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:	Alison Hughes
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:	**Richard C. Dart, MD, PhD** Denver Health and Hospital Authority Rocky Mountain Poison & Drug Safety 777 Bannock Street, Mail Code 0180 Denver, Colorado 80204 (United States)
REPORT DATE:	13 November 2019

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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 2017. 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. The majority (56.6%) of respondents who non-medically used loperamide reported NMU to treat a medical condition other than pain followed by 39.0% reporting NMU to self-treat pain. 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-containing products only was associated with 17.4% of all reported loperamide-containing product only 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-containing products only were evaluated in the context of product availability, rates per one million units (i.e., tablets, gelcaps, liquid equivalents) sold ranged from 0.029 (CI 0.016, 0.047) to 0.251 (CI 0.212, 0.296). This equates to a range of 1 exposure for every 34.483 million units (i.e., tablets, gelcaps, liquid equivalents) sold to 1 exposure for every 3.984 million units (i.e., tablets, gelcaps, liquid equivalents) sold. In both programs, the rates of NMU, intentional abuse, or intentional misuse of loperamide 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 of loperamide-containing product only exposures were more likely to involve an adult patient (91.8% ≥12 year of age) than exposures involving unintentional exposures (exposures resulting from an unforeseen or unplanned event; 26.4% ≥12 years of age). This is likely due to the unintentional category of exposures including pediatric accidental unsupervised ingestions (50.0% of exposures to loperamide-containing products only). In both data

programs, use of other substances was also associated with 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 scheme. Particular strengths of Survey of Non-Medical Use of Prescription Drugs include the richness of the survey data to capture detailed respondent 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

SPONSOR:	Johnson & Johnson Consumer Inc., McNeil Consumer Healthcare Division 7050 Camp Hill Road Fort Washington, PA 19034
SPONSOR CONTACT:	Alison Hughes
TARGET DRUG SUBSTANCES:	Loperamide
PROGRAMS:	RADARS® System Survey of Non-Medical Use of Prescription Drugs Program
REPORTING COUNTRIES:	United States
PRINCIPAL INVESTIGATORS:	**Richard C. Dart, MD, PhD** Denver Health and Hospital Authority Rocky Mountain Poison & Drug Safety 777 Bannock Street, Mail Code 0180 Denver, Colorado 80204 (United States)
REPORT DATE:	13 November 2019

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.

3 Table of Contents

4 List of Tables

5 List of Figures

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 Richard C. Dart, MD, PhD.

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).

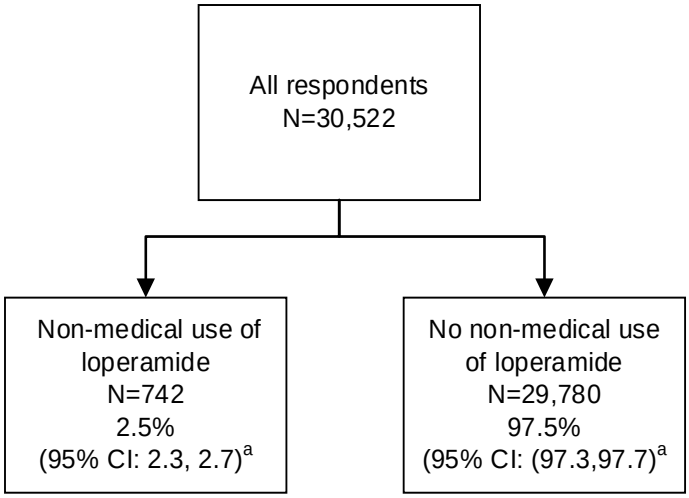
11.1.4 Rate of Recent Sales and Non-Medical Use of Loperamide

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

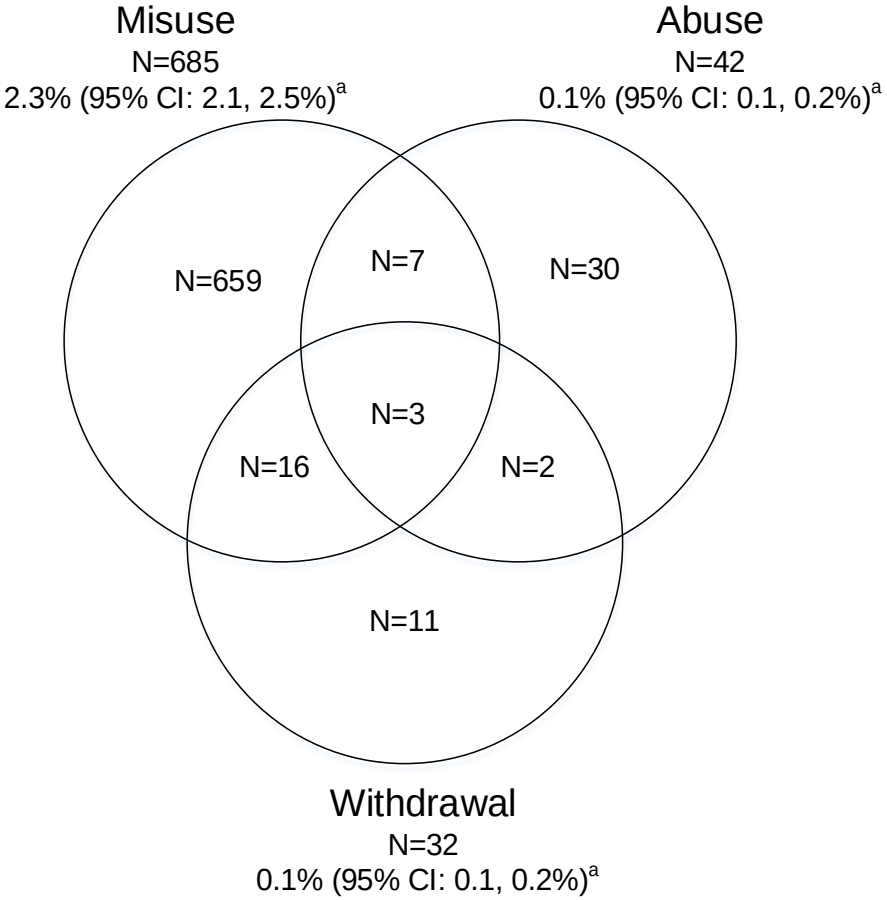
Table 11.4.2.1: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program Reasons for Non-Medical Use (NMU) of Loperamide by Route among Respondents 3rd Quarter 2016 United States Survey

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 ProgramDrug 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 ProgramCharacteristics 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.

It's estimated that nationally, 2.3% of adults have misused loperamide (to prevent or treat a medical condition other than pain or to self-treat pain), 0.1% have abused loperamide (use for enjoyment or to get high), and 0.1% have non-medically used loperamide in order to prevent or treat withdrawal symptoms. 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

SPONSOR:	Johnson & Johnson Consumer Inc., McNeil Consumer Healthcare Division 7050 Camp Hill Road Fort Washington, PA 19034
SPONSOR CONTACT:	Alison Hughes
TARGET DRUG SUBSTANCES:	Loperamide
PROGRAMS:	National Poison Data System
REPORTING COUNTRIES:	United States
PRINCIPAL INVESTIGATORS:	**Richard C. Dart, MD, PhD** Denver Health and Hospital Authority Rocky Mountain Poison & Drug Safety 777 Bannock Street, Mail Code 0180 Denver, Colorado 80204 (United States)
REPORT DATE:	13 November 2019

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 six year study period (2012 to 2017), 7,814 exposures involving a loperamide-containing product were reported to the National Poison Data System (NPDS). The majority (62.1%; n=4,855/7,814) of these exposures involved unintentional reasons for exposure (exposure resulting from an unforeseen or unplanned event). Intentional abuse (7.3%; n=571/7,814; 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 (8.9%; n=698/7,814; intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect) were reported infrequently (16.2% of all exposures).
- The overall rate of reported exposures in the context of sales of loperamide-containing products was low at 2.451 exposures per one million units sold (CI 2.397, 2.506) or one case per 0.408 million units (i.e., tablets, gelcaps, liquid equivalents) sold, which increased from 2.307 exposures per one million units sold (CI 2.179, 2.441) in 2012 to 2.703 exposures per one millions units sold (CI 2.571, 2.839) in 2017.
- Most exposures (74.2%) involved only the loperamide-containing product and no other substances. A loperamide-containing product plus at least one other substance was reported in 25.8% of exposures.
- Intentional exposures involving loperamide-containing products only were reported in 17.6% (n=1,378/7,814) of all reported loperamide exposures. Unintentional exposures involving loperamide-containing products only were reported in 52.2% (n=4,076/7,814) of all reported loperamide exposures.
- Intentional exposures to loperamide-containing products only involved mostly adults and children aged ≥12 years among intentional exposures (91.8%), while unintentional exposures involved mostly children aged <12 years (70.0%). Intentional exposures were referred for healthcare facility (HCF) care in 82.0% of exposures, of those referred for HCF care, 47.4% (n=536/1,130) were admitted to a HCF. Intentional exposures to loperamide-containing products only involved a remarkable medical outcome (moderate effect, major effect, or death) in 31.6% (n=436/1,378) of exposures. Unintentional exposures were referred for HCF care in 26.8% of exposures and admitted to a HCF in 11.1% (n=121/1,092). Unintentional exposures to loperamide-containing products only involved a remarkable medical outcome in 1.2% (n=47/4,076).
    - A total of 416 (7.2%) exposures to loperamide-containing products only involved intentional abuse. The median age of patients among intentional abuse exposures to loperamide-containing products only was 29.0 years. Intentional abuse exposures were referred for HCF care in 94.7% of exposures and admitted to a HCF in 62.9% (n=248/394) and involved a remarkable medical

outcome in 55.3% (n=230/416) of exposures. The overall sales-adjusted rate of intentional abuse exposures involving loperamide-containing products only was 0.130 exposures per one million units sold (CI 0.118, 0.144) or one case per 7.692 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The annual sales-adjusted rate of intentional abuse exposures increased over the study period.

- A total of 591 (10.2%) exposures to loperamide-containing products only involved intentional misuse. The median age of patients among intentional misuse exposures of loperamide-containing products only was 46.0 years. Intentional misuse exposures were referred for HCF care in 66.0% of exposures and admitted to a HCF in 26.4% (n=103/390) and involved a remarkable medical outcome in 16.1% (n=95/591) of exposures. The overall sales-adjusted rate of intentional misuse exposures involving loperamide-containing products only was 0.185 exposures per one million units sold (CI 0.171, 0.201) or one case per 5.405 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The annual sales-adjusted rate of intentional misuse exposures increased over the study period.
- Ten (10) fatalities involving loperamide-containing products only were reported between 2012 and 2017 (2012: n=2; 2013: n=1; 2014: n=3; 2016: n=1; 2017: n=3); no fatalities involving loperamide-containing products only were reported in 2015. Ages ranged from 21 to 41 years and the majority (n=7; 70.0%) involved male patients. Intentional abuse was the reason for exposure in seven (7) cases (70.0%) and the remaining cases had either an intentional unknown (n=2; 20.0%) or unknown reason for exposure (n=1; 10.0%). The loperamide-containing product was determined to be at least contributory to the fatality in all 10 cases.

- Exposures involved a loperamide-containing product plus another substance in 25.8% of all exposures to loperamide-containing products. Intentional exposures involving a loperamide-containing product plus another substance were reported in 14.0% (n=1,092/7,814) of all reported loperamide exposures. Unintentional exposures involving a loperamide-containing product plus another substance were reported in 10.0% (n=779/7,814) of all reported loperamide exposures.
- Intentional exposures to loperamide-containing products plus another substance involved mostly adults and children ≥12 years of age (97.3%), while the majority (62.0%) of unintentional exposures primarily involved children <12 years of age. Intentional exposures were referred for HCF care in 97.3% of exposures and admitted to a HCF in 71.0% (n=755/1,063). Intentional exposures to loperamide-containing products plus another substance involved a remarkable medical outcome in 47.6% (n=520/1,092) of exposures. Unintentional exposures were referred for HCF care in 49.3% of exposures and admitted to a HCF in 23.4% (n=90/384). Unintentional exposures to loperamide-containing products plus another substance involved a remarkable medical outcome in 6.5% (n=51/779) of exposures.
    - A total of 155 (7.7%) exposures to a loperamide-containing product plus another substance involved intentional abuse. The median age of patients among intentional abuse exposures to a loperamide-containing product plus another substance was 28.0 years. Intentional abuse exposures were referred for HCF care in 98.1% of exposures and admitted to a HCF in 66.4% (n=101/152), and involved a remarkable medical outcome in 70.3% (n=109/155). The overall sales-adjusted rate of intentional abuse exposures involving loperamide-containing products plus another substance was 0.049 exposures per 1 million units sold (CI 0.041, 0.057) or one case per 20.408 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The sales-adjusted rate of intentional abuse exposures

involving loperamide-containing products plus another substance increased from 2012 through 2016 followed by a decrease in 2017.

- A total of 107 (5.3%) exposures to a loperamide-containing product plus another substance involved intentional misuse. The median age of patients among intentional misuse exposures to a loperamide-containing product plus another substance was 36.0 years. Intentional misuse exposures were referred for HCF care in 81.3% of exposures and admitted to a HCF in 51.7% (n=45/87), and involved a remarkable medical outcome in 32.7% (n=35/107). The overall sales-adjusted rate of intentional misuse exposures involving loperamide-containing products plus another substance was 0.034 exposures per 1 million units sold (CI 0.028, 0.041) or one case per 29.412 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The sales-adjusted rate of intentional misuse exposures involving loperamide-containing products plus another substance fluctuated throughout the study period.
- Sixteen (16) fatalities involving a loperamide-containing product plus another substance were reported between 2012 and 2017 (2013: n=1; 2014: n=1; 2015: n=4; 2016: n=2; 2017: n=8); no fatalities involving loperamide-containing products plus another substance were reported in 2012. Ages ranged from 23 to 82 years and the majority (62.5%; n=10/16) were female. The reason for exposure was unknown in most (37.5%; n=6/16) cases, with the remaining cases involving intentional suspected suicide (31.3%; n=5/16), intentional abuse (18.8%; n=3/16), and intentional unknown (12.5%; n=2/16). The exposure (including loperamide-containing products and non-loperamide containing products) was determined to be at least contributory to the fatality in four (4) of the 16 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.
Acute-on-Chronic	A single exposure that was preceded by a continuous, repeated, or intermittent exposure occurring over a period exceeding eight hours.
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	Implies that the observed result was unlikely to have occurred by chance

significance	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 Sales-Adjusted Rates of Reported Exposures to Loperamide-Containing Products

Another secondary objective is to calculate an overall sales-adjusted rate of reported loperamide-containing product exposure using national sales data as a measure of product availability. This rate analysis will 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 2017 to loperamide-containing products with or without any other pharmaceutical or non-pharmaceutical substance. Cases that were confirmed later to be non-exposures or 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 C. 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 2017 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 2017 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 2017 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	518.5
2016	587.1
2017	584.6

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 B. 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 B).

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 B) 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 <12 years of age (pediatric) and ≥12 years of age (adults and children) were described in alignment with loperamide labeling, along with the estimated NPDS age categories (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 (e.g., loperamide plus any another pharmaceutical or non-pharmaceutical 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 with corresponding 95% exact Poisson confidence intervals. 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 C), 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 Richard C. Dart, MD, PhD.

11 Results

11.1 All Exposures to Loperamide-Containing Products

A total of 7,814 exposures involving loperamide-containing products were reported to the National Poison Data System (NPDS) from 01 January 2012 to 31 December 2017. The overall sales-adjusted rate of reported exposures to loperamide-containing products during this period was 2.451 exposures per one million units sold (CI 2.397, 2.506; Table 12.2.1.1). This equates to one exposure per 0.408 million units (i.e., tablets, gelcaps, liquid equivalents) sold.

Exposures to loperamide-containing products only (no non-loperamide-containing substances) were reported in 5,795 (74.2%) exposures, while 2,019 (25.8%) exposures involved a loperamide-containing product plus another substance (Figure 12.1.1.1).

The median age of patients among all loperamide-containing product exposures was 16.0 years. Just over one-half (52.4%) of patients was female. Exposure characteristics showed that most (93.4%) exposures occurred in the patient's own residence, involved ingestion of the product (99.2%), and involved an acute exposure (82.9%). The mean number of substances reported per exposure was 1.7 (SD 1.87), with 74.0% of exposures involving a single product, 10.9% involving two products, 5.7% involving three products, and 9.3% involving four or more products. Unintentional exposures occurred in 62.1% (n=4,855/7,814) of exposures, while intentional exposures occurred in 31.6% (n=2,470/7,814) of exposures, adverse reactions occurred in 4.7% (n=371/7,814) of exposures, and other or unknown reasons for exposure occurred in 1.5% (n=118/7,814; Figure 12.1.1.1; Table 12.2.1.2). Intentional abuse and misuse occurred in 16.2% (n=1,269/7,814) of all loperamide-containing product exposures (intentional abuse: 7.3%; intentional misuse: 8.9%).

11.2 Exposures to Loperamide-Containing Products Only

Exposures to loperamide-containing products only occurred in 5,795 (74.2%) of exposures (Figure 12.1.1.1). The overall sales-adjusted rate of reported exposures to loperamide-containing products only was 1.818 exposure per one million units sold (CI 1.771, 1.865). This equates to one exposure per every 0.550 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The sales-adjusted rate of reported exposures increased from 1.761 per million units sold (CI 1.649, 1.878) in 2012 to a peak rate of 1.988 per million units sold (CI 1.875, 2.105) in 2017 (Table 12.2.1.1).

The median age of patients exposed to loperamide-containing products only was 6.0 years, with half (50.1%) of exposures occurring in children <12 years of age. The slight majority (51.4%) of patients was female. Exposure characteristics showed that most (94.0%) exposures occurred in the patient's own residence. Route of exposures was primarily (99.3%) via ingestion. The majority (85.2%) of exposures involved an acute exposure. Fourteen (14; 0.2%) exposures involved two loperamide-containing products and no exposures involved more than two loperamide-containing products (Table 12.2.1.2).

The reason for exposure was intentional in 23.8% of exposures to loperamide-containing products only and unintentional in 70.3% (Figure 12.1.1.1; Table 12.2.1.2).

11.2.1 Intentional Exposures to Loperamide-Containing Products Only

Among exposures involving loperamide-containing products only, 23.8% (n=1,378/5,795) involved an intentional exposure reason (Figure 12.1.1.1). The overall sales-adjusted rate of reported intentional exposures to loperamide-containing products only from 2012 to 2017 was 0.432 per one million units sold (CI 0.410, 0.456). This equates to one case per 2.315 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The sales-adjusted rate of reported exposures increased from 0.247 per one million units sold (CI 0.206, 0.293) in 2012 to 0.642 per one million units sold (CI 0.578, 0.710) in 2017 (Table 12.2.2.1).

The median age of patients among intentional exposures to loperamide-containing products only was 32.0 years, with 91.8% involving adults and children ≥12 years of age. Nearly half (47.0%) of the exposures involved a female patient. Exposure site was primarily (91.2%) the

patient's own residence. Ingestion of the loperamide-containing product was the most common (99.6%) route of exposure. An acute exposure was most commonly (63.0%) reported. Five (5; 0.4%) intentional exposures to loperamide-containing products only involved two loperamide-containing products and no exposures involved more than two loperamide-containing products (Table 12.2.2.2).

Most (82.0%) 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, 29.1% were treated without being admitted, while 47.4% were admitted, (admitted to non-critical care unit: 12.6%; admitted to critical care unit: 27.5%; admitted to psychiatric care facility: 7.3%; Table 12.2.2.3). The majority (69.7%) of intentional exposures were followed to a known outcome, most of which involved no or an unrelated effect (22.4% of all intentional exposures involving loperamide-containing products only), moderate effect (21.9% of all intentional exposures involving loperamide-containing products only), or minor effect (15.7% of all intentional exposures involving loperamide-containing products only). Nine (9; 0.7%) deaths 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 (18.2%), conduction disturbance (11.5%), and respiratory depression (7.8%; Table 12.2.2.5). Among exposures resulting in at least moderate effect (n=436; moderate effect, major effect, or death), the most common related clinical effects reported were drowsiness/lethargy (38.1%), conduction disturbance (34.4%), and respiratory depression (24.3%; Table 12.2.2.6). Cardiovascular-related clinical effects were reported in 20.5% (n=283/1,378) of exposures. Among intentional exposures to loperamide-containing products only, 54.4% (n=750/1,378) did not receive any therapy. The most common therapies performed to treat clinical effects included fluids, IV (25.2%), other (unspecified; 16.2%), oxygen (13.6%), and naloxone (12.0%; Table 12.2.2.7).

Among intentional exposures to loperamide-containing products only, intentional abuse was reported in 416 exposures (30.2% of intentional exposures) and intentional misuse was reported in 591 exposures (42.9% of intentional exposures; Figure 12.1.1.1; Table 12.2.1.2).

11.2.1.1 Intentional Abuse Exposures to Loperamide-Containing Products Only

Intentional abuse was the reason for exposure in 416 of exposures involving loperamide-containing products only (30.2% of intentional exposures to loperamide-containing products only). The overall sales-adjusted rate of these exposures from 2012 to 2017 was 0.130 exposures per 1 million units sold (CI 0.118, 0.144). This equates to one exposure per every 7.692 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The sales-adjusted rate of reported exposures increased from 0.029 (CI 0.016, 0.047) in 2012 to a peak rate of 0.251 (CI 0.212, 0.296) in 2017 (Table 12.2.3.1).

The median age of patients among intentional abuse exposures involving loperamide-containing products only was 29.0 years, with 94.0% involving adults and children ≥12 years of age. Twenty-nine percent (28.6%) of patients were female and most (89.7%) exposures occurred in the patient's own residence. Ingestion of the loperamide-containing product was the most common (99.3%) route of exposure and most (47.1%) exposures were acute. One (1; 0.2%) exposure involved two loperamide-containing products and no exposures involved more than two loperamide-containing products (Table 12.2.3.2).

The majority (94.7%) of intentional abuse exposures to loperamide-containing products only were recommended to or received HCF care. Among those who received HCF care, 20.8% were treated/evaluated and released without admission, while 62.9% of patients were admitted (admitted to non-critical care unit: 11.7%; admitted to critical care unit: 45.7%; admitted to psychiatric care facility: 5.6%; Table 12.2.3.3). The majority (81.3%) of intentional abuse exposures to loperamide-containing products only were followed to a known outcome, with a remarkable medical outcome reported in 55.3% (moderate effect: 34.1%; major effect: 19.5%; death: 1.7%; Table 12.2.3.4).

Among intentional abuse exposures to loperamide-containing products only, the most common related clinical effects reported were drowsiness/lethargy (27.2%), conduction disturbance (26.0%), and respiratory depression (16.8%; Table 12.2.3.5). Among exposures resulting in at least moderate effect (n=230; moderate effect, major effect, or death), the most common related clinical effects reported were conduction disturbance (45.2%), drowsiness/lethargy (39.1%), respiratory depression (30.0%), and tachycardia (21.3%; Table 12.2.3.6). Cardiovascular-related clinical effects were reported in 38.2% (n=159/416) of exposures. The most common therapies performed to treat clinical effects included fluids, IV (39.2%), other (unspecified; 27.2%), oxygen (26.0%), and naloxone (22.4%; Table 12.2.3.7). Among intentional abuse exposures to loperamide-containing products only, 36.3% (n=151/416) 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 591 of exposures involving loperamide-containing products only (42.9% of intentional exposures to loperamide-containing products only; Figure 12.1.1.1; Table 12.2.1.2). The overall sales-adjusted rate of these exposures from 2012 to 2017 was 0.185 exposures per one million units sold (CI 0.171, 0.201). This equates to one exposure per every 5.405 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The sales-adjusted rate of reported intentional misuse exposures to loperamide-containing products only increased from 0.147 per one million units sold (CI 0.116, 0.184) in 2012 to a peak rate of 0.216 per one million units (CI 0.180, 0.257) in 2017 (Table 12.2.3.1).

The median age of patients among intentional misuse exposures to loperamide-containing products only was 46.0 years, with 89.3% of exposure occurring in adults and children ≥12 years of age. The majority (54.0%) of patients was female and most (93.4%) exposures occurred in the patient's own residence. Most (99.5%) intentional misuse exposures involved ingestion and the majority (62.3%) of exposures were acute. Three (3; 0.5%) exposures involved two loperamide-containing products and no exposures involved more than two loperamide-containing products (Table 12.2.3.2).

Most (66.0%) intentional misuse exposures involving loperamide-containing products only were recommended to receive or received HCF care. Most (40.5%) of these exposures were treated/evaluated and released, with admission to a HCF occurring in 26.4% (admitted to non-critical care unit: 13.3%; admitted to critical care unit: 11.5%; admitted to psychiatric care facility: 1.5%; Table 12.2.3.3). Over half (58.2%) of intentional misuse exposures involving loperamide-containing products only were followed to a known outcome, with exposures most commonly (26.6%) involving no or an unrelated effect. A remarkable medical outcome was reported in

16.1% (moderate effect: 13.4%; major effect: 2.7%; death: 0.0%) of exposures. 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 (9.0%), abdominal pain (6.9%), and nausea (5.2%; Table 12.2.3.5). Among exposures resulting in at least moderate effect (n=95; moderate effect, major effect, or death), the most common related clinical effects reported were drowsiness/lethargy (29.5%), conduction disturbance (26.3%), and confusion (17.9%; Table 12.2.3.6). Cardiovascular-related clinical effects were reported in 9.5% (n=56/591) of exposures. The most common therapies performed to treat clinical effects included fluids, IV (14.9%), other (unspecified; 11.7%), and dilute/irrigate/wash (6.3%; Table 12.2.3.7). Among intentional misuse exposures to loperamide-containing products only, 66.3% (n=392/591) did not have any reported therapies performed.

11.2.2 Unintentional Exposures to Loperamide-Containing Products Only

Among exposures involving loperamide-containing products only, 4,076 (70.3%) involved an unintentional exposure reason (Figure 12.1.1.1). The overall sales-adjusted rate of reported unintentional exposures to loperamide-containing products only from 2012 to 2017 was 1.278 per one million units sold (CI 1.239, 1.318). This equates to one exposure per 0.782 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The sales-adjusted rate of reported exposures decreased from 1.422 per one million units sold (CI 1.322, 1.528) in 2012 to 1.073 per one million units sold (CI 0.991, 1.160) in 2016 followed by an increase to 1.237 per one million units sold (CI 1.148, 1.330) in 2017 (Table 12.2.2.1).

The median age of patients among unintentional exposures to loperamide-containing products only was 2.0 years, with the majority (70.0%) of exposures occurring in children <12 years of age. The slight majority of exposures (52.3%) involved female patients. Nearly all exposures occurred in the patient's own residence (94.8%), involved an oral ingestion (99.2%), and involved an acute exposure (93.5%). Eight (8; 0.2%) unintentional exposures to loperamide-containing products only involved two loperamide-containing products (Table 12.2.2.2).

Most (71.8%) unintentional exposures to loperamide-containing products only were managed outside of a HCF (recommended to or received HCF care – No). Of those that were managed in a HCF, 62.2% were treated/evaluated and released without admission (Table 12.2.2.3). Less than half (48.7%) of exposures were followed to a known outcome, with most of those exposures resulting in no effect or unrelated effect (41.4% of all unintentional exposures to a loperamide-containing product only). Remarkable medical outcomes were reported in 1.2% of unintentional exposures to loperamide-containing products only, with 1.0% 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 (3.2%), abdominal pain (1.4%), and vomiting (1.3%; Table 12.2.2.5). Within exposures involving moderate or greater level of effect (n=47; moderate effect, major effect, or death), drowsiness/lethargy (38.3%), miosis (17.0%), hypotension (14.9%), and bradycardia (14.9%) were the most common clinical effects reported (Table 12.2.2.6). Cardiovascular-related clinical effects were reported in 0.5% (n=22/4,076) of exposures. Among unintentional exposures to loperamide-containing products only, 67.8% (n=2,764/4,076) did not receive any therapy. The most common therapies performed to treat

clinical effects included dilute/irrigate/wash (23.5%), food/snack (8.7%), other (unspecified; 3.1%), and charcoal, single dose (2.6%; Table 12.2.2.7).

11.2.3 Summary of Fatalities Involving Loperamide-Containing Products Only

Ten (10) fatalities involving loperamide-containing products only were reported between 2012 and 2017 (2012: n=2; 2013: n=1; 2014: n=3; 2016: n=1; 2017: n=3). No fatalities were reported in 2015.

Ages ranged from 21 to 41 years and the majority (70.0%; n=7/10) involved male patients. The majority (70.0%; n=7/10) of fatalities involved an intentional abuse exposure, with an eighth exposure (26 year old male) providing evidence of loperamide abuse reported in the case narrative though the fatality was categorized as unknown reason for exposure. The product involved was confirmed to be a single-ingredient loperamide product in nine fatalities, with no history of ingestion in the tenth fatality and no details regarding the products reported. In three fatalities additional substances were observed upon toxicology screening, but no history of ingestion was reported and these substances were not recorded in the fatality.

The exposure was determined to be undoubtedly responsible for the fatality in 50.0% (n=5/10) of fatalities, probably responsible in 33.3% (n=2/10) of fatalities, contributory in 33.3% (n=2/10) of fatalities, and contribution unknown in 10.0% (n=1/10). Because these fatalities involved only the loperamide product, the cause rank for loperamide was one in each of these fatalities. Autopsy findings were available for five fatalities and an autopsy was not performed for five fatalities. Loperamide levels were reported in five fatalities; results ranged from a 0.013 ng/mL to 170 ng/mL (Table 12.2.4.1).

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

Among 4,936 acute exposures to loperamide-containing products only, 3,801 (77.0%) reported quantity information. When quantity was evaluated by exposure reason, the mean quantity was highest among intentional abuse exposures (196.5 mg; SD 218.64 mg), followed by intentional misuse exposures (120.8 mg; SD 1,147.10 mg) and all other intentional exposures (104.8 mg; SD 127.56 mg; Table 12.2.5.1).

A severe cardiovascular-related clinical effect was reported in 45 (0.9%) of acute exposures, of which 31 reported quantity information. Analysis of quantity by report of severe cardiovascular-related clinical effect showed that mean quantity among exposures with a severe cardiovascular-related clinical effect was nearly 9 times that of exposures without a severe cardiovascular-related clinical effect (severe cardiovascular-related clinical effect: 251.0mg (SD 192.79 mg); no severe cardiovascular-related clinical effect: 28.7 mg (SD 333.52 mg)). Median quantity followed a similar pattern (severe cardiovascular-related clinical effect: 200.0 mg (IQR 128.0 mg, 300.0 mg); no severe cardiovascular-related clinical effect: 4.0 mg (IQR 2.0 mg, 12.0 mg)).

11.3 Exposures to a Loperamide-Containing Product Plus Another Substance

Exposures to a loperamide-containing product plus another substance occurred in 25.8% of exposures to loperamide-containing products (Figure 12.1.1.1). The overall sales-adjusted rate of reported exposures to a loperamide-containing product plus another substance from 2012 to 2017 was 0.633 exposures per one million units sold (CI 0.606, 0.661). This equates to one exposure per every 1.580 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The sales-adjusted rate of reported exposures increased from 0.547 (CI 0.485, 0.614) in 2012 to a peak rate of 0.715 (CI 0.648, 0.787) in 2017 (Table 12.2.1.1).

The median age of patients among exposures to loperamide-containing product plus another substance was 24.0 years, with more than half (72.0%) of exposures occurring in adults and children ≥12 years of age. The majority (55.3%) of patients was female. Exposure characteristics showed that most (91.5%) exposures to a loperamide-containing product plus another substance occurred in the patient's own residence. Route of exposure was primarily (98.8%) via ingestion and most (76.4%) exposures involved an acute exposure. Exposures most commonly (41.6%) involved two products/substances (one loperamide-containing product plus one other substance). Three products/substances (one loperamide-containing product plus two other substances) were reported in 22.2% of exposures and four or more products/substances (one loperamide-containing product plus three or more other products/substances) were reported in 36.2% (Table 12.2.1.2). Five thousand six hundred and forty-six other substances were reported in exposures to loperamide-containing products plus another substance. The other substances most commonly reported were ibuprofen (4.7%; n=265/5,646), benzodiazepines (4.5%; n=255/5,646), and other antihistamines alone (excluding cough and cold preparations; 4.1%; n=230/5,646). Opioid or opioid-containing products were reported in 11.0% (n=222/2,019) of exposures.

The reason for exposure was intentional in 54.1% of exposures to loperamide-containing products plus another substance and unintentional in 38.6% of exposures (Figure 12.1.1.1; Table 12.2.1.2).

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

Among exposures to loperamide-containing products plus another substance, 1,092 (54.1%) involved an intentional reason for exposure. The overall sales-adjusted rate of reported intentional exposures to a loperamide-containing product plus another substance from 2012 to 2017 was 0.342 per one million units sold (CI 0.322, 0.363). This equates to one exposure per 2.924 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The sales-adjusted rate of reported intentional exposures to a loperamide-containing product plus another substance increased from 0.247 per 1 million units sold (CI 0.206, 0.293) in 2012 to a peak rate of 0.431 per 1 million units sold (CI 0.380, 0.488) in 2017 (Table 12.2.6.1).

The median age of patients among intentional exposures to loperamide-containing products plus another substance was 28.0 years, with 97.3% of exposures involving adults and children ≥12 years of age. The majority (56.4%) of patients was female. Exposure site was primarily (91.5%) the patient's own residence. Ingestion of a loperamide-containing product plus another substance was the most common (98.8%) route of exposure. The majority (69.5%) of exposures

involved an acute exposure. Exposures most commonly (41.8%) involved four or more total products/substances (one loperamide-containing product plus three or more other substances; Table 12.2.6.2). The other substances most commonly reported included benzodiazepines (5.6%; n=186/3,353), ethanol beverage (5.0%; n=166/3,353), ibuprofen (4.2%; n=142/3,353), and other antihistamines alone (excluding cough and cold preparations; 4.1%; n=138/3,353). Opioid or opioid-containing products were reported in 14.6% (n=159/1,092) of intentional exposures to loperamide-containing products plus another substance.

Most (97.3%) intentional exposures to a loperamide-containing product plus another substance were recommended to or received HCF care. Of those that received care in a HCF, 20.6% were treated without being admitted (treated/evaluated and released), while 71.0% were admitted (admitted to non-critical care unit: 16.9%: admitted to critical care unit: 37.5%; admitted to psychiatric care facility: 16.6%; Table 12.2.6.3). The majority (89.1%) of exposures were followed to a known outcome. The most common (33.9%) medical outcome was moderate effect, with a remarkable medical outcome reported in 47.6% (moderate effect: 33.9%; major effect: 12.8%; death: 0.9%). Ten (10; 0.9%) deaths 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 (38.2%), tachycardia (22.7%), and vomiting (12.5%; Table 12.2.6.5). Among exposures resulting in at least moderate effect (n=520; moderate effect, major effect or death), the most common related clinical effects reported were drowsiness/lethargy (55.8%), tachycardia (35.4%), conduction disturbance (24.4%), and hypotension (20.6%; Table 12.2.6.6). A cardiovascular-related clinical effect was reported in 40.8% (n=445/1,092) of exposures. The most common therapies performed to treat clinical effects included fluids, IV (47.0%), oxygen (19.0%), and other (unspecified; 17.6%; Table 12.2.6.7). Among intentional exposures to a loperamide-containing product plus another product, 32.3% (n=353/1,092) did not have any reported therapies performed.

Among intentional exposures to a loperamide-containing product plus another substance, intentional abuse was reported in 155 exposures (14.2% of intentional exposures) and intentional misuse was reported in 107 (9.8% of intentional exposures; Figure 12.1.1.1; Table 12.2.1.2).

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

Intentional abuse was the reason for exposure in 155 of exposures to a loperamide-containing products plus another substance (14.2% of intentional exposures to loperamide-containing products plus another substance). The overall sales-adjusted rate of these exposures from 2012 to 2017 was 0.049 exposures per one million units sold (CI 0.041, 0.057). This equates to one exposure per every 20.408 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The sales-adjusted rate of reported intentional abuse exposures to a loperamide-containing product plus another substance increased from 0.019 per one million units sold (CI 0.009, 0.035) in 2012 to a peak sales-adjusted rate of 0.085 per one million units sold (CI 0.063, 0.112) in 2016, followed by a decrease to 0.077 per one million units sold (CI 0.056, 0.103) in 2017 (Table 12.2.7.1).

The median age of patients among intentional abuse exposures involving a loperamide-containing product plus another substance was 28.0 years, with most (99.4%) exposures involving adults and children ≥12 years of age. Thirty-four (21.9%) patients were female. Most

exposures (87.7%) occurred in the patient's own residence. Ingestion of a loperamide-containing product plus another substance was the most common (95.5%) route of exposure and the majority (58.1%) were acute exposures. Most (62.6%) exposures involved exposure to two total products/substances (a loperamide-containing product plus one other substance; Table 12.2.7.2). Two hundred and eighty-two other substances were reported in intentional abuse exposures to loperamide-containing products plus another substance. The most common other substances reported included benzodiazepines (11.0%; n=31/282), ethanol beverage (7.8%; n=22/282), gabapentin (5.3%; n=15/282), and dextromethorphan preparations (5.0%; n=14/282). Opioid or opioid-containing products were reported in 22.6% (n=35/155) of intentional abuse exposures to a loperamide-containing product plus another substance.

Almost all (98.1%) intentional abuse exposures involving a loperamide-containing product plus another substance were recommended to or received HCF care. Among those who received HCF care, 24.3% were treated/evaluated and released without admission. A total of 66.4% of patients were admitted (admitted to non-critical care unit: 16.4%; admitted to critical care unit: 45.4%; admitted to psychiatric care facility: 4.6%; Table 12.2.7.3). Most (89.7%) exposures were followed to a known outcome, with exposures resulting in a remarkable medical outcome reported in 70.3% (moderate effect: 45.8%; major effect: 22.6%; death: 1.9%). Three (3; 1.9%) deaths were reported (Table 12.2.7.4).

Among intentional abuse exposures to a loperamide-containing product plus another substance, the most common related clinical effects reported were drowsiness/lethargy (42.6%), tachycardia (32.9%), conduction disturbance (23.9%), and respiratory depression (22.6%; Table 12.2.7.5). Among exposures resulting in at least moderate effect (n=109; moderate effect, major effect, or death), the most common related clinical effects reported were drowsiness/lethargy (51.4%), tachycardia (40.4%), conduction disturbance (33.9%), and respiratory depression (31.2%; Table 12.2.7.6). Cardiovascular-related clinical effects were reported in 54.8% (n=85/155) of exposures. The most common therapies performed to treat clinical effects included fluids, IV (50.3%), naloxone (31.6%), oxygen (30.3%), and other (unspecified; 26.5%; Table 12.2.7.7). Among intentional abuse exposures to a loperamide-containing product plus another substance, 25.8% (n=40/155) 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 107 of exposures to a loperamide-containing product plus another substance (9.8% of intentional exposures to a loperamide-containing product plus another substance). The overall sales-adjusted rate of these exposures from 2012 to 2017 was 0.034 exposures per one million units sold (CI 0.028, 0.041). This equates to one exposure per every 2.941 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The sales-adjusted rate of reported intentional misuse exposures to a loperamide-containing product plus another substance decreased from 0.031 per one million units sold (CI 0.017, 0.050) to a low of 0.018 per one million units sold (CI 0.008, 0.034) in 2013, followed by an increase to 0.044 per one million units sold (CI 0.029, 0.065) in 2017 (Table 12.2.7.1).

The median age of patients among intentional misuse exposures involving a loperamide-containing product plus another substance was 36.0 years, with 91.6% of exposures occurring in adults and children ≥12 years of age. Forty-six (46; 43.0%) exposures involved a female patient and most (93.5%) exposures occurred in the patient's own residence. Ingestion of a loperamide-containing product plus another substance was the most common (99.1%) route of

exposure and most (67.3%) exposures were acute exposures. The majority (64.5%) of exposures involved two total substances (a loperamide-containing product plus one other substance; Table 12.2.7.2). Cardiovascular-related clinical effects were reported in 31 (29.0%) exposures. One hundred and seventy-two (172) other substances were reported in intentional misuse exposures to loperamide-containing products plus another substance. The most common other substances reported included salicylate-containing antacids (7.0%; n=12/172) and laxatives (5.8%; n=10/172). Opioid or opioid-containing products were reported in 12.1% (n=13/107) of exposures.

The majority (81.3%) of intentional misuse exposures involving a loperamide-containing product plus another substance were recommended to receive or received HCF care. Among those who received HCF care, 28.7% were treated/evaluated and released without admission. A total of 51.7% of patients were admitted (admitted to non-critical care unit: 18.4%; admitted to critical care unit: 26.4%; admitted to psychiatric care facility: 6.9%; Table 12.2.7.3). The majority (71.0%) of exposures were followed to a known outcome, with exposures resulting in a remarkable medical outcome reported in 32.7% (moderate effect: 23.4%; major effect: 9.3%; death: 0.0%). No deaths were reported (Table 12.2.7.4)

Among intentional misuse exposures to a loperamide-containing product plus another substance, the most common related clinical effects reported were drowsiness/lethargy (20.6%), tachycardia (19.6%), and hypertension (11.2%; Table 12.2.7.5). Among exposures resulting in at least moderate effect (n=35; moderate effect, major effect, or death), the most common related clinical effects reported were tachycardia (48.6%), drowsiness/lethargy (45.7%), and conduction disturbance (31.4%; Table 12.2.7.6). Among intentional misuse exposures to a loperamide-containing product plus another substance, 45.8% (n=49/107) did not receive any therapy. The most common therapies performed to treat clinical effects included fluids, IV (28.0%), other (unspecified; 16.8%), oxygen (12.1%), and benzodiazepines (12.1%; Table 12.2.7.7).

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

Among exposures to a loperamide-containing product plus another product, 38.6% involved an unintentional exposure reason (Figure 12.1.1.1). The overall sales-adjusted rate of reported unintentional exposures to a loperamide-containing product plus another substance from 2012 to 2017 was 0.244 per one million units sold (CI 0.227, 0.262). This equates to one exposure per 4.098 million units (i.e., tablets, gelcaps, liquid equivalents) sold. The sales-adjusted rate of reported exposures increased from 0.250 per one million units sold (CI 0.209, 0.297) in 2012 to 0.315 per one million units sold (CI 0.267, 0.370), followed by a decrease through 2016 (0.204 per one million units sold (CI 0.169, 0.244) and an increase in 2017 (0.238 per one million units sold (CI 0.200, 0.281); Table 12.2.6.1).

The median age of patients among unintentional exposures to a loperamide-containing product plus another substance was 3.0 years, with the majority (62.0%) of exposures occurring in children <12 years of age. The slight majority (52.9%) of exposures involved female patients. Nearly all exposures occurred in the patient's own residence (92.0%), involved an oral ingestion (99.6%), and involved an acute exposure (88.7%). Most commonly (48.1%), exposures involved two total products (a loperamide-containing product plus another substance; Table 12.2.6.2. One thousand nine hundred and forty-four (1,944) other substances were reported in unintentional exposures to loperamide-containing products plus another substance. The most

common other substances reported were ibuprofen (5.81%; n=113/1,944) and acetaminophen (4.12%; n=80/1,944). Opioid-containing products were reported in 5.8% (n=45/779) of exposures.

Approximately half (49.3%) of unintentional exposures to a loperamide-containing product plus another substance were recommended to receive or received HCF care. Most (63.8%) of the exposures managed in a HCF were treated/evaluated and released, with admission to a HCF occurring in 23.4% (admitted to non-critical care unit: 12.1%; admitted to critical care unit: 9.6%; admitted to psychiatric care facility: 1.8%; Table 12.2.6.3). The majority (64.1%) of exposures were followed to a known outcome, most of which involved no or an unrelated effect (47.6% of all unintentional exposures involving a loperamide-containing product plus another substance). Remarkable medical outcomes were reported in 6.5% of exposures (moderate effect: 5.5%; major effect: 1.0%; death: 0.0%). No deaths were reported (Table 12.2.6.4).

Among all unintentional exposures to a loperamide-containing product plus another substance, the most common clinical effects reported were drowsiness/lethargy (8.1%), vomiting (3.2%), and nausea (2.7%; Table 12.2.6.5). Within exposures involving moderate or greater level of effect (n=51; moderate effect, major effect, or death), drowsiness/lethargy (47.1%), bradycardia (27.5%), and hypotension (21.6%), were the most common clinical effects reported (Table 12.2.6.6). Cardiovascular-related clinical effects were reported in 4.0% (n=31/779) of exposures. The most common therapies performed to treat clinical effects were dilute/irrigate/wash (17.6%), food/snack (9.5%), and fluids, IV (6.5%; Table 12.2.6.7). Among unintentional exposures to a loperamide-containing product plus another substance, 62.8% (n=489/779) did not have any reported therapies performed.

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

Sixteen (16) fatalities involving a loperamide-containing product plus another substance were reported between 2012 and 2017 (2013: n=1; 2014: n=1; 2015: n=4; 2016: n=2; 2017: n=8); no fatalities involving a loperamide-containing product plus another substance were reported in 2012. Ages ranged from 23 to 82 years of age and the majority (62.5%; n=10/16) were female. The reason for exposure was unknown in most (37.5%; n=6/16) fatalities, with the remaining fatalities involving intentional suspected suicide (31.3%; n=5/16), intentional abuse (18.8%; n=3/16), and intentional unknown (12.5%; n=2/16). Single-ingredient loperamide products were confirmed in 15 (93.8%; n=15/16) fatalities. The remaining fatalities involved an unknown loperamide-containing product as no history of ingestion was reported. A range of other substances were reported among these fatalities including benzodiazepines in five fatalities (31.3%; n=5/16) and opioids in four (4; 25.0%; n=4/16) fatalities (Table 12.2.8.1).

The exposure was determined to be probably responsible for the fatality in five fatalities and undoubtedly responsible in three fatalities. Among the remaining fatalities, the exposure was determined to be probably not responsible for the fatality in three fatalities and the relatedness was unknown in another five. Among the fatalities 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 fatalities. Autopsy findings were available for six fatalities, unavailable for six fatalities, and an autopsy was not performed for four fatalities. Loperamide levels were reported in two fatalities; results ranged from a 18 ng/mL to 77 ng/mL (Table 12.2.8.1).

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 1,542 acute exposures to a loperamide-containing product plus another substance, 844 (54.7%) reported quantity information. When quantity was evaluated by exposure reason, the mean quantity was highest among intentional abuse exposures (213.7 mg; SD 291.13 mg), followed by other or unknown (105.4 mg; SD 169.47 mg), all other intentional (65.6 mg; SD 125.28 mg), and intentional misuse (32.4 mg; SD 62.80 mg). Median quantity by exposure reason followed a similar pattern (Table 12.2.9.1).

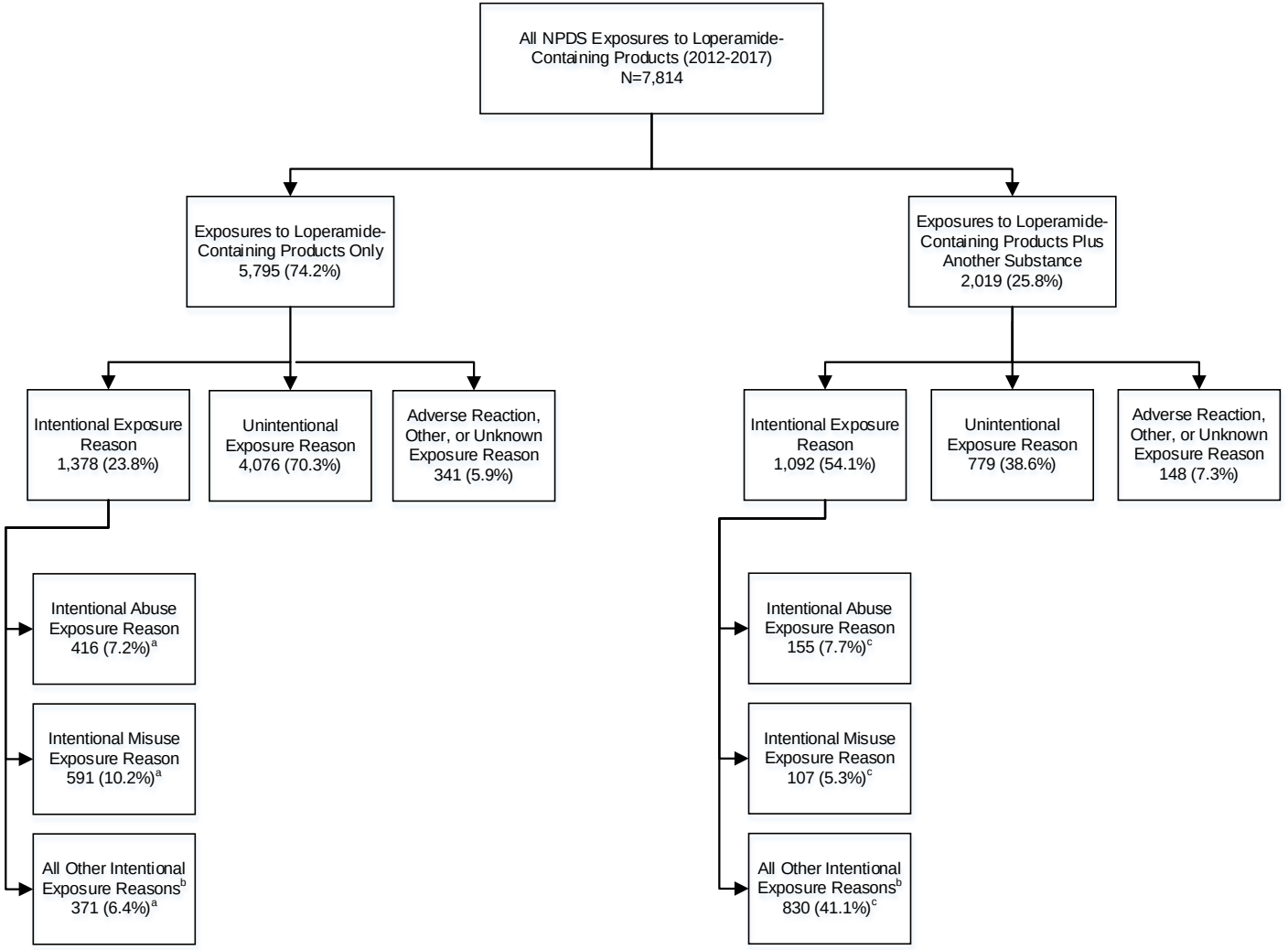
A severe cardiovascular-related clinical effect was reported in 72 (4.7%) of acute exposures, of which 25 reported quantity information. Analysis of quantity by report of severe cardiovascular-related clinical effect showed that mean quantity among exposures with a severe cardiovascular-related clinical effect was nearly 7 times that of exposures without a severe cardiovascular-related clinical effect (severe cardiovascular-related clinical effect 239.8 mg (SD 311.49 mg); no severe cardiovascular-related clinical effect 34.2 mg (SD 100.67 mg)). Median quantity among exposures with severe cardiovascular-related clinical effect was nearly 24 times that of exposures without a severe cardiovascular-related effect (severe cardiovascular-related clinical effect 96.0 mg (IQR 30.0 mg, 400.0 mg); no severe cardiovascular-related clinical effect 4.0 mg (IQR 2.0 mg, 20.0 mg); Table 12.2.9.2).

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 2017



[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: Annual Sales-Adjusted Rates of Exposures to All Loperamide-Containing Products by Number of Substances

Year	Rates of Exposures to Loperamide-Containing Products Only per 1 Million Units Sold (95% CI)	Rates of Exposures to Loperamide-Containing Products Plus Another Substance per 1 Million Units Sold (95% CI)	Rates of All Exposures to Loperamide-Containing Products per 1 Million Units Sold (95% CI)
2012	1.761 (1.649, 1.878)	0.547 (0.485, 0.614)	2.307 (2.179, 2.441)
2013	1.795 (1.679, 1.917)	0.600 (0.534, 0.672)	2.395 (2.261, 2.535)
2014	1.859 (1.739, 1.986)	0.710 (0.637, 0.790)	2.570 (2.428, 2.717)
2015	1.768 (1.656, 1.887)	0.604 (0.539, 0.674)	2.372 (2.241, 2.508)
2016	1.727 (1.622, 1.837)	0.620 (0.558, 0.687)	2.347 (2.225, 2.474)
2017	1.988 (1.875, 2.105)	0.715 (0.648, 0.787)	2.703 (2.571, 2.839)
Total	**1.818 (1.771, 1.865)**	**0.633 (0.606, 0.661)**	**2.451 (2.397, 2.506)**

Table 12.2.1.2: Demographics and Exposure Characteristics of All Loperamide-Containing Product Exposures by Number of Substances

Characteristics	Exposures to Loperamide-Containing Products Only (N=5,795)	Exposures to a Loperamide-Containing Product Plus Another Substance (N=2,019)	All Exposures to Loperamide-Containing Products (N=7,814)
Age			
Median, years	6.0	24.0	16.0
Mean (SD), years	23.2 (26.88)	28.7 (23.48)	24.7 (26.14)
Age (categorical)			
Pediatric (<12 years)	2,901 (50.1%)	505 (25.0%)	3,406 (43.6%)
Adults and Children (≥12 years)	2,596 (44.8%)	1,453 (72.0%)	4,049 (51.8%)
Unknown Child (≤19 years)	2 (<0.1%)	0 (0.0%)	2 (<0.1%)
Unknown Adult (>19 years)	259 (4.5%)	53 (2.6%)	312 (4.0%)
Unknown Age	37 (0.6%)	8 (0.4%)	45 (0.6%)
Female	2,976 (51.4%)	1,117 (55.3%)	4,093 (52.4%)
Exposure Site			
Own Residence	5,448 (94.0%)	1,848 (91.5%)	7,296 (93.4%)
Other Residence	168 (2.9%)	54 (2.7%)	222 (2.8%)
Workplace	13 (0.2%)	8 (0.4%)	21 (0.3%)
Health Care Facility	15 (0.3%)	10 (0.5%)	25 (0.3%)
School	9 (0.2%)	8 (0.4%)	17 (0.2%)
Other	98 (1.7%)	52 (2.6%)	150 (1.9%)
Unknown	44 (0.8%)	39 (1.9%)	83 (1.1%)
Route of Exposure[a]			
Ingestions	5,756 (99.3%)	1,994 (98.8%)	7,750 (99.2%)
Aspiration (with ingestion)	9 (0.2%)	4 (0.2%)	13 (0.2%)
Inhalation/nasal	15 (0.3%)	21 (1.0%)	36 (0.5%)
Ocular	16 (0.3%)	2 (0.1%)	18 (0.2%)
Dermal	9 (0.2%)	6 (0.3%)	15 (0.2%)
Parenteral	5 (0.1%)	23 (1.1%)	28 (0.4%)
Other	2 (0.0%)	1 (0.0%)	3 (0.0%)

Characteristics	Exposures to Loperamide-Containing Products Only (N=5,795)	Exposures to a Loperamide-Containing Product Plus Another Substance (N=2,019)	All Exposures to Loperamide-Containing Products (N=7,814)
Unknown	8 (0.1%)	22 (1.1%)	30 (0.4%)
Chronicity			
Acute	4,936 (85.2%)	1,542 (76.4%)	6,478 (82.9%)
Acute-on-Chronic	363 (6.3%)	308 (15.3%)	671 (8.6%)
Chronic	423 (7.3%)	63 (3.1%)	486 (6.2%)
Unknown	73 (1.3%)	106 (5.3%)	179 (2.3%)
Number of Substances			
Mean (SD)	1.0 (0.05)	3.8 (2.78)	1.7 (1.87)
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	5,781 (99.8%)	0 (0.0%)	5,781 (74.0%)
2 Products/Substances	14 (0.2%)	840 (41.6%)	854 (10.9%)
3 Products/Substances	0 (0.0%)	449 (22.2%)	449 (5.7%)
4+ Products/Substances	0 (0.0%)	730 (36.2%)	730 (9.3%)
Reason for Exposure			
Unintentional – Therapeutic error	1,030 (17.8%)	194 (9.6%)	1,224 (15.7%)
Unintentional – General	2,899 (50.0%)	554 (27.4%)	3,453 (44.2%)
Unintentional – Misuse	138 (2.4%)	21 (1.0%)	159 (2.0%)
Unintentional – Other	9 (0.2%)	10 (0.5%)	19 (0.2%)
Intentional – Misuse	591 (10.2%)	107 (5.3%)	698 (8.9%)
Intentional – Abuse	416 (7.2%)	155 (7.7%)	571 (7.3%)
Intentional – Suspected suicide	282 (4.9%)	777 (38.5%)	1,059 (13.6%)
Intentional – Unknown	89 (1.5%)	53 (2.6%)	142 (1.8%)
Adverse reaction – Drug	262 (4.5%)	101 (5.0%)	363 (4.6%)
Adverse reaction – Other	6 (0.1%)	2 (0.1%)	8 (0.1%)
Other	23 (0.4%)	8 (0.4%)	31 (0.4%)

Characteristics	Exposures to Loperamide-Containing Products Only (N=5,795)	Exposures to a Loperamide-Containing Product Plus Another Substance (N=2,019)	All Exposures to Loperamide-Containing Products (N=7,814)
Unknown reason	50 (0.9%)	37 (1.8%)	87 (1.1%)

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

12.2.2 Exposures to Loperamide-Containing Products Only

Table 12.2.2.1: Annual Sales-Adjusted Rate of Exposures to Loperamide-Containing Products Only by Intentional or Unintentional Reason for Exposure

Year	Rate of Intentional Exposures per 1 Million Units Sold (95% CI)	Rate of Unintentional Exposures per 1 Million Units Sold (95% CI)
2012	0.247 (0.206, 0.293)	1.422 (1.322, 1.528)
2013	0.292 (0.246, 0.344)	1.396 (1.294, 1.504)
2014	0.401 (0.346, 0.462)	1.322 (1.221, 1.430)
2015	0.397 (0.345, 0.455)	1.259 (1.165, 1.360)
2016	0.564 (0.505, 0.628)	1.073 (0.991, 1.160)
2017	0.642 (0.578, 0.710)	1.237 (1.148, 1.330)
Total	**0.432 (0.410, 0.456)**	**1.278 (1.239, 1.318)**

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=1,378)	Unintentional Exposure Reason (N=4,076)
Age		
Median, years	32.0	2.0
Mean (SD), years	38.4 (18.84)	16.6 (26.22)
Age (categorical)		
Pediatric (<12 years)	17 (1.2%)	2,853 (70.0%)
Adults and Children (≥12 years)	1,265 (91.8%)	1,077 (26.4%)
Unknown Child (≤19 years)	0 (0.0%)	2 (<0.1%)
Unknown Adult (>19 years)	83 (6.0%)	125 (3.1%)
Unknown Age	13 (0.9%)	19 (0.5%)
Female	648 (47.0%)	2,131 (52.3%)
Exposure Site		
Own Residence	1,257 (91.2%)	3,866 (94.8%)
Other Residence	32 (2.3%)	133 (3.3%)
Workplace	5 (0.4%)	6 (0.1%)
Health Care Facility	8 (0.6%)	7 (0.2%)
School	1 (0.1%)	7 (0.2%)
Other	46 (3.3%)	46 (1.1%)
Unknown	29 (2.1%)	11 (0.3%)
Route of Exposure[a]		
Ingestions	1,372 (99.6%)	4,044 (99.2%)
Aspiration (with ingestion)	4 (0.3%)	4 (0.1%)
Inhalation/nasal	3 (0.2%)	12 (0.3%)
Ocular	0 (0.0%)	16 (0.4%)
Dermal	0 (0.0%)	8 (0.2%)
Parenteral	2 (0.1%)	3 (0.1%)
Other	0 (0.0%)	1 (0.0%)
Unknown	4 (0.3%)	4 (0.1%)
Chronicity		
Acute	868 (63.0%)	3,812 (93.5%)
Acute-on-Chronic	185 (13.4%)	146 (3.6%)
Chronic	277 (20.1%)	108 (2.6%)
Unknown	48 (3.5%)	10 (0.2%)
Number of Substances		
Mean (SD)	1.0 (0.06)	1.0 (0.04)
Median	1.0	1.0
Range	(1.0, 2.0)	(1.0, 2.0)
Number of Substances (Categories)		
1 Product/Substance	1,373 (99.6%)	4,068 (99.8%)
2 Products/Substances	5 (0.4%)	8 (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=1,378)	Unintentional Exposure Reason (N=4,076)
Recommended to or Received Healthcare Facility (HCF) Care		
Yes	1,130 (82.0%)	1,092 (26.8%)
No	211 (15.3%)	2,928 (71.8%)
Unknown	37 (2.7%)	56 (1.4%)
Level of Care[a]		
Treated/evaluated and released	329 (29.1%)	679 (62.2%)
Admitted to non-critical care unit	142 (12.6%)	79 (7.2%)
Admitted to critical care unit	311 (27.5%)	37 (3.4%)
Admitted to psychiatric care facility	83 (7.3%)	5 (0.5%)
Patient refused referral/did not arrive at HCF	76 (6.7%)	109 (10.0%)
Patient lost to follow-up/left AMA	189 (16.7%)	183 (16.8%)

[a]*Denominator is the number of exposures that were recommended to or received HCF 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=1,378)	Unintentional Exposure Reason (N=4,076)
Followed to a Known Outcome	961 (69.7%)	1,987 (48.7%)
Death	9 (0.7%)	0 (0.0%)
Major Effect	125 (9.1%)	5 (0.1%)
Moderate Effect	302 (21.9%)	42 (1.0%)
Minor Effect	216 (15.7%)	253 (6.2%)
No Effect or Unrelated Effect	309 (22.4%)	1,687 (41.4%)
Not Followed to Known Outcome	417 (30.3%)	2,089 (51.3%)
Unable to follow, potentially toxic	210 (15.2%)	209 (5.1%)
Not followed, non-toxic	16 (1.2%)	328 (8.0%)
Not followed, minimal clinical effects expected	191 (13.9%)	1,552 (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=1,378)	Unintentional Exposure Reason (N=4,076)
Drowsiness/lethargy	251 (18.2%)	129 (3.2%)
Abdominal Pain	78 (5.7%)	57 (1.4%)
Nausea	89 (6.5%)	41 (1.0%)
Vomiting	74 (5.4%)	52 (1.3%)
Other	35 (2.5%)	17 (0.4%)
Respiratory depression	107 (7.8%)	4 (0.1%)
Dizziness/vertigo	43 (3.1%)	21 (0.5%)
Miosis	57 (4.1%)	13 (0.3%)
Tachycardia	102 (7.4%)	3 (0.1%)
Constipation	29 (2.1%)	17 (0.4%)
Hypotension	50 (3.6%)	7 (0.2%)
Coma	73 (5.3%)	1 (<0.1%)
Agitated/irritable	19 (1.4%)	1 (<0.1%)
Confusion	55 (4.0%)	5 (0.1%)
Bradycardia	58 (4.2%)	9 (0.2%)
Conduction disturbance	159 (11.5%)	6 (0.1%)
Syncope	37 (2.7%)	1 (<0.1%)
Diarrhea	15 (1.1%)	12 (0.3%)
Dysrhythmia (v tach/v fib)	10 (0.7%)	0 (0.0%)
Electrolyte abnormality	50 (3.6%)	1 (<0.1%)
Cough/choke	2 (0.1%)	12 (0.3%)
ECG change (other)	9 (0.7%)	0 (0.0%)
Headache	12 (0.9%)	4 (0.1%)
Ataxia	11 (0.8%)	3 (0.1%)
Tremor	18 (1.3%)	1 (<0.1%)
Diaphoresis	28 (2.0%)	1 (<0.1%)
Acidosis	29 (2.1%)	0 (0.0%)
Blurred vision	6 (0.4%)	2 (<0.1%)
CPK elevated	20 (1.5%)	0 (0.0%)
Chest pain (including noncardiac)	12 (0.9%)	1 (<0.1%)
Dysrhythmia (other)	6 (0.4%)	0 (0.0%)
Hypertension	33 (2.4%)	2 (<0.1%)
Slurred speech	15 (1.1%)	4 (0.1%)

Clinical Effect	Intentional Exposure Reason (N=1,378)	Unintentional Exposure Reason (N=4,076)
Throat irritation	0 (0.0%)	8 (0.2%)
X-ray findings(+)	24 (1.7%)	1 (<0.1%)
Fever/hyperthermia	15 (1.1%)	3 (0.1%)
Mydriasis	8 (0.6%)	2 (<0.1%)
Respiratory arrest	14 (1.0%)	0 (0.0%)
Urinary retention	8 (0.6%)	2 (<0.1%)
ADR to treatment	3 (0.2%)	2 (<0.1%)
Dyspnea	15 (1.1%)	0 (0.0%)
Dystonia	3 (0.2%)	1 (<0.1%)
Ileus/no bowel sounds	5 (0.4%)	1 (<0.1%)
Rhabdomyolysis	9 (0.7%)	0 (0.0%)
Seizure (single)	13 (0.9%)	2 (<0.1%)
Cardiac arrest	24 (1.7%)	1 (<0.1%)
Edema	1 (0.1%)	2 (<0.1%)
Muscle weakness	4 (0.3%)	1 (<0.1%)
Ocular - Irritation/pain	1 (0.1%)	10 (0.2%)
Pneumonitis	15 (1.1%)	0 (0.0%)
AST, ALT>100≤1,000	14 (1.0%)	0 (0.0%)
Anion gap increased	13 (0.9%)	0 (0.0%)
Asystole	9 (0.7%)	0 (0.0%)
Creatinine increased	17 (1.2%)	1 (<0.1%)
Cyanosis	8 (0.6%)	0 (0.0%)
Dehydration	2 (0.1%)	1 (<0.1%)
Hallucinations/delusions	6 (0.4%)	0 (0.0%)
Hyperglycemia	8 (0.6%)	0 (0.0%)
Hyperventilation/tachypnea	14 (1.0%)	0 (0.0%)
Hypothermia	8 (0.6%)	0 (0.0%)
Oral irritation	0 (0.0%)	3 (0.1%)
Pain (not dermal, GI, ocular)	3 (0.2%)	0 (0.0%)
Pallor	3 (0.2%)	0 (0.0%)
Pupil(s) nonreactive	6 (0.4%)	0 (0.0%)
Red eye/conjunctivitis	1 (0.1%)	6 (0.1%)
Renal failure	5 (0.4%)	0 (0.0%)
Anorexia	2 (0.1%)	1 (<0.1%)
Bullae	1 (0.1%)	0 (0.0%)

Clinical Effect	Intentional Exposure Reason (N=1,378)	Unintentional Exposure Reason (N=4,076)
Erythema/flushed	1 (0.1%)	1 (<0.1%)
Fecal incontinence	2 (0.1%)	0 (0.0%)
Hives/welts	0 (0.0%)	1 (<0.1%)
Oliguria/anuria	4 (0.3%)	0 (0.0%)
Pruritus	0 (0.0%)	2 (<0.1%)
Seizures (multi/discrete)	5 (0.4%)	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=436)	Unintentional Exposure Reason (N=47)
Drowsiness/lethargy	166 (38.1%)	18 (38.3%)
Respiratory depression	106 (24.3%)	4 (8.5%)
Hypotension	47 (10.8%)	7 (14.9%)
Tachycardia	86 (19.7%)	2 (4.3%)
Miosis	45 (10.3%)	8 (17.0%)
Coma	72 (16.5%)	1 (2.1%)
Conduction disturbance	150 (34.4%)	6 (12.8%)
Vomiting	45 (10.3%)	5 (10.6%)
Bradycardia	52 (11.9%)	7 (14.9%)
Nausea	42 (9.6%)	6 (12.8%)
Agitated/irritable	16 (3.7%)	0 (0.0%)
Confusion	47 (10.8%)	3 (6.4%)
Other	12 (2.8%)	2 (4.3%)
Syncope	36 (8.3%)	1 (2.1%)
Dizziness/vertigo	24 (5.5%)	2 (4.3%)
Dysrhythmia (v tach/v fib)	10 (2.3%)	0 (0.0%)
Electrolyte abnormality	49 (11.2%)	1 (2.1%)
Abdominal Pain	20 (4.6%)	5 (10.6%)
ECG change (other)	9 (2.1%)	0 (0.0%)
Tremor	18 (4.1%)	0 (0.0%)
Acidosis	29 (6.7%)	0 (0.0%)
CPK elevated	20 (4.6%)	0 (0.0%)
Diaphoresis	24 (5.5%)	1 (2.1%)
Dysrhythmia (other)	6 (1.4%)	0 (0.0%)
Hypertension	31 (7.1%)	2 (4.3%)
X-ray findings(+)	24 (5.5%)	1 (2.1%)
Ataxia	6 (1.4%)	1 (2.1%)
Constipation	14 (3.2%)	0 (0.0%)
Fever/hyperthermia	14 (3.2%)	1 (2.1%)
Respiratory arrest	14 (3.2%)	0 (0.0%)
Blurred vision	4 (0.9%)	1 (2.1%)
Chest pain (including noncardiac)	8 (1.8%)	0 (0.0%)

Clinical Effect	Intentional Exposure Reason (N=436)	Unintentional Exposure Reason (N=47)
Dyspnea	13 (3.0%)	0 (0.0%)
Headache	7 (1.6%)	1 (2.1%)
Rhabdomyolysis	8 (1.8%)	0 (0.0%)
Seizure (single)	12 (2.8%)	2 (4.3%)
Slurred speech	10 (2.3%)	1 (2.1%)
Urinary retention	7 (1.6%)	2 (4.3%)
Cardiac arrest	23 (5.3%)	1 (2.1%)
Diarrhea	9 (2.1%)	1 (2.1%)
Dystonia	2 (0.5%)	1 (2.1%)
Pneumonitis	15 (3.4%)	0 (0.0%)
ADR to treatment	2 (0.5%)	1 (2.1%)
AST, ALT>100≤1,000	13 (3.0%)	0 (0.0%)
Anion gap increased	11 (2.5%)	0 (0.0%)
Asystole	8 (1.8%)	0 (0.0%)
Cough/choke	2 (0.5%)	0 (0.0%)
Creatinine increased	15 (3.4%)	1 (2.1%)
Cyanosis	8 (1.8%)	0 (0.0%)
Dehydration	2 (0.5%)	1 (2.1%)
Edema	1 (0.2%)	1 (2.1%)
Hallucinations/delusions	5 (1.1%)	0 (0.0%)
Hyperglycemia	8 (1.8%)	0 (0.0%)
Hyperventilation/tachypnea	14 (3.2%)	0 (0.0%)
Hypothermia	7 (1.6%)	0 (0.0%)
Ileus/no bowel sounds	4 (0.9%)	0 (0.0%)
Pallor	3 (0.7%)	0 (0.0%)
Pupil(s) nonreactive	6 (1.4%)	0 (0.0%)
Renal failure	5 (1.1%)	0 (0.0%)
Bullae	1 (0.2%)	0 (0.0%)
Fecal incontinence	2 (0.5%)	0 (0.0%)
Hives/welts	0 (0.0%)	1 (2.1%)
Muscle weakness	3 (0.7%)	0 (0.0%)
Mydriasis	5 (1.1%)	1 (2.1%)
Oliguria/anuria	4 (0.9%)	0 (0.0%)
Pain (not dermal, GI, ocular)	2 (0.5%)	0 (0.0%)
Seizures (multi/discrete)	5 (1.1%)	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=1,378)	Unintentional Exposure Reason (N=4,076)
Dilute/irrigate/wash	50 (3.6%)	957 (23.5%)
Food/snack	23 (1.7%)	355 (8.7%)
Fluids, IV	347 (25.2%)	55 (1.3%)
Other	223 (16.2%)	126 (3.1%)
Charcoal, single dose	35 (2.5%)	106 (2.6%)
Oxygen	188 (13.6%)	10 (0.2%)
Naloxone	165 (12.0%)	8 (0.2%)
Benzodiazepines	94 (6.8%)	8 (0.2%)
Intubation	80 (5.8%)	5 (0.1%)
Vasopressors	56 (4.1%)	2 (<0.1%)
Ventilator	74 (5.4%)	6 (0.1%)
Antiemetics	38 (2.8%)	11 (0.3%)
Alkalinization	96 (7.0%)	6 (0.1%)
Antibiotics	49 (3.6%)	7 (0.2%)
Sedation (other)	58 (4.2%)	3 (0.1%)
Antiarrhythmic	77 (5.6%)	0 (0.0%)
Other emetic	2 (0.1%)	25 (0.6%)
CPR	38 (2.8%)	2 (<0.1%)
Cathartic	10 (0.7%)	7 (0.2%)
Cardioversion	31 (2.2%)	0 (0.0%)
Antihistamines	14 (1.0%)	2 (<0.1%)
Pacemaker	19 (1.4%)	0 (0.0%)
Antihypertensives	20 (1.5%)	1 (<0.1%)
Atropine	9 (0.7%)	0 (0.0%)
Calcium	21 (1.5%)	0 (0.0%)
Hemodialysis	4 (0.3%)	4 (0.1%)
Insulin	10 (0.7%)	0 (0.0%)
Steroids	4 (0.3%)	1 (<0.1%)
Bronchodilators	5 (0.4%)	0 (0.0%)
Glucose, > 5%	7 (0.5%)	1 (<0.1%)
Flumazenil	2 (0.1%)	0 (0.0%)
NAC, IV	7 (0.5%)	1 (<0.1%)
Anticonvulsants	5 (0.4%)	1 (<0.1%)

Therapy	Intentional Exposure Reason (N=1,378)	Unintentional Exposure Reason (N=4,076)
ECMO	2 (0.1%)	0 (0.0%)
Fresh air	0 (0.0%)	2 (<0.1%)
Lavage	1 (0.1%)	0 (0.0%)
NAC, PO	2 (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: Annual Sales-Adjusted Rate of Exposures to Loperamide-Containing Products Only by Intentional Abuse or Intentional Misuse Reason for Exposure

Year	Rate of Intentional Abuse Exposures per 1 Million Units Sold (95% CI)	Rate of Intentional Misuse Exposures per 1 Million Units Sold (95% CI)
2012	0.029 (0.016, 0.047)	0.147 (0.116, 0.184)
2013	0.040 (0.025, 0.062)	0.159 (0.126, 0.198)
2014	0.090 (0.065, 0.121)	0.198 (0.161, 0.243)
2015	0.091 (0.067, 0.121)	0.197 (0.160, 0.239)
2016	0.245 (0.207, 0.289)	0.191 (0.157, 0.230)
2017	0.251 (0.212, 0.296)	0.216 (0.180, 0.257)
Total	**0.130 (0.118, 0.144)**	**0.185 (0.171, 0.201)**

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=416)	Intentional Misuse Exposure (N=591)
Age, years		
Median	29.0	46.0
Mean (SD)	30.2 (9.72)	47.0 (20.29)
Age (categorical)		
Pediatric (<12 years)	0 (0.0%)	11 (1.9%)
Adults and Children (≥12 years)	391 (94.0%)	528 (89.3%)
Unknown Child (≤19 years)	0 (0.0%)	0 (0.0%)
Unknown Adult (>19 years)	19 (4.6%)	49 (8.3%)
Unknown Age	6 (1.4%)	3 (0.5%)
Female	119 (28.6%)	319 (54.0%)
Exposure Site		
Own Residence	373 (89.7%)	552 (93.4%)
Other Residence	6 (1.4%)	15 (2.5%)
Workplace	0 (0.0%)	4 (0.7%)
Health Care Facility	3 (0.7%)	2 (0.3%)
School	0 (0.0%)	0 (0.0%)
Other	15 (3.6%)	13 (2.2%)
Unknown	19 (4.6%)	5 (0.8%)
Route of Exposure[a]		
Ingestions	413 (99.3%)	588 (99.5%)
Aspiration (with ingestion)	2 (0.5%)	0 (0.0%)
Inhalation/nasal	1 (0.2%)	2 (0.3%)
Ocular	0 (0.0%)	0 (0.0%)
Dermal	0 (0.0%)	0 (0.0%)
Parenteral	1 (0.2%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)
Unknown	1 (0.2%)	2 (0.3%)
Chronicity		
Acute	196 (47.1%)	368 (62.3%)
Acute-on-Chronic	70 (16.8%)	85 (14.4%)
Chronic	127 (30.5%)	131 (22.2%)
Unknown	23 (5.5%)	7 (1.2%)

Characteristics	Intentional Abuse Exposure (N=416)	Intentional Misuse Exposure (N=591)
Number of Substances		
Mean (SD)	1.0 (0.05)	1.0 (0.07)
Median	1.0	1.0
Range	(1.0, 2.0)	(1.0, 2.0)
Number of Substances (Categorical)		
1 Product/Substance	415 (99.8%)	588 (99.5%)
2 Products/Substances	1 (0.2%)	3 (0.5%)
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=416)	Intentional Misuse Exposure (N=591)
Recommended to or Received Healthcare Facility (HCF) Care		
Yes	394 (94.7%)	390 (66.0%)
No	14 (3.4%)	179 (30.3%)
Unknown	8 (1.9%)	22 (3.7%)
Level of HCF Care[a]		
Treated/evaluated and released	82 (20.8%)	158 (40.5%)
Admitted to non-critical care unit	46 (11.7%)	52 (13.3%)
Admitted to critical care unit	180 (45.7%)	45 (11.5%)
Admitted to psychiatric care facility	22 (5.6%)	6 (1.5%)
Patient refused referral/did not arrive at HCF	18 (4.6%)	32 (8.2%)
Patient lost to follow-up/left AMA	46 (11.7%)	97 (24.9%)

[a]*Denominator is the number that were recommended to or received HCF 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=416)	Intentional Misuse Exposure (N=591)
Followed to a Known Outcome	338 (81.3%)	344 (58.2%)
Death	7 (1.7%)	0 (0.0%)
Major Effect	81 (19.5%)	16 (2.7%)
Moderate Effect	142 (34.1%)	79 (13.4%)
Minor Effect	60 (14.4%)	92 (15.6%)
No Effect or Unrelated Effect	48 (11.5%)	157 (26.6%)
Not Followed to Known Outcome	78 (18.8%)	247 (41.8%)
Unable to follow, potentially toxic	57 (13.7%)	87 (14.7%)
Not followed, non-toxic	0 (0.0%)	12 (2.0%)
Not followed, minimal clinical effects expected	21 (5.0%)	148 (25.0%)

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=416)	Intentional Misuse Exposure (N=591)
Drowsiness/lethargy	113 (27.2%)	53 (9.0%)
Abdominal Pain	23 (5.5%)	41 (6.9%)
Other	11 (2.6%)	19 (3.2%)
Nausea	35 (8.4%)	31 (5.2%)
Vomiting	33 (7.9%)	22 (3.7%)
Dizziness/vertigo	12 (2.9%)	24 (4.1%)
Respiratory depression	70 (16.8%)	8 (1.4%)
Agitated/irritable	13 (3.1%)	5 (0.8%)
Confusion	18 (4.3%)	22 (3.7%)
Conduction disturbance	108 (26.0%)	29 (4.9%)
Tachycardia	54 (13.0%)	14 (2.4%)
Bradycardia	34 (8.2%)	15 (2.5%)
Miosis	28 (6.7%)	15 (2.5%)
Coma	41 (9.9%)	5 (0.8%)
Hypotension	27 (6.5%)	10 (1.7%)
Constipation	13 (3.1%)	13 (2.2%)
Syncope	27 (6.5%)	7 (1.2%)
Dysrhythmia (v tach/v fib)	7 (1.7%)	1 (0.2%)
Tremor	10 (2.4%)	5 (0.8%)
Ataxia	4 (1.0%)	6 (1.0%)
Diaphoresis	21 (5.0%)	3 (0.5%)
Dysrhythmia (other)	5 (1.2%)	1 (0.2%)
ECG change (other)	3 (0.7%)	3 (0.5%)
Electrolyte abnormality	33 (7.9%)	6 (1.0%)
CPK elevated	13 (3.1%)	2 (0.3%)
Diarrhea	9 (2.2%)	4 (0.7%)
Acidosis	16 (3.8%)	5 (0.8%)
Blurred vision	1 (0.2%)	4 (0.7%)
Chest pain (including noncardiac)	6 (1.4%)	4 (0.7%)
Headache	4 (1.0%)	4 (0.7%)
Mydriasis	6 (1.4%)	1 (0.2%)
Seizure (single)	9 (2.2%)	3 (0.5%)
Urinary retention	4 (1.0%)	4 (0.7%)

Clinical Effect	Intentional Abuse Exposure (N=416)	Intentional Misuse Exposure (N=591)
Fever/hyperthermia	13 (3.1%)	0 (0.0%)
Hypertension	21 (5.0%)	4 (0.7%)
Respiratory arrest	12 (2.9%)	0 (0.0%)
Rhabdomyolysis	5 (1.2%)	1 (0.2%)
ADR to treatment	2 (0.5%)	0 (0.0%)
Anion gap increased	5 (1.2%)	4 (0.7%)
Cardiac arrest	18 (4.3%)	4 (0.7%)
Cough/choke	2 (0.5%)	0 (0.0%)
Dyspnea	7 (1.7%)	3 (0.5%)
Hallucinations/delusions	1 (0.2%)	1 (0.2%)
Hyperglycemia	8 (1.9%)	0 (0.0%)
Hypothermia	7 (1.7%)	1 (0.2%)
Pain (not dermal, GI, ocular)	1 (0.2%)	2 (0.3%)
Pallor	2 (0.5%)	1 (0.2%)
Slurred speech	6 (1.4%)	3 (0.5%)
X-ray findings(+)	15 (3.6%)	1 (0.2%)
AST, ALT>100≤1,000	7 (1.7%)	2 (0.3%)
Asystole	7 (1.7%)	0 (0.0%)
Creatinine increased	7 (1.7%)	5 (0.8%)
Cyanosis	5 (1.2%)	0 (0.0%)
Dehydration	2 (0.5%)	0 (0.0%)
Dystonia	0 (0.0%)	1 (0.2%)
Edema	0 (0.0%)	1 (0.2%)
Erythema/flushed	1 (0.2%)	0 (0.0%)
Fecal incontinence	1 (0.2%)	1 (0.2%)
Ileus/no bowel sounds	0 (0.0%)	2 (0.3%)
Muscle weakness	2 (0.5%)	1 (0.2%)
Oliguria/anuria	1 (0.2%)	2 (0.3%)
Pneumonitis	9 (2.2%)	1 (0.2%)
Pupil(s) nonreactive	3 (0.7%)	2 (0.3%)
Renal failure	2 (0.5%)	2 (0.3%)
Seizures (multi/discrete)	3 (0.7%)	2 (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=230)	Intentional Misuse Exposure (N=95)
Drowsiness/lethargy	90 (39.1%)	28 (29.5%)
Respiratory depression	69 (30.0%)	8 (8.4%)
Agitated/irritable	10 (4.3%)	5 (5.3%)
Conduction disturbance	104 (45.2%)	25 (26.3%)
Vomiting	27 (11.7%)	9 (9.5%)
Confusion	17 (7.4%)	17 (17.9%)
Bradycardia	31 (13.5%)	12 (12.6%)
Coma	41 (17.8%)	5 (5.3%)
Hypotension	25 (10.9%)	9 (9.5%)
Miosis	22 (9.6%)	10 (10.5%)
Tachycardia	49 (21.3%)	7 (7.4%)
Nausea	24 (10.4%)	11 (11.6%)
Syncope	26 (11.3%)	7 (7.4%)
Dizziness/vertigo	10 (4.3%)	11 (11.6%)
Other	6 (2.6%)	3 (3.2%)
Dysrhythmia (v tach/v fib)	7 (3.0%)	1 (1.1%)
Abdominal Pain	7 (3.0%)	11 (11.6%)
Tremor	10 (4.3%)	5 (5.3%)
Dysrhythmia (other)	5 (2.2%)	1 (1.1%)
ECG change (other)	3 (1.3%)	3 (3.2%)
Electrolyte abnormality	33 (14.3%)	6 (6.3%)
CPK elevated	13 (5.7%)	2 (2.1%)
Diaphoresis	17 (7.4%)	3 (3.2%)
Acidosis	16 (7.0%)	5 (5.3%)
Ataxia	3 (1.3%)	3 (3.2%)
Seizure (single)	8 (3.5%)	3 (3.2%)
Chest pain (including noncardiac)	5 (2.2%)	2 (2.1%)
Constipation	8 (3.5%)	4 (4.2%)
Fever/hyperthermia	12 (5.2%)	0 (0.0%)
Hypertension	20 (8.7%)	4 (4.2%)
Respiratory arrest	12 (5.2%)	0 (0.0%)
Rhabdomyolysis	5 (2.2%)	1 (1.1%)

Clinical Effect	Intentional Abuse Exposure (N=230)	Intentional Misuse Exposure (N=95)
Urinary retention	4 (1.7%)	3 (3.2%)
ADR to treatment	2 (0.9%)	0 (0.0%)
Anion gap increased	5 (2.2%)	3 (3.2%)
Blurred vision	1 (0.4%)	2 (2.1%)
Cardiac arrest	18 (7.8%)	3 (3.2%)
Cough/choke	2 (0.9%)	0 (0.0%)
Dyspnea	5 (2.2%)	3 (3.2%)
Hallucinations/delusions	1 (0.4%)	1 (1.1%)
Headache	3 (1.3%)	2 (2.1%)
Hyperglycemia	8 (3.5%)	0 (0.0%)
Hypothermia	7 (3.0%)	0 (0.0%)
Pallor	2 (0.9%)	1 (1.1%)
Slurred speech	4 (1.7%)	2 (2.1%)
X-ray findings(+)	15 (6.5%)	1 (1.1%)
AST, ALT>100≤1,000	6 (2.6%)	2 (2.1%)
Asystole	6 (2.6%)	0 (0.0%)
Creatinine increased	7 (3.0%)	4 (4.2%)
Cyanosis	5 (2.2%)	0 (0.0%)
Dehydration	2 (0.9%)	0 (0.0%)
Diarrhea	6 (2.6%)	1 (1.1%)
Dystonia	0 (0.0%)	1 (1.1%)
Edema	0 (0.0%)	1 (1.1%)
Fecal incontinence	1 (0.4%)	1 (1.1%)
Muscle weakness	2 (0.9%)	1 (1.1%)
Mydriasis	3 (1.3%)	1 (1.1%)
Oliguria/anuria	1 (0.4%)	2 (2.1%)
Pain (not dermal, GI, ocular)	1 (0.4%)	1 (1.1%)
Pneumonitis	9 (3.9%)	1 (1.1%)
Pupil(s) nonreactive	3 (1.3%)	2 (2.1%)
Renal failure	2 (0.9%)	2 (2.1%)
Seizures (multi/discrete)	3 (1.3%)	2 (2.1%)

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=416)	Intentional Misuse Exposure (N=591)
Fluids, IV	163 (39.2%)	88 (14.9%)
Other	113 (27.2%)	69 (11.7%)
Oxygen	108 (26.0%)	31 (5.2%)
Naloxone	93 (22.4%)	23 (3.9%)
Benzodiazepines	59 (14.2%)	22 (3.7%)
Dilute/irrigate/wash	5 (1.2%)	37 (6.3%)
Intubation	50 (12.0%)	9 (1.5%)
Antiarrhythmic	59 (14.2%)	13 (2.2%)
Ventilator	49 (11.8%)	8 (1.4%)
Vasopressors	34 (8.2%)	8 (1.4%)
Alkalinization	59 (14.2%)	18 (3.0%)
Sedation (other)	38 (9.1%)	8 (1.4%)
Antibiotics	29 (7.0%)	4 (0.7%)
Antiemetics	18 (4.3%)	11 (1.9%)
Food/snack	3 (0.7%)	17 (2.9%)
CPR	29 (7.0%)	5 (0.8%)
Cardioversion	25 (6.0%)	3 (0.5%)
Calcium	16 (3.8%)	3 (0.5%)
Pacemaker	15 (3.6%)	3 (0.5%)
Antihistamines	8 (1.9%)	3 (0.5%)
Atropine	7 (1.7%)	1 (0.2%)
Charcoal, single dose	4 (1.0%)	4 (0.7%)
Insulin	7 (1.7%)	1 (0.2%)
Antihypertensives	13 (3.1%)	4 (0.7%)
Bronchodilators	2 (0.5%)	2 (0.3%)
Cathartic	1 (0.2%)	3 (0.5%)
Flumazenil	2 (0.5%)	0 (0.0%)
Glucose, > 5%	5 (1.2%)	0 (0.0%)
Steroids	2 (0.5%)	1 (0.2%)
Anticonvulsants	5 (1.2%)	0 (0.0%)
ECMO	2 (0.5%)	0 (0.0%)
Hemodialysis	1 (0.2%)	2 (0.3%)
Lavage	1 (0.2%)	0 (0.0%)

Therapy	Intentional Abuse Exposure (N=416)	Intentional Misuse Exposure (N=591)
NAC, IV	4 (1.0%)	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

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, 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

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
2016	34 Years, Male	Intentional Abuse	Unknown	Loperamide-Containing Product: Single-ingredient loperamide (1)	Undoubtedly responsible	*Autopsy not performed* **Loperamide Levels:** Not reported	• History of opioid, marijuana, tobacco, and ethanol abuse • Stopped using opioids and began using 200 mg of loperamide per day for the last 2 years • Stopped using loperamide 5 days prior after suffering a syncopal episode at work

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
2017	21 Years, Male	Intentional Abuse	Acute	**Loperamide-Containing Product:** Single-ingredient loperamide (1)	Unknown	*Autopsy not performed* **Cause of Death:** Complications of chronic drug abuse **Manner of Death:** Natural **Loperamide Levels:** Not reported	• Past history of drug abuse • Had been discussing loperamide with friends on phone; mother claimed patient had been looking on the internet for instructions on using OTC medication
2017	30 Years, Female	Intentional Abuse	Acute	**Loperamide-Containing Product:** Single-ingredient loperamide (1) **Other Products/ Substances**: Amphetamine[a,b] Benzodiazepines[a,b] Cannabinoids[a,b]	Undoubtedly responsible	*Autopsy not performed* **Loperamide Levels:** Antemortem - 54 ng/mL (blood)	• History of polysubstance abuse including loperamide misuse • Patient was admitted in August 2016 for altered mental status following loperamide misuse

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
2017	41 Years, Female	Intentional Abuse	Acute	**Loperamide-Containing Product:** Single-ingredient loperamide (1)	Undoubtedly responsible	**Cause of Death:** Anoxic Encephalopathy as a consequence of loperamide intoxication **Manner of death:** Not reported **Loperamide Levels:** Antemortem - 170 ng/mL (blood)	• History of norco and cocaine abuse • Patient's brother reported recent laxative abuse to get high • Mother reportedly found several empty loperamide boxes at home

[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 (mg) 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)	196.5 (218.64)	120.8 (1,147.10)	104.8 (127.56)	7.2 (25.58)	4.6 (3.86)	78.2 (112.45)
Median	144.0	24.0	50.0	3.0	4.0	34.0
Range	(6.0, 1600)	(0.2, 20000)	(2.0, 800.0)	(0.0, 1200)	(0.3, 24.0)	(0.7, 400.0)
IQR	(70.0, 250.0)	(15.9, 51.0)	(20.0, 140.0)	(2.0, 8.0)	(2.0, 5.0)	(4.0, 96.0)
N	154	304	242	2,911	168	22

Table 12.2.5.2: Reported Quantity (mg) by Severe Cardiovascular-Related Clinical Effect for Exposures to Loperamide-Containing Products Only

Statistic	Severe Cardiovascular-Related Clinical Effect	No Severe Cardiovascular-Related Clinical Effect
Mean (SD)	251.0 (192.79)	28.7 (333.52)
Median	200.0	4.0
Range	(10.0, 800.0)	(0.0, 20000)
IQR	(128.0, 300.0)	(2.0, 12.0)
N	31	3,770

12.2.6 Exposures to a Loperamide-Containing Product Plus Another Substances

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

Year	Rate of Intentional Exposures per 1 Million Units Sold (95% CI)	Rate of Unintentional Exposures per 1 Million Units Sold (95% CI)
2012	0.247 (0.206, 0.293)	0.250 (0.209, 0.297)
2013	0.298 (0.252, 0.350)	0.254 (0.211, 0.302)
2014	0.357 (0.306, 0.415)	0.315 (0.267, 0.370)
2015	0.334 (0.286, 0.387)	0.216 (0.178, 0.260)
2016	0.373 (0.325, 0.426)	0.204 (0.169, 0.244)
2017	0.431 (0.380, 0.488)	0.238 (0.200, 0.281)
Total	**0.342 (0.322, 0.363)**	**0.244 (0.227, 0.262)**

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=1,092)	Unintentional Exposure Reason (N=779)
Age, years		
Median	28.0	3.0
Mean (SD)	32.1 (16.97)	21.6 (29.18)
Age (categorical)		
Pediatric (<12 years)	13 (1.2%)	483 (62.0%)
Adults and Children (≥12 years)	1,062 (97.3%)	271 (34.8%)
Unknown Child (≤19 years)	0 (0.0%)	0 (0.0%)
Unknown Adult (>19 years)	14 (1.3%)	24 (3.1%)
Unknown Age	3 (0.3%)	1 (0.1%)
Female	616 (56.4%)	412 (52.9%)
Exposure Site		
Own Residence	999 (91.5%)	717 (92.0%)
Other Residence	14 (1.3%)	37 (4.7%)
Workplace	4 (0.4%)	3 (0.4%)
Health Care Facility	4 (0.4%)	5 (0.6%)
School	7 (0.6%)	1 (0.1%)
Other	32 (2.9%)	15 (1.9%)
Unknown	32 (2.9%)	1 (0.1%)
Route of Exposure[a]		
Ingestions	1,079 (98.8%)	776 (99.6%)
Inhalation/nasal	13 (1.2%)	5 (0.6%)
Ocular	0 (0.0%)	2 (0.3%)
Dermal	5 (0.5%)	1 (0.1%)
Parenteral	17 (1.6%)	2 (0.3%)
Other	0 (0.0%)	0 (0.0%)
Unknown	11 (1.0%)	3 (0.4%)
Chronicity		
Acute	759 (69.5%)	691 (88.7%)
Acute-on-Chronic	217 (19.9%)	70 (9.0%)
Chronic	40 (3.7%)	10 (1.3%)
Unknown	76 (7.0%)	8 (1.0%)
Number of Substances		
Mean (SD)	4.1 (2.99)	3.5 (2.45)
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	380 (34.8%)	375 (48.1%)
3 Products/Substances	256 (23.4%)	166 (21.3%)
4+ Products/Substances	456 (41.8%)	238 (30.6%)

[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=1,092)	Unintentional Exposure Reason (N=779)
Recommended to or Received Healthcare Facility (HCF) Care		
Yes	1,063 (97.3%)	384 (49.3%)
No	22 (2.0%)	383 (49.2%)
Unknown	7 (0.6%)	12 (1.5%)
Level of Care[a]		
Treated/evaluated and released	219 (20.6%)	245 (63.8%)
Admitted to non-critical care unit	180 (16.9%)	46 (12.0%)
Admitted to critical care unit	399 (37.5%)	37 (9.6%)
Admitted to psychiatric care facility	176 (16.6%)	7 (1.8%)
Patient refused referral/did not arrive at HCF	20 (1.9%)	18 (4.7%)
Patient lost to follow-up/left AMA	69 (6.5%)	31 (8.1%)

[a]*Denominator is the number that were recommended to or received HCF 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=1,092)	Unintentional Exposure Reason (N=779)
Followed to a Known Outcome	973 (89.1%)	499 (64.1%)
Death	10 (0.9%)	0 (0.0%)
Major Effect	140 (12.8%)	8 (1.0%)
Moderate Effect	370 (33.9%)	43 (5.5%)
Minor Effect	269 (24.6%)	77 (9.9%)
No Effect or Unrelated Effect	184 (16.8%)	371 (47.6%)
Not Followed to Known Outcome	119 (10.9%)	280 (35.9%)
Unable to follow, potentially toxic	76 (7.0%)	33 (4.2%)
Not followed, non-toxic	0 (0.0%)	34 (4.4%)
Not followed, minimal clinical effects expected	43 (3.9%)	213 (27.3%)

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=1,092)	Unintentional Exposure Reason (N=779)
Drowsiness/lethargy	417 (38.2%)	63 (8.1%)
Tachycardia	248 (22.7%)	7 (0.9%)
Vomiting	137 (12.5%)	25 (3.2%)
Nausea	92 (8.4%)	21 (2.7%)
Agitated/irritable	58 (5.3%)	5 (0.6%)
Confusion	94 (8.6%)	9 (1.2%)
Other	52 (4.8%)	4 (0.5%)
Hypotension	112 (10.3%)	12 (1.5%)
Coma	97 (8.9%)	2 (0.3%)
Conduction disturbance	130 (11.9%)	5 (0.6%)
Hypertension	78 (7.1%)	1 (0.1%)
Respiratory depression	112 (10.3%)	4 (0.5%)
Abdominal Pain	46 (4.2%)	16 (2.1%)
Bradycardia	61 (5.6%)	14 (1.8%)
Dizziness/vertigo	35 (3.2%)	12 (1.5%)
Electrolyte abnormality	64 (5.9%)	2 (0.3%)
Mydriasis	43 (3.9%)	6 (0.8%)
Acidosis	52 (4.8%)	2 (0.3%)
Slurred speech	42 (3.8%)	1 (0.1%)
Miosis	37 (3.4%)	6 (0.8%)
CPK elevated	36 (3.3%)	0 (0.0%)
Ataxia	17 (1.6%)	6 (0.8%)
Hallucinations/delusions	23 (2.1%)	2 (0.3%)
Diarrhea	14 (1.3%)	16 (2.1%)
Fever/hyperthermia	26 (2.4%)	0 (0.0%)
ECG change (other)	13 (1.2%)	1 (0.1%)
Tremor	22 (2.0%)	3 (0.4%)
Diaphoresis	23 (2.1%)	1 (0.1%)
Hyperventilation/tachypnea	20 (1.8%)	2 (0.3%)
Creatinine increased	25 (2.3%)	0 (0.0%)
Hypoglycemia	11 (1.0%)	1 (0.1%)
X-ray findings(+)	24 (2.2%)	0 (0.0%)

Clinical Effect	Intentional Exposure Reason (N=1,092)	Unintentional Exposure Reason (N=779)
ADR to treatment	15 (1.4%)	0 (0.0%)
Dysrhythmia (v tach/v fib)	8 (0.7%)	0 (0.0%)
Headache	10 (0.9%)	2 (0.3%)
Seizure (single)	11 (1.0%)	3 (0.4%)
AST, ALT>100≤1,000	15 (1.4%)	0 (0.0%)
Pneumonitis	9 (0.8%)	0 (0.0%)
Urinary retention	11 (1.0%)	0 (0.0%)
Cardiac arrest	16 (1.5%)	0 (0.0%)
Rhabdomyolysis	12 (1.1%)	0 (0.0%)
Anion gap increased	17 (1.6%)	1 (0.1%)
Blurred vision	7 (0.6%)	1 (0.1%)
Dyspnea	9 (0.8%)	2 (0.3%)
Erythema/flushed	6 (0.5%)	2 (0.3%)
Numbness	4 (0.4%)	1 (0.1%)
Nystagmus	7 (0.6%)	3 (0.4%)
Pallor	7 (0.6%)	2 (0.3%)
Respiratory arrest	13 (1.2%)	1 (0.1%)
Syncope	7 (0.6%)	0 (0.0%)
Tinnitus	8 (0.7%)	0 (0.0%)
Constipation	8 (0.7%)	1 (0.1%)
Dysrhythmia (other)	4 (0.4%)	0 (0.0%)
Hypothermia	6 (0.5%)	2 (0.3%)
Cough/choke	2 (0.2%)	1 (0.1%)
Muscle rigidity	3 (0.3%)	1 (0.1%)
Muscle weakness	3 (0.3%)	1 (0.1%)
Pupil(s) nonreactive	5 (0.5%)	0 (0.0%)
Seizures (multi/discrete)	4 (0.4%)	0 (0.0%)
Urinary incontinence	4 (0.4%)	0 (0.0%)
Alkalosis	3 (0.3%)	0 (0.0%)
Chest pain (including noncardiac)	6 (0.5%)	0 (0.0%)
Cyanosis	3 (0.3%)	0 (0.0%)
Dermal - Irritation/pain	2 (0.2%)	0 (0.0%)
Dystonia	2 (0.2%)	0 (0.0%)
Edema	2 (0.2%)	0 (0.0%)
Excess secretions	2 (0.2%)	1 (0.1%)

Clinical Effect	Intentional Exposure Reason (N=1,092)	Unintentional Exposure Reason (N=779)
Hyperglycemia	6 (0.5%)	0 (0.0%)
Ileus/no bowel sounds	4 (0.4%)	0 (0.0%)
Oliguria/anuria	7 (0.6%)	0 (0.0%)
PT prolonged	2 (0.2%)	0 (0.0%)
Polyuria	1 (0.1%)	1 (0.1%)
Pruritus	2 (0.2%)	0 (0.0%)
Urine color change	2 (0.2%)	0 (0.0%)
AST, ALT>1,000	8 (0.7%)	0 (0.0%)
Asystole	5 (0.5%)	0 (0.0%)
Bleeding (other)	2 (0.2%)	0 (0.0%)
Bronchospasm	1 (0.1%)	0 (0.0%)
CVA	1 (0.1%)	0 (0.0%)
Dehydration	1 (0.1%)	0 (0.0%)
Hemo/myoglobinuria	1 (0.1%)	0 (0.0%)
Multiple Chemical Sensitivities	1 (0.1%)	0 (0.0%)
Ocular - Irritation/pain	0 (0.0%)	1 (0.1%)
Other LFT abnormality	1 (0.1%)	0 (0.0%)
Other coagulopathy	1 (0.1%)	0 (0.0%)
Pain (not dermal, GI, ocular)	2 (0.2%)	0 (0.0%)
Red eye/conjunctivitis	1 (0.1%)	1 (0.1%)
Renal failure	2 (0.2%)	0 (0.0%)
Throat irritation	1 (0.1%)	1 (0.1%)
Visual defect	1 (0.1%)	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=520)	Unintentional Exposure Reason (N=51)
Drowsiness/lethargy	290 (55.8%)	24 (47.1%)
Tachycardia	184 (35.4%)	5 (9.8%)
Coma	94 (18.1%)	2 (3.9%)
Conduction disturbance	127 (24.4%)	5 (9.8%)
Hypotension	107 (20.6%)	11 (21.6%)
Confusion	79 (15.2%)	6 (11.8%)
Vomiting	86 (16.5%)	5 (9.8%)
Hypertension	73 (14.0%)	1 (2.0%)
Respiratory depression	111 (21.3%)	4 (7.8%)
Agitated/irritable	34 (6.5%)	2 (3.9%)
Other	35 (6.7%)	1 (2.0%)
Bradycardia	59 (11.3%)	14 (27.5%)
Electrolyte abnormality	63 (12.1%)	2 (3.9%)
Nausea	49 (9.4%)	4 (7.8%)
Acidosis	52 (10.0%)	2 (3.9%)
CPK elevated	35 (6.7%)	0 (0.0%)
Hallucinations/delusions	23 (4.4%)	2 (3.9%)
Mydriasis	32 (6.2%)	4 (7.8%)
Miosis	33 (6.3%)	3 (5.9%)
ECG change (other)	13 (2.5%)	1 (2.0%)
Fever/hyperthermia	24 (4.6%)	0 (0.0%)
Slurred speech	31 (6.0%)	0 (0.0%)
Tremor	21 (4.0%)	2 (3.9%)
Ataxia	13 (2.5%)	4 (7.8%)
Creatinine increased	25 (4.8%)	0 (0.0%)
Diaphoresis	21 (4.0%)	0 (0.0%)
Dizziness/vertigo	14 (2.7%)	3 (5.9%)
Hyperventilation/tachypnea	18 (3.5%)	2 (3.9%)
Abdominal Pain	13 (2.5%)	2 (3.9%)
Hypoglycemia	11 (2.1%)	1 (2.0%)
X-ray findings(+)	24 (4.6%)	0 (0.0%)
Dysrhythmia (v tach/v fib)	8 (1.5%)	0 (0.0%)

Clinical Effect	Intentional Exposure Reason (N=520)	Unintentional Exposure Reason (N=51)
Seizure (single)	10 (1.9%)	3 (5.9%)
AST, ALT>100≤1,000	14 (2.7%)	0 (0.0%)
Pneumonitis	9 (1.7%)	0 (0.0%)
ADR to treatment	13 (2.5%)	0 (0.0%)
Cardiac arrest	16 (3.1%)	0 (0.0%)
Rhabdomyolysis	12 (2.3%)	0 (0.0%)
Anion gap increased	17 (3.3%)	1 (2.0%)
Respiratory arrest	13 (2.5%)	1 (2.0%)
Syncope	7 (1.3%)	0 (0.0%)
Urinary retention	9 (1.7%)	0 (0.0%)
Dysrhythmia (other)	4 (0.8%)	0 (0.0%)
Nystagmus	6 (1.2%)	2 (3.9%)
Tinnitus	6 (1.2%)	0 (0.0%)
Blurred vision	4 (0.8%)	1 (2.0%)
Dyspnea	6 (1.2%)	1 (2.0%)
Headache	5 (1.0%)	0 (0.0%)
Hypothermia	6 (1.2%)	1 (2.0%)
Muscle rigidity	3 (0.6%)	1 (2.0%)
Muscle weakness	3 (0.6%)	1 (2.0%)
Numbness	2 (0.4%)	1 (2.0%)
Pallor	6 (1.2%)	1 (2.0%)
Pupil(s) nonreactive	5 (1.0%)	0 (0.0%)
Seizures (multi/discrete)	4 (0.8%)	0 (0.0%)
Urinary incontinence	4 (0.8%)	0 (0.0%)
Alkalosis	3 (0.6%)	0 (0.0%)
Chest pain (including noncardiac)	6 (1.2%)	0 (0.0%)
Constipation	5 (1.0%)	0 (0.0%)
Cough/choke	1 (0.2%)	1 (2.0%)
Cyanosis	3 (0.6%)	0 (0.0%)
Dystonia	2 (0.4%)	0 (0.0%)
Hyperglycemia	6 (1.2%)	0 (0.0%)
Ileus/no bowel sounds	4 (0.8%)	0 (0.0%)
Oliguria/anuria	7 (1.3%)	0 (0.0%)
PT prolonged	2 (0.4%)	0 (0.0%)
Urine color change	2 (0.4%)	0 (0.0%)

Clinical Effect	Intentional Exposure Reason (N=520)	Unintentional Exposure Reason (N=51)
AST, ALT>1,000	8 (1.5%)	0 (0.0%)
Asystole	5 (1.0%)	0 (0.0%)
Bleeding (other)	2 (0.4%)	0 (0.0%)
Bronchospasm	1 (0.2%)	0 (0.0%)
CVA	1 (0.2%)	0 (0.0%)
Dehydration	1 (0.2%)	0 (0.0%)
Diarrhea	4 (0.8%)	3 (5.9%)
Edema	1 (0.2%)	0 (0.0%)
Erythema/flushed	3 (0.6%)	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 (2.0%)
Other LFT abnormality	1 (0.2%)	0 (0.0%)
Other coagulopathy	1 (0.2%)	0 (0.0%)
Pain (not dermal, GI, ocular)	2 (0.4%)	0 (0.0%)
Polyuria	1 (0.2%)	0 (0.0%)
Renal failure	2 (0.4%)	0 (0.0%)
Visual defect	1 (0.2%)	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=1,092)	Unintentional Exposure Reason (N=779)
Fluids, IV	513 (47.0%)	51 (6.5%)
Other	192 (17.6%)	43 (5.5%)
Oxygen	208 (19.0%)	16 (2.1%)
Charcoal, single dose	123 (11.3%)	44 (5.6%)
Dilute/irrigate/wash	22 (2.0%)	137 (17.6%)
Benzodiazepines	124 (11.4%)	10 (1.3%)
Naloxone	142 (13.0%)	7 (0.9%)
Intubation	121 (11.1%)	7 (0.9%)
Ventilator	109 (10.0%)	6 (0.8%)
Food/snack	13 (1.2%)	74 (9.5%)
NAC, IV	93 (8.5%)	0 (0.0%)
Sedation (other)	95 (8.7%)	8 (1.0%)
Alkalinization	85 (7.8%)	2 (0.3%)
Antiemetics	62 (5.7%)	4 (0.5%)
Cathartic	26 (2.4%)	9 (1.2%)
Vasopressors	49 (4.5%)	2 (0.3%)
Antibiotics	46 (4.2%)	0 (0.0%)
Other emetic	4 (0.4%)	13 (1.7%)
Glucose, > 5%	19 (1.7%)	2 (0.3%)
Calcium	15 (1.4%)	2 (0.3%)
Antiarrhythmic	36 (3.3%)	0 (0.0%)
Antihistamines	9 (0.8%)	2 (0.3%)
Antihypertensives	15 (1.4%)	2 (0.3%)
Neuromuscular blocker	13 (1.2%)	0 (0.0%)
NAC, PO	12 (1.1%)	0 (0.0%)
Flumazenil	9 (0.8%)	0 (0.0%)
Lavage	5 (0.5%)	1 (0.1%)
CPR	20 (1.8%)	0 (0.0%)
Atropine	6 (0.5%)	4 (0.5%)
Glucagon	7 (0.6%)	1 (0.1%)
Anticonvulsants	4 (0.4%)	0 (0.0%)
Bronchodilators	3 (0.3%)	1 (0.1%)

Therapy	Intentional Exposure Reason (N=1,092)	Unintentional Exposure Reason (N=779)
Cardioversion	6 (0.5%)	0 (0.0%)
Charcoal, multiple doses	2 (0.2%)	0 (0.0%)
Octreotide	2 (0.2%)	0 (0.0%)
Steroids	2 (0.2%)	0 (0.0%)
Folate	3 (0.3%)	0 (0.0%)
Fresh air	0 (0.0%)	1 (0.1%)
Hemodialysis	2 (0.2%)	0 (0.0%)
Insulin	8 (0.7%)	0 (0.0%)
Pacemaker	2 (0.2%)	0 (0.0%)
Pyridoxine	1 (0.1%)	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: Annual Sales-Adjusted Rate of Exposures to a Loperamide-Containing Product Plus Another Substance by Intentional Abuse or Intentional Misuse Reason for Exposure

Year	Rate of Intentional Abuse Exposures per 1 Million Units Sold (95% CI)	Rate of Intentional Misuse Exposures per 1 Million Units Sold (95% CI)
2012	0.019 (0.009, 0.035)	0.031 (0.017, 0.050)
2013	0.036 (0.021, 0.057)	0.018 (0.008, 0.034)
2014	0.033 (0.019, 0.054)	0.038 (0.022, 0.059)
2015	0.031 (0.018, 0.050)	0.042 (0.027, 0.064)
2016	0.085 (0.063, 0.112)	0.027 (0.016, 0.044)
2017	0.077 (0.056, 0.103)	0.044 (0.029, 0.065)
Total	**0.049 (0.041, 0.057)**	**0.034 (0.028, 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=155)	Intentional Misuse Exposure (N=107)
Age, years		
Median	28.0	36.0
Mean (SD)	30.9 (10.15)	40.9 (20.51)
Age (categorical)		
Pediatric (<12 years)	0 (0.0%)	4 (3.7%)
Adults and Children (≥12 years)	154 (99.4%)	98 (91.6%)
Unknown Child (≤19 years)	0 (0.0%)	0 (0.0%)
Unknown Adult (>19 years)	1 (0.6%)	5 (4.7%)
Unknown Age	0 (0.0%)	0 (0.0%)
Female	34 (21.9%)	46 (43.0%)
Exposure Site		
Own Residence	136 (87.7%)	100 (93.5%)
Other Residence	4 (2.6%)	2 (1.9%)
Workplace	0 (0.0%)	1 (0.9%)
Health Care Facility	0 (0.0%)	0 (0.0%)
School	0 (0.0%)	0 (0.0%)
Other	4 (2.6%)	4 (3.7%)
Unknown	11 (7.1%)	0 (0.0%)
Route of Exposure[a]		
Ingestions	148 (95.5%)	106 (99.1%)
Inhalation/nasal	6 (3.9%)	1 (0.9%)
Ocular	0 (0.0%)	0 (0.0%)
Dermal	1 (0.6%)	2 (1.9%)
Parenteral	9 (5.8%)	1 (0.9%)
Other	0 (0.0%)	0 (0.0%)
Unknown	6 (3.9%)	0 (0.0%)
Chronicity		
Acute	90 (58.1%)	72 (67.3%)
Acute-on-Chronic	28 (18.1%)	18 (16.8%)
Chronic	20 (12.9%)	14 (13.1%)
Unknown	17 (11.0%)	3 (2.8%)
Number of Substances		

Characteristics	Intentional Abuse Exposure (N=155)	Intentional Misuse Exposure (N=107)
Mean (SD)	2.8 (2.00)	2.6 (1.10)
Median	2.0	2.0
Range	(2.0, 22.0)	(2.0, 8.0)
Number of Substances (Categories)		
1 Product/Substance	0 (0.0%)	0 (0.0%)
2 Products/Substances	97 (62.6%)	69 (64.5%)
3 Products/Substances	33 (21.3%)	23 (21.5%)
4+ Products/Substances	25 (16.1%)	15 (14.0%)

[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=155)	Intentional Misuse Exposure (N=107)
Recommended to or Received Healthcare Facility (HCF) Care		
Yes	152 (98.1%)	87 (81.3%)
No	2 (1.3%)	18 (16.8%)
Unknown	1 (0.6%)	2 (1.9%)
Level of Care[a]		
Treated/evaluated and released	37 (24.3%)	25 (28.7%)
Admitted to non-critical care unit	25 (16.4%)	16 (18.4%)
Admitted to critical care unit	69 (45.4%)	23 (26.4%)
Admitted to psychiatric care facility	7 (4.6%)	6 (6.9%)
Patient refused referral/did not arrive at HCF	2 (1.3%)	7 (8.0%)
Patient lost to follow-up/left AMA	12 (7.9%)	10 (11.5%)

[a]*Denominator is the number of exposures that were recommended to or received HCF 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=155)	Intentional Misuse Exposure (N=107)
Followed to a Known Outcome	139 (89.7%)	76 (71.0%)
Death	3 (1.9%)	0 (0.0%)
Major Effect	35 (22.6%)	10 (9.3%)
Moderate Effect	71 (45.8%)	25 (23.4%)
Minor Effect	27 (17.4%)	21 (19.6%)
No Effect or Unrelated Effect	3 (1.9%)	20 (18.7%)
Not Followed to Known Outcome	16 (10.3%)	31 (29.0%)
Unable to follow, potentially toxic	11 (7.1%)	13 (12.1%)
Not followed, non-toxic	0 (0.0%)	0 (0.0%)
Not followed, minimal clinical effects expected	5 (3.2%)	18 (16.8%)

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=155)	Intentional Misuse Exposure (N=107)
Drowsiness/lethargy	66 (42.6%)	22 (20.6%)
Tachycardia	51 (32.9%)	21 (19.6%)
Confusion	19 (12.3%)	11 (10.3%)
Other	6 (3.9%)	10 (9.3%)
Agitated/irritable	9 (5.8%)	6 (5.6%)
Hypertension	18 (11.6%)	12 (11.2%)
Conduction disturbance	37 (23.9%)	11 (10.3%)
Respiratory depression	35 (22.6%)	10 (9.3%)
Nausea	12 (7.7%)	10 (9.3%)
Diaphoresis	9 (5.8%)	6 (5.6%)
Hypotension	19 (12.3%)	7 (6.5%)
Vomiting	18 (11.6%)	7 (6.5%)
Abdominal Pain	10 (6.5%)	8 (7.5%)
Coma	20 (12.9%)	2 (1.9%)
Miosis	16 (10.3%)	3 (2.8%)
Bradycardia	9 (5.8%)	3 (2.8%)
CPK elevated	7 (4.5%)	3 (2.8%)
ECG change (other)	4 (2.6%)	2 (1.9%)
Fever/hyperthermia	8 (5.2%)	2 (1.9%)
Tremor	7 (4.5%)	3 (2.8%)
Ataxia	5 (3.2%)	0 (0.0%)
Creatinine increased	6 (3.9%)	6 (5.6%)
Dysrhythmia (v tach/v fib)	2 (1.3%)	2 (1.9%)
Electrolyte abnormality	10 (6.5%)	4 (3.7%)
Hallucinations/delusions	5 (3.2%)	2 (1.9%)
Mydriasis	9 (5.8%)	2 (1.9%)
Syncope	4 (2.6%)	2 (1.9%)
Urinary retention	6 (3.9%)	0 (0.0%)
Acidosis	10 (6.5%)	3 (2.8%)
Cardiac arrest	6 (3.9%)	1 (0.9%)
Diarrhea	3 (1.9%)	5 (4.7%)
Dizziness/vertigo	2 (1.3%)	6 (5.6%)

Clinical Effect	Intentional Abuse Exposure (N=155)	Intentional Misuse Exposure (N=107)
Muscle rigidity	2 (1.3%)	1 (0.9%)
Pneumonitis	4 (2.6%)	1 (0.9%)
Respiratory arrest	5 (3.2%)	1 (0.9%)
X-ray findings(+)	8 (5.2%)	1 (0.9%)
AST, ALT>100≤1,000	4 (2.6%)	3 (2.8%)
Constipation	1 (0.6%)	3 (2.8%)
Cough/choke	1 (0.6%)	1 (0.9%)
Cyanosis	1 (0.6%)	1 (0.9%)
Erythema/flushed	1 (0.6%)	1 (0.9%)
Muscle weakness	2 (1.3%)	1 (0.9%)
Pallor	4 (2.6%)	0 (0.0%)
Pruritus	0 (0.0%)	2 (1.9%)
Rhabdomyolysis	4 (2.6%)	0 (0.0%)
Slurred speech	10 (6.5%)	2 (1.9%)
Tinnitus	1 (0.6%)	2 (1.9%)
ADR to treatment	4 (2.6%)	1 (0.9%)
Alkalosis	1 (0.6%)	0 (0.0%)
Anion gap increased	3 (1.9%)	1 (0.9%)
Asystole	3 (1.9%)	0 (0.0%)
Blurred vision	1 (0.6%)	1 (0.9%)
Bronchospasm	1 (0.6%)	0 (0.0%)
CVA	0 (0.0%)	1 (0.9%)
Dehydration	1 (0.6%)	0 (0.0%)
Dermal - Irritation/pain	0 (0.0%)	1 (0.9%)
Dysrhythmia (other)	1 (0.6%)	0 (0.0%)
Edema	0 (0.0%)	1 (0.9%)
Excess secretions	1 (0.6%)	0 (0.0%)
Headache	0 (0.0%)	1 (0.9%)
Hyperglycemia	1 (0.6%)	1 (0.9%)
Hypoglycemia	0 (0.0%)	2 (1.9%)
Multiple Chemical Sensitivities	0 (0.0%)	1 (0.9%)
Numbness	0 (0.0%)	1 (0.9%)
Nystagmus	2 (1.3%)	0 (0.0%)
Other LFT abnormality	1 (0.6%)	0 (0.0%)
Pain (not dermal, GI, ocular)	2 (1.3%)	0 (0.0%)

Clinical Effect	Intentional Abuse Exposure (N=155)	Intentional Misuse Exposure (N=107)
Seizure (single)	3 (1.9%)	1 (0.9%)
Seizures (multi/discrete)	2 (1.3%)	0 (0.0%)
Urinary incontinence	1 (0.6%)	0 (0.0%)
Visual defect	1 (0.6%)	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=109)	Intentional Misuse Exposure (N=35)
Drowsiness/lethargy	56 (51.4%)	16 (45.7%)
Tachycardia	44 (40.4%)	17 (48.6%)
Confusion	17 (15.6%)	8 (22.9%)
Hypertension	17 (15.6%)	10 (28.6%)
Conduction disturbance	37 (33.9%)	11 (31.4%)
Respiratory depression	34 (31.2%)	10 (28.6%)
Agitated/irritable	7 (6.4%)	4 (11.4%)
Other	5 (4.6%)	6 (17.1%)
Hypotension	19 (17.4%)	7 (20.0%)
Diaphoresis	9 (8.3%)	5 (14.3%)
Nausea	12 (11.0%)	5 (14.3%)
Vomiting	16 (14.7%)	5 (14.3%)
Coma	18 (16.5%)	2 (5.7%)
Miosis	15 (13.8%)	3 (8.6%)
CPK elevated	7 (6.4%)	3 (8.6%)
ECG change (other)	4 (3.7%)	2 (5.7%)
Bradycardia	8 (7.3%)	3 (8.6%)
Fever/hyperthermia	8 (7.3%)	1 (2.9%)
Tremor	7 (6.4%)	3 (8.6%)
Abdominal Pain	5 (4.6%)	2 (5.7%)
Ataxia	5 (4.6%)	0 (0.0%)
Creatinine increased	6 (5.5%)	6 (17.1%)
Dysrhythmia (v tach/v fib)	2 (1.8%)	2 (5.7%)
Electrolyte abnormality	10 (9.2%)	4 (11.4%)
Hallucinations/delusions	5 (4.6%)	2 (5.7%)
Syncope	4 (3.7%)	2 (5.7%)
Urinary retention	6 (5.5%)	0 (0.0%)
Acidosis	10 (9.2%)	3 (8.6%)
Cardiac arrest	6 (5.5%)	1 (2.9%)
Muscle rigidity	2 (1.8%)	1 (2.9%)
Mydriasis	8 (7.3%)	0 (0.0%)
Pneumonitis	4 (3.7%)	1 (2.9%)

Clinical Effect	Intentional Abuse Exposure (N=109)	Intentional Misuse Exposure (N=35)
Respiratory arrest	5 (4.6%)	1 (2.9%)
X-ray findings(+)	8 (7.3%)	1 (2.9%)
AST, ALT>100≤1,000	3 (2.8%)	3 (8.6%)
Cyanosis	1 (0.9%)	1 (2.9%)
Muscle weakness	2 (1.8%)	1 (2.9%)
Rhabdomyolysis	4 (3.7%)	0 (0.0%)
ADR to treatment	4 (3.7%)	1 (2.9%)
Alkalosis	1 (0.9%)	0 (0.0%)
Anion gap increased	3 (2.8%)	1 (2.9%)
Asystole	3 (2.8%)	0 (0.0%)
Blurred vision	1 (0.9%)	1 (2.9%)
Bronchospasm	1 (0.9%)	0 (0.0%)
CVA	0 (0.0%)	1 (2.9%)
Constipation	1 (0.9%)	1 (2.9%)
Cough/choke	1 (0.9%)	0 (0.0%)
Dehydration	1 (0.9%)	0 (0.0%)
Dysrhythmia (other)	1 (0.9%)	0 (0.0%)
Erythema/flushed	1 (0.9%)	0 (0.0%)
Hyperglycemia	1 (0.9%)	1 (2.9%)
Hypoglycemia	0 (0.0%)	2 (5.7%)
Multiple Chemical Sensitivities	0 (0.0%)	1 (2.9%)
Numbness	0 (0.0%)	1 (2.9%)
Nystagmus	2 (1.8%)	0 (0.0%)
Other LFT abnormality	1 (0.9%)	0 (0.0%)
Pain (not dermal, GI, ocular)	2 (1.8%)	0 (0.0%)
Pallor	3 (2.8%)	0 (0.0%)
Seizure (single)	3 (2.8%)	1 (2.9%)
Seizures (multi/discrete)	2 (1.8%)	0 (0.0%)
Slurred speech	7 (6.4%)	2 (5.7%)
Tinnitus	1 (0.9%)	1 (2.9%)
Urinary incontinence	1 (0.9%)	0 (0.0%)
Visual defect	1 (0.9%)	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=155)	Intentional Misuse Exposure (N=107)
Fluids, IV	78 (50.3%)	30 (28.0%)
Oxygen	47 (30.3%)	13 (12.1%)
Other	41 (26.5%)	18 (16.8%)
Naloxone	49 (31.6%)	9 (8.4%)
Benzodiazepines	36 (23.2%)	13 (12.1%)
Alkalinization	24 (15.5%)	8 (7.5%)
Intubation	22 (14.2%)	4 (3.7%)
Ventilator	19 (12.3%)	4 (3.7%)
Sedation (other)	19 (12.3%)	3 (2.8%)
Antibiotics	16 (10.3%)	3 (2.8%)
Dilute/irrigate/wash	4 (2.6%)	6 (5.6%)
Antiarrhythmic	13 (8.4%)	2 (1.9%)
Antiemetics	6 (3.9%)	5 (4.7%)
Charcoal, single dose	5 (3.2%)	0 (0.0%)
Neuromuscular blocker	6 (3.9%)	1 (0.9%)
Vasopressors	7 (4.5%)	3 (2.8%)
CPR	9 (5.8%)	2 (1.9%)
Calcium	4 (2.6%)	1 (0.9%)
Food/snack	3 (1.9%)	4 (3.7%)
Antihistamines	1 (0.6%)	3 (2.8%)
Cardioversion	3 (1.9%)	1 (0.9%)
NAC, IV	7 (4.5%)	2 (1.9%)
Antihypertensives	3 (1.9%)	0 (0.0%)
Bronchodilators	2 (1.3%)	0 (0.0%)
Cathartic	1 (0.6%)	1 (0.9%)
NAC, PO	3 (1.9%)	0 (0.0%)
Other emetic	0 (0.0%)	1 (0.9%)
Pacemaker	2 (1.3%)	0 (0.0%)
Steroids	1 (0.6%)	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 information unavailable* **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

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	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

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
2016	34 Years, Male	Intentional Abuse	Unknown	**Loperamide-Containing Product:** Single-ingredient loperamide (1) **Other Products/Substances:** Bupropion (2) Venlafaxine (3) Mirtazipine (4) Cyclobenzaprine (5)	Probably responsible	**Cause of death:** Mixed drug intoxication **Manner of death:** Accidental **Loperamide Levels:** Postmortem - 18 ng/mL (blood)	• Seen in the emergency room the day prior for reported loperamide overdose
2016	58 Years, Female	Intentional Suspected Suicide	Acute-on-chronic	**Loperamide-Containing Product:** Single-ingredient loperamide **Other Products/Substances:** Quetiapine	Unknown	*Autopsy information unavailable* **Loperamide Levels:** Not reported	• Found unresponsive in car with suicide note and 4 empty bottles of quetiapine and partially empty bottles of loperamide and acetaminophen

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
2017	23 Years, Female	Intentional Unknown	Acute	**Loperamide-Containing Product:** Single-ingredient loperamide (1) **Other Products/Substances:** Atropine/Diphenoxylate (2) Trazodone (3)[b]	Undoubtedly responsible	**Cause of death:** Not reported **Manner of death:** Not reported **Final Diagnosis:** Mixed Drug Toxicity **Loperamide Levels:** Not reported	• Patient was in emergency department the day prior for using high quantities of loperamide and diphenyoxylate/ atropine for opioid dependency • History of opioid addiction and recent use of loperamide (approximately 70 pills unaccounted for)
2017	26 Years, Male	Intentional Abuse	Unknown	**Loperamide-Containing Product:** Single-ingredient loperamide **Other Products/Substances:** Heroin	Unknown	*Autopsy information unavailable* **Loperamide Levels:** Not reported	• History of injection heroin use as well as loperamide use

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
2017	29 Years, Female	Unknown Reason	Acute	**Loperamide-Containing Product:** Single-ingredient loperamide **Other Products/Substances:** Diphenhydramine Miscellaneous Unknown Drugs Benzodiazepines[b]	Unknown	*Autopsy not performed* **Loperamide Levels:** Not reported	• Police found empty bottle of diphenhydramine and loperamide at scene • History of alcohol and substance abuse
2017	30 Years, Male	Intentional Suspected Suicide	Acute	**Loperamide-Containing Product:** Single-ingredient loperamide (1) **Other Products/Substances:** Gabapentin (2) Ethanol (3)	Undoubtedly responsible	*Autopsy information unavailable* **Loperamide Levels***:* Not reported	• Psychiatric history and opioid abuse • Admitted to abuse of 480 tablets daily of loperamide 2 mg

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
2017	31 Years, Male	Intentional Suspected Suicide	Acute	**Loperamide-Containing Product:** Single-ingredient loperamide **Other Products/Substances:** Alprazolam Hydrocodone[b]	Probably responsible	**Cause of Death:** Acute alprazolam intoxication **Manner of Death:** Accident **Loperamide Levels:** Not reported	• Patient had been abusing alprazolam and loperamide
2017	39 Years, Male	Intentional Unknown	Acute	**Loperamide-Containing Product:** Single-ingredient loperamide (1) **Other Products/Substances:** Dirt (2)	Probably responsible	*Autopsy not performed* **Loperamide Levels:** Not reported	• History of IV heroin and cocaine abuse 6-9 years prior • Had been having diarrhea recently and might have used loperamide
2017	40 Years, Female	Unknown Reason	Unknown	**Loperamide-Containing Product:** Single-ingredient loperamide (1) **Other Products/Substances:** Miscellaneous Unknown Drugs (2)	Probably responsible	*Autopsy information unavailable* **Loperamide Levels:** Not reported	• History of alcohol abuse • History of taking “animal cough syrup” in excess • Mother believed drug responsible was loperamide

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
2017	82 Years, Female	Intentional Suspected Suicide	Acute-on-chronic	**Loperamide-Containing Product:** Single-ingredient loperamide **Other Products/Substances:** Acetaminophen	Probably not responsible	*Autopsy not performed* **Loperamide Levels:** Not reported	• Husband reports 25 tablets of extra strength acetaminophen (120 mg/kg) and 30 tablets of 2 mg loperamide tablets may have been taken by patient over the last 24 hours

[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)	213.7 (291.13)	32.4 (62.80)	65.6 (125.28)	5.4 (10.96)	5.9 (14.12)	105.4 (169.47)
Median	100.0	12.0	24.0	2.0	2.0	20.0
Range	(4.0, 1656)	(1.3, 400.0)	(2.0, 1000)	(0.2, 144.0)	(0.3, 100.0)	(3.0, 400.0)
IQR	(40.0, 300.0)	(4.0, 38.0)	(10.0, 60.0)	(2.0, 4.0)	(2.0, 5.0)	(4.0, 100.0)
N	57	56	258	413	55	5

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)	239.8 (311.49)	34.2 (100.67)
Median	96.0	4.0
Range	(2.0, 1200)	(0.2, 1656)
IQR	(30.0, 400.0)	(2.0, 20.0)
N	25	819

13 Conclusions

13.1 Data Implications

The majority of exposures to loperamide-containing products reported to the National Poison Data System (NPDS) involved loperamide-containing products only (no other substance). One loperamide-containing product exposure was reported for every 0.408 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 involved unintentional reasons for exposures like therapeutic errors and accidental unsupervised ingestions. Intentional abuse and intentional misuse of loperamide-containing products were reported in approximately 17% of exposures to loperamide-containing products only and occurred more commonly when multiple substances were involved. These other substances commonly included both over-the-counter medications like ibuprofen and anti-histamines, but also included other substances that can be abused including alcohol and opioids. While sales-adjusted rates of exposure to loperamide-containing products remain low, sales-adjusted rates of intentional misuse exposures of these products may be increasing as intentional misuse of loperamide-containing products only nearly doubled from 2012 to 2017 (2012: 0.147 intentional misuse exposures per 1 million units sold (CI 0.116, 0.184); 2017: 0.216 intentional misuse exposures per 1 million units sold (CI 0.180, 0.257)). Sales-adjusted rates of intentional abuse exposures of these products in 2017 were approximately 9 times greater than in 2012 (2012: 0.029 intentional abuse exposures per 1 million units sold (CI 0.016, 0.047); 2017: 0.251 intentional abuse exposures per 1 million units sold (CI 0.212, 0.296)).

Generally, intentional exposures involved more remarkable outcomes like moderate effect, major effect, and death. Intentional exposures also involved higher levels of healthcare facility care, including admission to a critical care unit. Among fatalities involving loperamide-containing products only, intentional abuse of the loperamide-containing product was clearly evident in seven of ten fatalities. 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 ten fatalities involving loperamide-containing products only, 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=5) in seven cases total. Loperamide overdose was apparent in five fatalities involving loperamide-containing products only with evidence of either missing tablets or reports of large quantities of ingestion. History of ingestion was less clear in the other five fatalities, but antemortem and postmortem loperamide levels were reported in four of the fatalities.

Among the sixteen 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 death in five (5) fatalities and undoubtedly responsible for the fatality in three fatalities. Suicide was reported in three of these fatalities, while intentional abuse of loperamide was reported in two fatalities. In the remaining eight fatalities, the responsibility of the exposure to the fatality was unknown in five fatalities and probably not responsible in three fatalities.

Reported quantity was explored by exposure reason and for exposures associated with severe 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) maintains the National Poison Data System (NPDS), which houses de-identified case records of self-reported information collected from callers during exposure management and poison information calls managed by the country's poison control centers (PCCs). NPDS data do not reflect the entire universe of exposures to a particular substance as additional exposures may go unreported to PCCs; accordingly, NPDS data should not be construed to represent the complete incidence of U.S. exposures to any substance(s). Exposures do not necessarily represent a poisoning or overdose and AAPCC is not able to completely verify the accuracy of every report. Findings based on NPDS data do not necessarily reflect the opinions of AAPCC.

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. Gummin DD, Mowery JB, Spyker DA, Brooks DE, Ostherhaler, KM, Banner, W. 2017 Annual Report of the American Association of the Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. Clinical Toxicology, 2018; 56(12): 1213-1415.

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.