loperamide-containing product plus another substance.

Of exposures involving loperamide-containing products only, most involve unintentional reasons for exposures like therapeutic errors and accidental unsupervised ingestions. Intentional abuse and intentional misuse of loperamide-containing products are reported in approximately 12% of exposures and occur more commonly when multiple substances are involved. These other substances commonly include both over-the-counter medications like ibuprofen and anti-histamines, but also include other substances that can be abused including alcohol and opioids. While rates of exposure to loperamide-containing products remain low, rates of intentional misuse of these products may be increasing as intentional misuse of loperamide-containing products only nearly doubled from 2012 to 2015 (2012: 0.131 intentional misuse exposures per million units (CI 0.099, 0.173) sold; 2015: 0.229 intentional misuse exposures per million units (CI 0.180, 0.290) sold). Rates of intentional abuse of these products did not change significantly during this period (2012: 0.046 intentional abuse exposures per million units (CI 0.032, 0.066) sold; 2015: 0.081 intentional abuse exposures per million units (CI 0.058, 0.112) sold).

Generally, intentional exposures involve more remarkable outcomes like moderate effect, major effect, and death. Intentional exposures also tend to involve higher levels of healthcare facility care, including admission to critical care unit. Among fatalities involving loperamide-containing products only, intentional abuse of the loperamide-containing product was clearly evident in four of six cases. Examination of the narrative records of these fatalities showed that the loperamide-containing product was often being used to achieve opioid-like effects or to withdraw from opioids. In all six fatalities, the loperamide-containing product was determined to be at least contributory to the death, with the loperamide-containing product probably responsible (n=2) or undoubtedly responsible (n=2) in four cases. Loperamide overdose was apparent in four cases with evidence of missing tablets or reports of large quantities of ingestion. History of ingestion was less clear in the other two cases, but antemortem and postmortem loperamide levels were reported.

Among the six fatalities involving multiple substances, the role of poly-pharmacy in the exposure complicated the understanding of the relationship between exposure and outcome. However, the exposure (including both loperamide-containing products and non-loperamide products) was determined to be probably responsible for the fatality in one case and undoubtedly responsible for the fatality in another case. In both of these deaths, the single-ingredient loperamide product was the primary causative substance and both involved an apparent history of loperamide overdose as evidenced by missing loperamide tablets or empty loperamide bottles. Suicide was reported in one of these cases, while intentional abuse of loperamide was reported in the other. In the remaining four cases, the responsibility of the exposure to the fatality was unknown in two cases and probably not responsible in two cases.

Reported quantity was explored by exposure reason and for exposures associated with cardiovascular-related clinical effects. For both exposures to loperamide-containing products

only and exposures to loperamide-containing products plus another substance, intentional reasons for exposure were associated with a higher quantity of exposure, with intentional abuse associated with the highest reported quantities. Similarly, exposures with severe cardiovascular-related clinical effects were associated with greater reported quantities than exposures that did not involve severe cardiovascular-related clinical effects. When reported quantity among exposures with severe cardiovascular-related clinical effects was compared between exposures to loperamide-containing products only and exposures to loperamide-containing products plus another substance, exposures to loperamide-containing products only involved nearly twice as much loperamide.

13.2 Data Strengths

NPDS data strengths include that data are collected nationwide and can be tracked over time. These data involve actual experiences with the use of loperamide over a large sample size, which often provides insights about the safety of a substance that cannot be evaluated via a conventional clinical trial. In addition, NPDS data are collected and entered into a standardized data collection system using quality control measures at the entry and upload of data.

13.3 Data Limitations

NPDS data are spontaneously reported, which may lead to the underreporting of some types of exposures. While data are spontaneously reported, the use of national sales data helps control for the impact of product availability on reporting.

14 Disclaimers

14.1 American Association of Poison Control Centers

The American Association of Poison Control Centers (AAPCC: http://www.aapcc.org) maintains the national database of information logged by the country's Poison Control Centers (PCCs). Case records in this database are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g. an ingestion, inhalation, or topical exposure, etc.), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

14.2 Information Resources, Inc.

The information contained herein is based in part on data from Information Resources, Inc. as solely interpreted by Denver Health and Hospital Authority and not by Information Resources, Inc.

15 References

1. Eggleston W. Cardiac dysrhythmias after loperamide abuse-New York, 2008-2016. Morbidity and Mortality Weekly Report. 2016; 65(45): 1276-1277.
2. Bronstein AC, Spyker DA, Cantilena LR, Green JL, Rumack BH, Griifin SL. 2008 Annual Report of the American Association of the Poison Control Centers' National Poison Data System (NPDS): 26th Annual Report. Clinical Toxicology, 2009; 47: 911-1084.
3. Mowry J.B., Spyker DA, Brooks DE, Zimmerman A, Schauben JL. 2015 Annual Report of the American Association of the Poison Control Centers' National Poison Data System (NPDS): 33rd Annual Report. Clinical Toxicology, 2016; 54(10): 924-1109.

V. Appendices

Appendix A: Loperamide Survey Questions in RADARS® System Survey of Non-Medical Use of Prescription Drugs Program 3rd Quarter 2016 Survey in the United States

Please note: for the purposes of this report, only survey items related to loperamide are presented. All non-applicable products and language have been omitted.

1. Have you ever used a non-prescription medication (e.g. loperamide)?

Yes
No

<Skip Logic>. If yes, proceed to next question. If no, skip to next section.

2. Have you ever used a non-prescription medication (e.g. loperamide) for any reason other than what was recommended by your doctor/dentist/pharmacist/the packet insert?

Yes
No

<Skip Logic>. If yes, proceed to next question. If no, skip to next section.

The following questions refer to medications that do <u>not</u> require a prescription.

3. What non-prescription medications have you ever used for any reason other than what was recommended by your doctor/dentist/pharmacist/the packet insert? Please read each of the products below and check all that apply.

	No, I have not used this medication	Yes, I have used this medication	I am not sure if I have used this medication
Loperamide (e.g. Imodium® A-D, Imodium® Multi-Symptom Relief, generics, etc.)	○	○	○

<Skip Logic>. Respondents are not required to select an answer for every product, but must select "Yes, I have used this medication" or "I am not sure I have used this medication" for at least one. For the remaining questions in this section, only include the products where "Yes, I have used this medication" or "I am not sure I have used this medication" was selected in the previous question.

The following questions refer to medications that do <u>not</u> require a prescription.

4. What was the reason/s you used each non-prescription medication listed below without a doctor's prescription or for any reason other than what was recommended by your

doctor/dentist/pharmacist? For products used, please check all that apply (at least one reason required).

	To self-treat my pain	To treat a medical condition, other than pain	For enjoyment/ to get high	To come down	To prevent or treat withdrawal symptoms	Other reason (please specify on the next page)
Loperamide (e.g. Imodium® A-D, Imodium® Multi-Symptom Relief, generics, etc.)	□	□	□	□	□	□

The following questions refer to medications that do <u>not</u> require a prescription.

5. How often have you used each non-prescription medication listed below without a doctor's prescription or for any reason other than what was recommended by your doctor/dentist/pharmacist?

	I have not used it within the last 90 days (I used it longer ago)	Number of days within last 90 days	Number of days within last 30 days	Number of days within last 7 days
Loperamide (e.g. Imodium® A-D, Imodium® Multi-Symptom Relief, generics, etc.)	○	Days	Days	Days

The following questions refer to medications that do <u>not</u> require a prescription.

6. Which routes have you ever used for each non-prescription medication listed below without a doctor's prescription or for any reason other than what was recommended by your doctor/dentist/pharmacist, even if just once? If more than one route was used, please check all that apply.

	Swallowed		Chewed and then swallowed		Dissolved in mouth (e.g. between cheek and gum, under tongue)		Inhaled (snorted or smoked)		Injected (shot it up)		Other route (please specify on the next page)	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Loperamide (e.g. Imodium® A-D, Imodium® Multi-Symptom Relief, generics, etc.)	○	○	○	○	○	○	○	○	○	○	○	○

Appendix B: National Poison Data System (NPDS) Definitions

EXPOSURE
Actual or suspected contact with any substance which has been ingested, inhaled, absorbed, applied to, or injected into the body, regardless of toxicity or clinical manifestation.

REASON FOR EXPOSURE
Unintentional Exposure
An unintentional exposure results from an unforeseen or unplanned event. Includes all subtypes: unintentional general, environmental, occupational, therapeutic error, misuse, bite/sting, food poisoning and unintentional unknown.

1) **Unintentional - General**: All unintended exposures that are not specifically defined below. Most unintentional exposures in children should be coded here. Never use this code if there is another code that fits the case.
2) **Unintentional - Environmental**: Any passive, non-occupational exposure that results from contamination of air, water, or soil. Environmental exposures are usually, but not always, caused by manmade contaminants.
3) **Unintentional - Occupational**: Any exposure that occurs as a *direct* result of the person being on the job or in the workplace.
4) **Unintentional - Therapeutic error**: An unintentional deviation from a proper *therapeutic* regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance. Includes instances in which any type of substance (medications, herbals, non-pharmaceuticals or other products) is substituted for a medication. Drug interactions (or drug/food interactions) resulting from unintentional administration of drugs/foods which are known to interact should also be included.
5) **Unintentional - Misuse**: Unintentional improper or incorrect use of a non-pharmaceutical substance. *Unintentional* misuse differs from *intentional* misuse in that the exposure was unplanned or not foreseen by the patient.
6) **Unintentional - Bite/sting:** All animal bites and stings, with or without envenomation.
7) **Unintentional - Food poisoning**: All suspected or confirmed food poisoning regardless of clinical manifestation. This would include ingestion of any food contaminated with microorganisms. Select this reason even if the patient develops no symptoms from the contaminated food.
8) **Unintentional - Unknown**: An exposure determined to be unintentional but the exact reason is unknown.

Intentional Exposure
A purposeful action results in an exposure. Includes all subtypes: suspected suicide, misuse, abuse and intentional unknown.

9) **Intentional - Suspected suicidal**: An exposure resulting from the inappropriate use of a substance for self-harm or for self-destructive or manipulative reasons.
10) **Intentional - Misuse**: An exposure resulting from the intentional improper or incorrect use of a substance for reasons **other** than the pursuit of a psychotropic effect.
11) **Intentional - Abuse**: An exposure resulting from the intentional improper or incorrect use of a substance where 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.

12) **Intentional - Unknown**: An exposure that is determined to be intentional but the specific motive is unknown.

Adverse Reaction - Drug
A key element in adverse reactions is that the event occurred with normal, prescribed, labeled or recommended use of the product, as opposed to situations involving overdose, misuse, or abuse of the product. Adverse reaction is coded whenever the patient had an unwanted effect due to an allergic, hypersensitive, or idiosyncratic response to the active ingredient(s), inactive ingredient(s) or excipient of a drug, chemical, cosmetic, food or other substance.

15) **Adverse Reaction – Drug:** Unwanted effects due to an allergic, hypersensitivity, or idiosyncratic response to the active ingredient(s), inactive ingredient(s) or excipient of a drug, chemical, or other drug substance when the exposure involves the normal, prescribed, labeled or recommended use of the substance.
16) **Adverse Reaction – Food:** Unwanted effects due to an allergic, hypersensitivity, or idiosyncratic response to a food substance.
17) **Adverse Reaction - Other:** Unwanted effects due to an allergic, hypersensitivity, or idiosyncratic response to a substance other than drug or food.

Other/Unknown Reason
Other reason such as withdrawal, malicious intent, contamination/tampering, etc. OR, unknown reason which indicates the reason for the exposure cannot be determined or no other category is appropriate

CHRONICITY
Chronicity of the exposure.

Acute: A single, repeated or continuous exposure occurring over a period of eight hours or less.

Acute-on-Chronic: A single exposure that was preceded by a continuous, repeated, or intermittent exposure occurring over a period exceeding eight hours.

Chronic: A continuous, repeated, or intermittent exposure to the same substance lasting longer than eight hours.

Unknown: It is not possible to determine whether the exposure is acute, acute-on-chronic, or chronic.

MEDICAL OUTCOME
Case followed to known outcome:
A response is appropriate in this area only if follow-up continues until medical outcome can be documented with reasonable certainty.

Unrelated effect: Based upon all the information available, the exposure was probably not responsible for the effect(s).

No effect: The patient developed no symptoms as a result of the exposure. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long after the exposure that you are reasonably certain no effects will occur.

Minor effect: The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and usually involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of wellbeing and has no residual disability or disfigurement.

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. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement.

Major effect: The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement.

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. Only includes deaths which are probably or undoubtedly related to the exposure.

Case <u>not</u> followed to a known outcome:
In some circumstances it is not appropriate or possible to follow a patient to a reasonably certain medical outcome.

Not followed, judged as nontoxic exposure. The patient was not followed because in the clinical judgment of the specialist in poison information, the exposure was likely to be nontoxic because:

- the agent involved was nontoxic
- the amount implicated in the exposure was insignificant (nontoxic), and/or
- the route of exposure was unlikely to result in a clinical effect

Not followed, minimal clinical effects possible. The patient was not followed because, in the clinical judgment of the specialist in poison information, the exposure was likely to result in only minimal toxicity of a trivial nature. This outcome is selected only when reasonably certain, in a worst case scenario, that the patient will experience no more than a minor effect. This also includes cases that refused follow-up if the exposure would possibly result in minimal clinical effects and would cause no more than a minor effect.

Unable to follow, judged as a potentially toxic exposure. The patient was lost to follow-up (or the poison center neglected to provide follow-up) and in the judgment of the specialist in poison information the exposure was significant and may have resulted in toxic manifestations with a moderate, major or fatal outcome.

Death, indirect report: A reported fatality is coded as “indirect” if no inquiry was placed to the poison center. For example, if the case was obtained from a medical examiner who sends post mortem reports to the poison center or from a newspaper article. An inquiry to the poison center after the patient died is not necessarily indirect. For example, a medical examiner calling with a question about the cause of death or a family member calling with a question about a toxicology laboratory result is not an indirect report.

CLINICAL EFFECT
Reported signs, symptoms and clinical findings associated with an exposure, recorded by relationship to the exposure.

Cardiovascular-Related Clinical Effects

Asystole	Conduction disturbance	Hypertension
Bradycardia	Dysrhythmia (other)	Hypotension
Cardiac arrest	Dysrhythmia (v tach/v fib)	Tachycardia
Chest pain (incl. noncardiac)	ECG change (other)	

THERAPIES
Therapies that were recommended and/or performed in relation to the exposure reported.

Appendix C: National Poison Data System (NPDS) Relative Contributions to Fatality (RCF)

Undoubtedly responsible
In the opinion of the Case Review Team (CRT) the Clinical Case Evidence establishes beyond reasonable doubt that the SUBSTANCES actually caused the death.

Probably responsible
In the opinion of the CRT the Clinical Case Evidence suggests that the SUBSTANCES caused the death, but some reasonable doubt remained.

Contributory
In the opinion of the CRT the Clinical Case Evidence establishes that the SUBSTANCES contributed to the death, but did not solely cause the death. That is, the SUBSTANCES alone would not have caused the death, but combined with other factors, were partially responsible for the death.

Probably not responsible
In the opinion of the CRT the Clinical Case Evidence establishes to a reasonable probability, but not conclusively, that the SUBSTANCES associated with the death did not cause the death.

Clearly not responsible
In the opinion of the CRT the Clinical Case Evidence established beyond a reasonable doubt that the SUBSTANCES did not cause this death.

Unknown
In the opinion of the CRT the Clinical Case Evidence is insufficient to impute or refute a causative relationship for the SUBSTANCES in this death.