

Clinical and Regulatory Perspectives on Naloxone Products Intended for Use in the Community

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee
and the Drug Safety and Risk Management Advisory Committee

October 5, 2016

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Addiction Products

Opioid Overdose and Death is a Public Health Crisis

- US experiencing a devastating public health crisis associated with the use, misuse, and abuse of illicit and/or prescription opioids
- Drug overdose is currently the leading cause of accidental death in the US
- Can occur in a patient prescribed an opioid medication and in people who misuse or abuse opioids
 - Accidental exposure may also occur in any household or close contacts, such as children
 - Accounts for largest percentage of accidental drug exposures resulting in ED visits and subsequent hospitalizations in children < 6 years old
- Characterized by life-threatening respiratory and central nervous system depression that may lead to irreversible hypoxic injury – requires immediate treatment

Naloxone Saves Lives

- Naloxone is a nonselective opioid receptor antagonist with the greatest affinity for the mu opioid receptor
- Naloxone can reverse the life-threatening effects of an opioid overdose
- When administered quickly, naloxone can prevent hypoxia-associated injury and death

Challenges Associated with Naloxone Use in the Community

- Risk of recurrent respiratory and central nervous system depression
 - Opioid duration of action may exceed that of naloxone
 - Requires continued surveillance and, possibly, repeat doses
 - Extended-release products of particular concern
- Risk of limited efficacy with partial agonists or mixed agonist/antagonists (e.g., buprenorphine)
 - Reversal may be incomplete or require higher doses of naloxone
- Potential for adverse events associated with opioid withdrawal

Precipitation of Severe Opioid Withdrawal

- Signs and symptoms include body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure

Precipitation of Severe Opioid Withdrawal

- Abrupt postoperative reversal of opioid depression after using naloxone may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, cardiac arrest, death, coma, and encephalopathy
 - Events have primarily occurred in patients who had pre-existing cardiovascular disorders or received other drugs that may have similar adverse cardiovascular effects

Risk of Acute Opioid Withdrawal

- **In neonates**, acute opioid withdrawal manifesting as **seizures** may be life-threatening if not recognized and properly treated
 - Less serious signs and symptoms include excessive crying and hyperactive reflexes
- Potentially greatest risk in neonates born to opioid dependent mothers
- Low risk in children 1 month to < 12 years
 - More likely to acutely overdose from isolated, accidental opioid exposure to prescription opioids or illicit drugs

Naloxone Intended for Use in a Healthcare Setting

- Initially approved in 1971 as Narcan with subsequent approvals of generic products
 - Labeled for intravenous (IV), intramuscular (IM), or subcutaneous (SC) use
 - 0.4 mg/ml and 1 mg/ml preparations currently available
 - Initial doses for opioid overdose: 0.4 mg to 2 mg
 - May repeat at 2 to 3 minute intervals
 - Question diagnosis if no response is observed after 10 mg

Naloxone for Pediatrics in a Healthcare Setting



- Children: 0.01 mg/kg; then 0.1 mg/kg if initial dose ineffective
- Neonates: 0.01 mg/kg, may be repeated
- AAP issued a statement on naloxone in 1990
 - 0.1 mg/kg: birth to 5 years of age or ≤ 20 kg
 - 2 mg: > 5 years of age or > 20 kg
 - The initial dose is often higher than what is recommended in adults
 - Statement was not based on controlled clinical data, but a concern that 0.01 mg/kg may not provide optimal reversal in some infants
 - The statement has been retired and is no longer considered active policy of the AAP
 - However, it is incorporated into pediatric resuscitation guidelines and pediatric drug references and is widely accepted

Pediatric Weight-Based Dose vs. Fixed-Dose

- Weight-based dosing relies on ability to monitor patients and identify the need for re-dosing
- Fixed-dosing relies on ability to deliver a single dose which can safely achieve and sustain opioid reversal in all pediatric patients
- Preference may depend on setting of use
 - Supervised medical settings when dose-titration is needed by trained healthcare professionals
 - Community settings for use by individuals without medical training and where limited to no other therapeutic options exist
- Preference may require weighing risk of precipitating acute withdrawal symptoms with potentially life-threatening consequences of ineffective or no treatment



FDA is Committed to Naloxone as One Component of Our Approach

- FDA held public meetings on naloxone intended for use in the community
- FDA has worked with sponsors to develop a pathway to approval
- FDA has reviewed and approved these products under a variety of expedited programs (e.g., fast track, priority review)
- FDA announced the Opioids Action Plan on February 4, 2016
 - Support better treatment, including providing broader access to naloxone

<http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm>

2012 Naloxone Workshop

- Sponsored by FDA, CDC, NIDA, and the Office of the Assistant Secretary for HHS
- Scope: Discuss expanding access to naloxone in the community
 - Approved formulations of naloxone, at that time, consisted of injectable products used by medical professionals
- Speaker Highlights
 - Abuse of prescription opioids and deaths associated with prescription opioid overdose a significant problem in the U.S.
 - Naloxone is an important tool in addressing the problem of opioid overdose and access to naloxone should be made easily available
 - Encouraged FDA to expand access by approving non-injectable forms of naloxone

2012 Naloxone Workshop

- FDA Discussion
 - Discussed the general pathways for approving new formulations of naloxone and making naloxone available OTC
 - Approval of new formulations would be based upon a comparative bioavailability study due to ethical concerns with conducting an efficacy study
 - Drug levels with the new and an already-approved injectable formulation of naloxone will be compared
 - Switching naloxone to OTC status would likely require additional clinical data
- Conclusions: Need for better coordination among federal agencies, manufacturers, and stakeholders to resolve regulatory issues and expand access

2015 Public Meeting

- Discussed a variety of scientific, legal, regulatory, logistical, and clinical issues surrounding the use of naloxone
- Broad general agreement that naloxone should be made widely available to persons at risk for overdose and to those who might witness an overdose
- Naloxone access has greatly increased since 2012
 - However, many states and communities lack programs to make it available
- Co-prescribing of naloxone was broadly supported
- Agreement that training on use of naloxone is needed

FDA Approach to New Formulations of Naloxone

- FDA has had the opportunity to work with companies that were partnering with NIDA to establish a pharmacokinetic standard for new formulations of naloxone in lieu of conducting efficacy studies
 - Ethical challenges associated with conducting efficacy studies in this clinical setting
 - Pharmacodynamic outcomes not an adequate surrogate
- FDA leveraged what is known about the safety and efficacy of existing approved naloxone products and pharmacokinetics as a path forward for these products
 - Match or exceed the naloxone exposures achieved via an approved route of administration (**0.4 mg IM**), particularly in the early critical period, in healthy adult volunteers

Pediatric Considerations with New Formulations of Naloxone

- Have not found a feasible study design to evaluate
 - Pharmacokinetic profile of new naloxone products in children
 - Age-specific safety questions associated with novel routes and anatomic differences, e.g., intranasal delivery and risk of choking or aspiration in infants
 - Some local safety questions may be suitable for nonclinical evaluation, e.g., IM injectors and needle length
- Human factors validation studies:
 - Selection of distinct user groups
 - Simulation methods
- Safety of choice and quantity of excipients



Naloxone Products Approved for Community Use

- Approved products
 - Evzio (naloxone auto-injector)
 - Narcan Nasal Spray
- Approved indication
 - The emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression
 - Intended for immediate administration as emergency therapy in settings where opioids may be present
 - **Not a substitute for emergency medical care**
- Approved with Instructions for Use
 - Patient labeling targeted to the layperson
 - Evaluated in human factors studies
 - Expected that laypersons can use these products without any additional training required

Naloxone Products Approved for Community Use

- **Evzio** – Naloxone auto-injector
 - 1st product approved in this setting
 - Fast Track designation; Priority NDA review
 - Approved April 2014 over two months ahead of six-month PDUFA goal date
 - Labeled for intramuscular or subcutaneous use
 - Delivers a 0.4 mg dose
 - Packaged with two single-use auto-injectors as well as a trainer

Naloxone Products Approved for Community Use

- **Narcan Nasal Spray**
 - Fast Track designation; Priority NDA review
 - Approved November 2015 over two months ahead of six-month PDUFA goal date
 - Labeled for intranasal use
 - Delivers a 4 mg dose in a 0.1 ml spray
 - Packaged with two single-use devices

Off-Label Intranasal Use in the Community



- Provided in a kit containing
 - Naloxone for injection (2 mg/2 ml)
 - Luer lock syringe barrel
 - Mucosal atomizer device (MAD)
- Half of the volume (~1 ml) sprayed in one nostril and remaining volume sprayed in other nostril
- Unapproved route for the approved parenteral product



<http://www.providencejournal.com/article/20140215/SPECIAL-REPORTS/302159991>



<http://www.medpagetoday.com/publichealthpolicy/publichealth/52118>

Off-Label Intranasal Use in the Community

- Predominantly used by a variety of organizations and state and local programs including first responders to make naloxone available in the community
- In general, training is provided for these kits
- FDA is aware that this off-label use is associated with efficacy; however, it is unclear if these products meet the standard previously outlined and how often these products fail to reverse an opioid overdose
- Limited pharmacokinetic data for these products

Outstanding Issues

- Failure to reverse outcomes may be associated with a variety of scenarios in a community setting
 - Life-saving treatment was delivered too late
 - Person is not suffering from an opioid overdose
 - Overdose secondary to a potent opioid, multi-drug combination, or a partial agonist
- Confusion over terminology
 - “Narcan” term is being used broadly in the community

What is the Appropriate Naloxone Dose?

- Ideally, dose should be suited for all subpopulations to avoid potential for not having an appropriate product in any given clinical scenario
- High potency opioids may require a higher dose
 - Reports of heroin being laced with extremely potent opioids (i.e., “street fentanyl” and carfentanil)
 - Carfentanil is a sedative for large animals and analogue to fentanyl that is 10,000 times more potent than morphine
 - Recent overdose outbreaks in Ohio, Indiana, and Florida
 - Reports of these overdoses requiring as much as a 3-fold the ordinary dose of naloxone

Conclusions

- FDA has established a minimum pharmacokinetic standard for approval of new naloxone products based on the exposures associated with 0.4 mg IM
- The feasibility of this standard has been demonstrated by approval of two naloxone products intended for use in the community
- Dosing recommendations vary based on the source
- Although AAP does not have a current guideline on naloxone in pediatric patients, many commonly used treatment guidelines still cite the **retired** AAP recommendations

Conclusions

- New concerns over high potency illicit opioids requiring higher doses of naloxone
- We now have companies approaching us about different dosing regimens for these products
- FDA is seeking advice on how to approach these new questions
 - Is our minimum standard high enough?
 - Is there a place for products of different doses/strengths?
 - How would we label a product so a prescriber would know which to choose?



The Current Approach to Relative Bioavailability Studies in Support of Approval of New Naloxone Products

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Pharmacokinetics of Naloxone

- Rapidly distributed in body
- Relatively weak protein binding
 - Mainly with plasma albumin
- Mainly metabolized in liver by glucuronidation
- Excreted in urine as metabolites
- Short half-life in adults (~1-2 hour)
 - Administering additional doses may be necessary

Regulatory Background

- Original approval of Naloxone Injection (NDA16636)
 - No longer on market, generics available
 - Initial dose of 0.4 mg to 2 mg for IV, IM or SC, followed by repeated doses up to 10 mg in adults
- Recent approvals
 - Evzio, Naloxone Auto-injector (NDA205787)
 - Narcan Nasal Spray (NDA208411)

Development Pathway

- Infeasible to study minimal effective dose, or conduct efficacy trial
 - Life-threatening nature of opioid overdose
 - Ethical and logistical issue
- Reliance on Agency's previous findings for approved Naloxone Injection
 - To establish a scientific bridge via relative bioavailability (BA) study between new product (test) and the reference

Relative Bioavailability Study Design

- Randomized, cross-over study in healthy adults
- Adequate sample size
- Using label recommended dose and route
- Adequate wash-out period
- Adequate blood sampling to capture entire PK profile
 - Especially in the first thirty minutes for onset-of-action
- Free (unconjugated) naloxone levels
- Generic product to approved Naloxone Injection, designated a reference listed drug (RLD), may be used as comparator
- Final to-be-marketed product (formulation and device) needs to be used for test

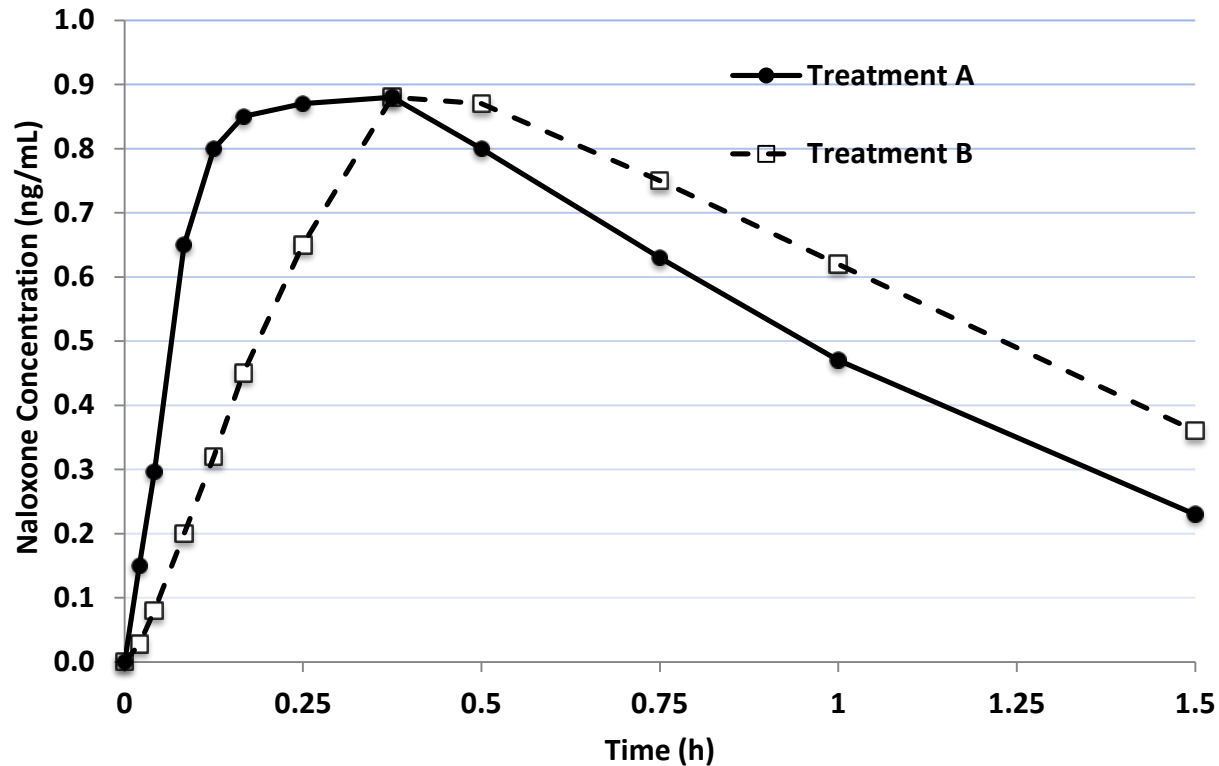
Data Analysis

- C_{\max} , T_{\max} , AUC_{0-t} , $AUC_{0-\infty}$, half-life
- Partial AUC (pAUC)
 - To assess onset of therapeutic effect
- Bioequivalence (BE) statistical approach to analyze C_{\max} and AUC
 - Demonstration of BE is NOT required

Acceptance Criteria

- Test product matches or exceeds the systemic naloxone exposure to the comparator
 - C_{\max} , AUC_{0-t} , AUC_{0-inf}
 - pAUC at early time points to assess onset of action
 - Entire PK profiles
- May not be acceptable for product with lower exposure at early time points (i.e. pAUC), even if C_{\max} , AUC_{0-t} , and AUC_{0-inf} meet criteria

Importance of pAUCs

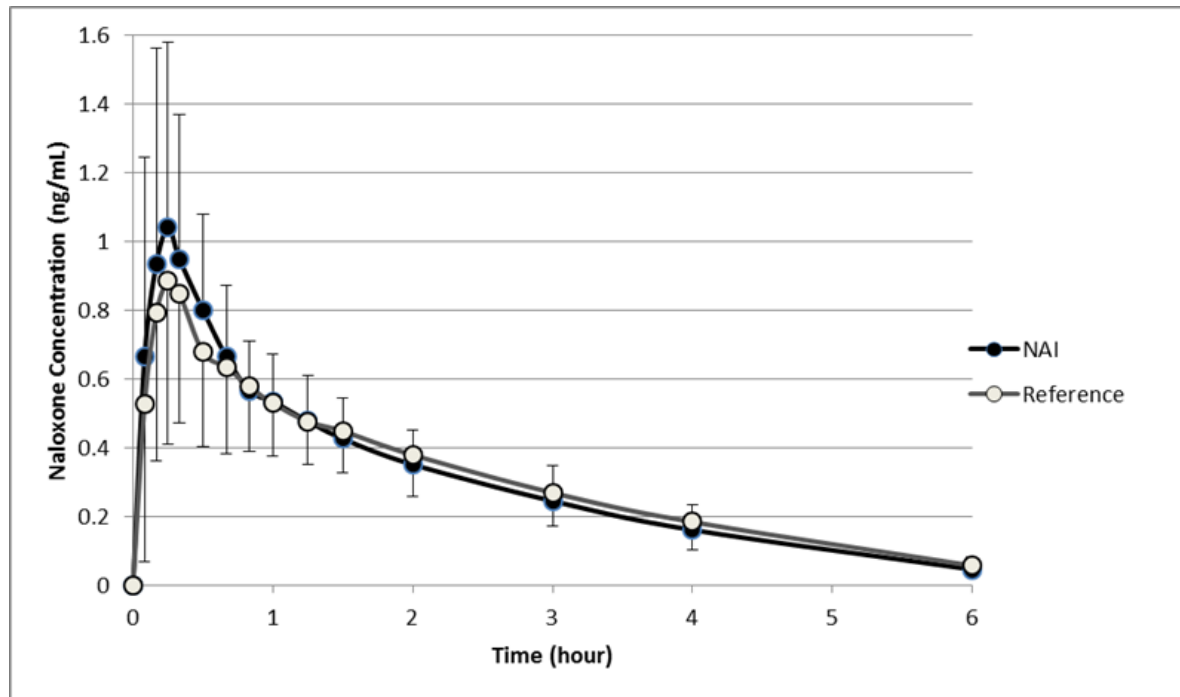


- Potentially unacceptable scenario
 - Similar C_{max} , T_{max} , AUC_{0-t} , AUC_{0-inf} values
 - Lower pAUC values at early time points for Treatment B

Evzio Auto-Injector (NDA205787)

- 0.4 mg naloxone HCl in 0.4 mL solution in a pre-filled auto-injector
 - Initial dose of one injection of 0.4 mg
 - Another dose may be administered
- Relative BA study with Naloxone Injection
 - Randomized, cross-over study
 - 0.4 mg dose for both products
 - IM or SC injection

Concentration-time Profiles

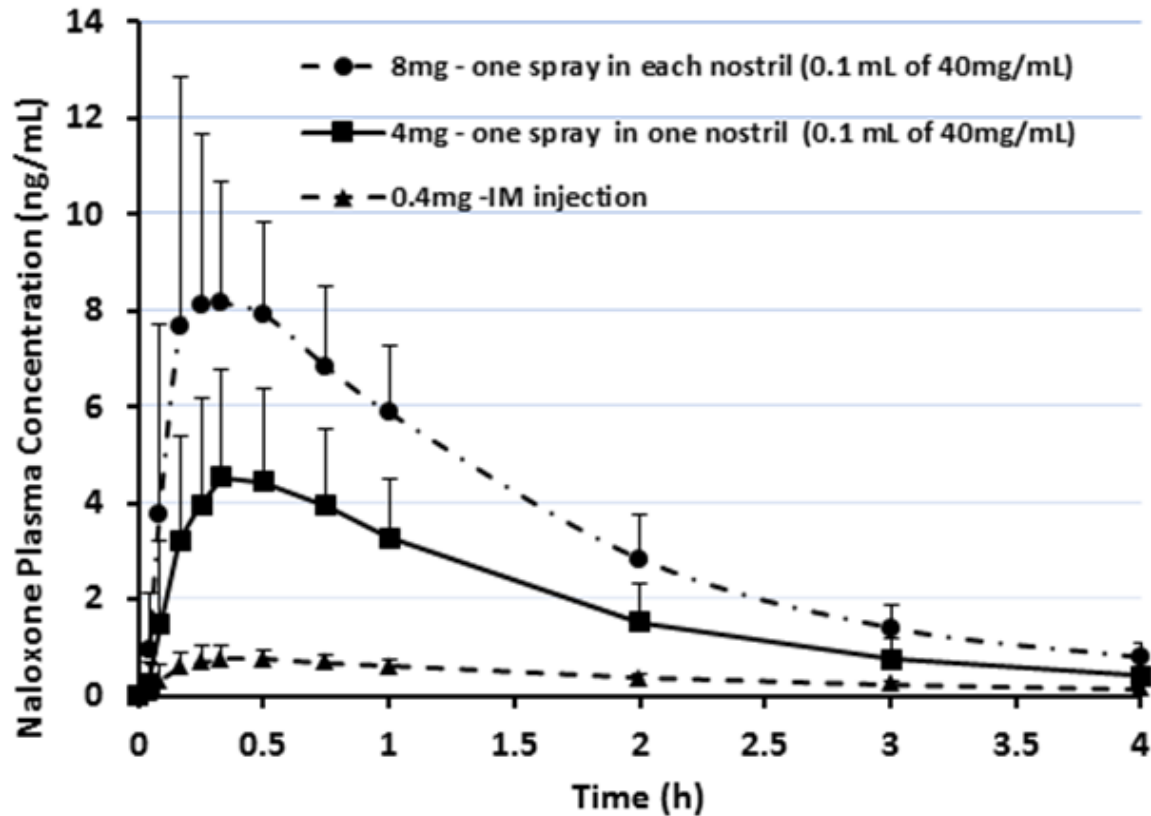


- Similar T_{max}
- Slightly higher (15%) C_{max} for Evzio Auto-Injector
- Bioequivalence for AUC_{0-t} and AUC_{0-inf}

Narcan Nasal Spray (NDA208411)

- 4 mg naloxone HCl in one 0.1 mL spray
 - Initial dose of one spray of 4 mg
 - Another dose may be administered
- Relative BA study with Naloxone Injection
 - Randomized, cross-over study
 - 0.4 mg IM dose for Naloxone Injection, 4 mg (one spray) and 8 mg (two spray) for Nasal Spray

Concentration-time Profiles



- Similar T_{max}
- Higher C_{max} and AUC (~5-fold) for 4 mg Nasal Spray

Relevant Guidance

- *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations*
 (<http://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm389370.pdf>)
- *Guidance for industry: Statistical Approaches to Establishing Bioequivalence*
 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070244.pdf>)



Thank you!



Drug Utilization of Naloxone

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October 5, 2016

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Outline

- Drug utilization databases
 - Sales Distribution Data
 - Dispensed Prescription Data
- Other data sources
 - NEMESIS - National Emergency Medical Services Information System
 - NPDS - National Poison Data System
 - NEISS-CADES - National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance
- Published literature on utilization in the community setting
- Summary

Naloxone Product Information



Manufacturer/ Product Name	Strength	Approval date
<u>Branded Products</u>		
Adapt® Pharma (Narcan Nasal Spray)	4mg/spray	11/18/2015
Kaleo® Pharma (EVZIO® auto-injector)*	0.4mg/0.4ml	04/03/2014
<u>Generic Products (injectables)</u>		
Mylan®	0.4mg/ml	03/06/2014
Hospira®	0.4mg/ml	04/18/1986
Amphastar®	0.4mg/ml 1mg/ml	01/17/1986 03/24/1988
Euro health International Sarl.	0.4mg/ml	10/22/1982

Outline

- **Drug utilization databases**
 - Sales Distribution Data
 - Dispensed Prescription Data
- Other data sources
 - NEMESIS - National Emergency Medical Services Information System
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Database Description – Sales Data

- Measures the volume of drug products sold from manufacturers to settings of care
 - Non-federal hospitals
 - Retail pharmacies
 - Clinics
 - Miscellaneous other
 - All other
- Measures naloxone products distributed through traditional channels of distribution
- Products measured in units sold e.g., vial, ampule, syringe, or device



Settings of Care

Nationally estimated number of naloxone products (in units) sold from manufacturers to channels of distribution from July 2011 to June 2012 vs July 2015 to June 2016

Channel	Jul 2011-Jun 2012	Share %	Jul 2015-Jun 2016	Share %
Grand Total	2,861,420	100%	3,918,446	100%
Non-Federal Hospitals*	2,182,164	76.3%	2,092,609	53.4%
Clinics	282,134	9.9%	887,926	22.7%
Retail	71,795	2.5%	331,584	8.5%
Misc.-Other**	89,451	3.1%	246,946	6.3%
Federal Facilities	140,215	4.9%	130,343	3.3%
All other***	95,661	3.3%	229,038	5.9%

* Non-federal hospitals include distribution intended for inpatient, clinic, and ambulances

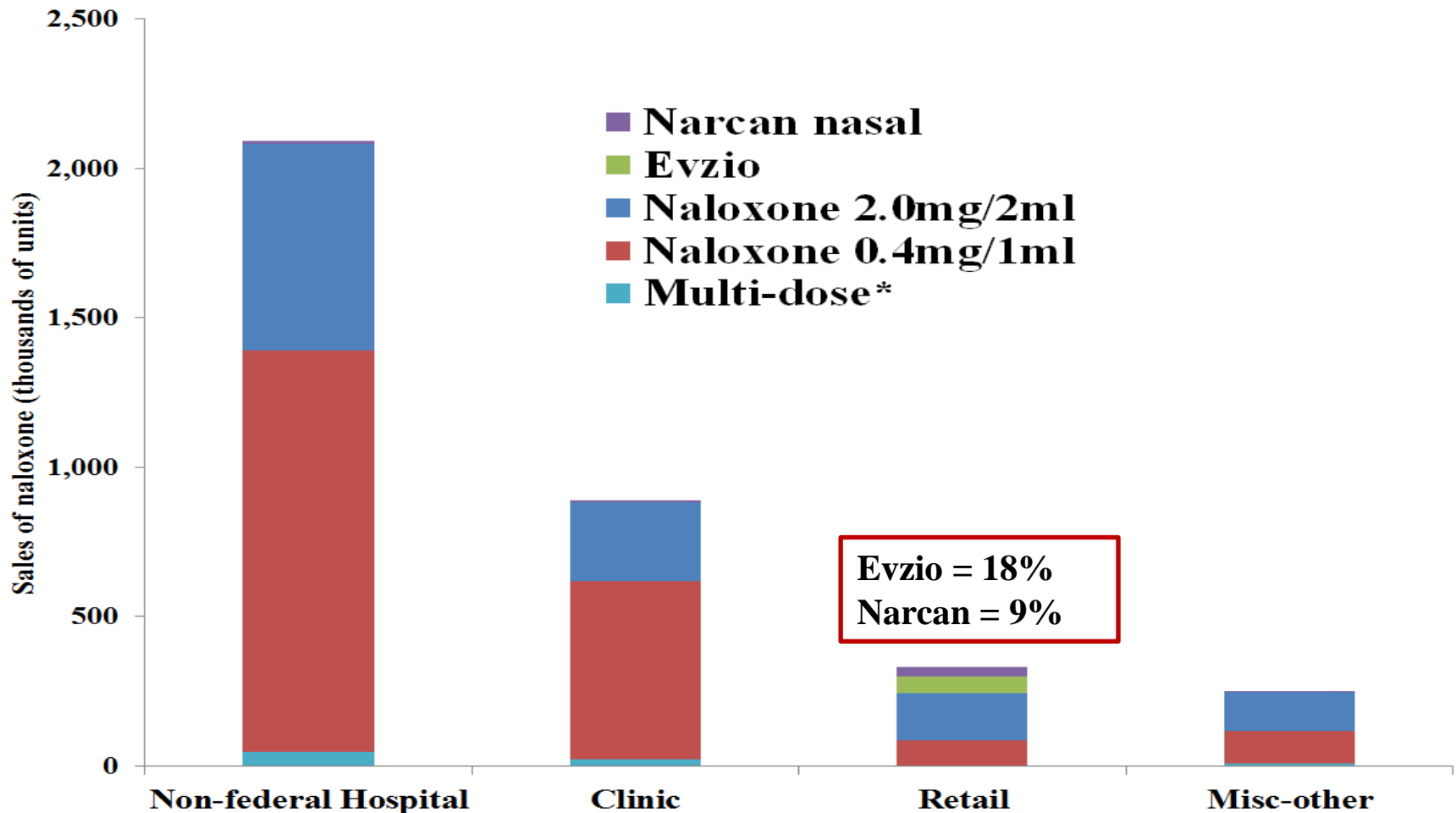
**Misc-Other includes sales to state and local government and may supply Emergency Medical Services (EMS)

***All Other includes HMO, home health care, long-term care, mail service, miscellaneous/prisons, and miscellaneous/universities

Settings of Care – by Product



Nationally estimated number of naloxone units sold from manufacturers to selected channels of distribution by product (strength and vial size) from July 2015 to June 2016

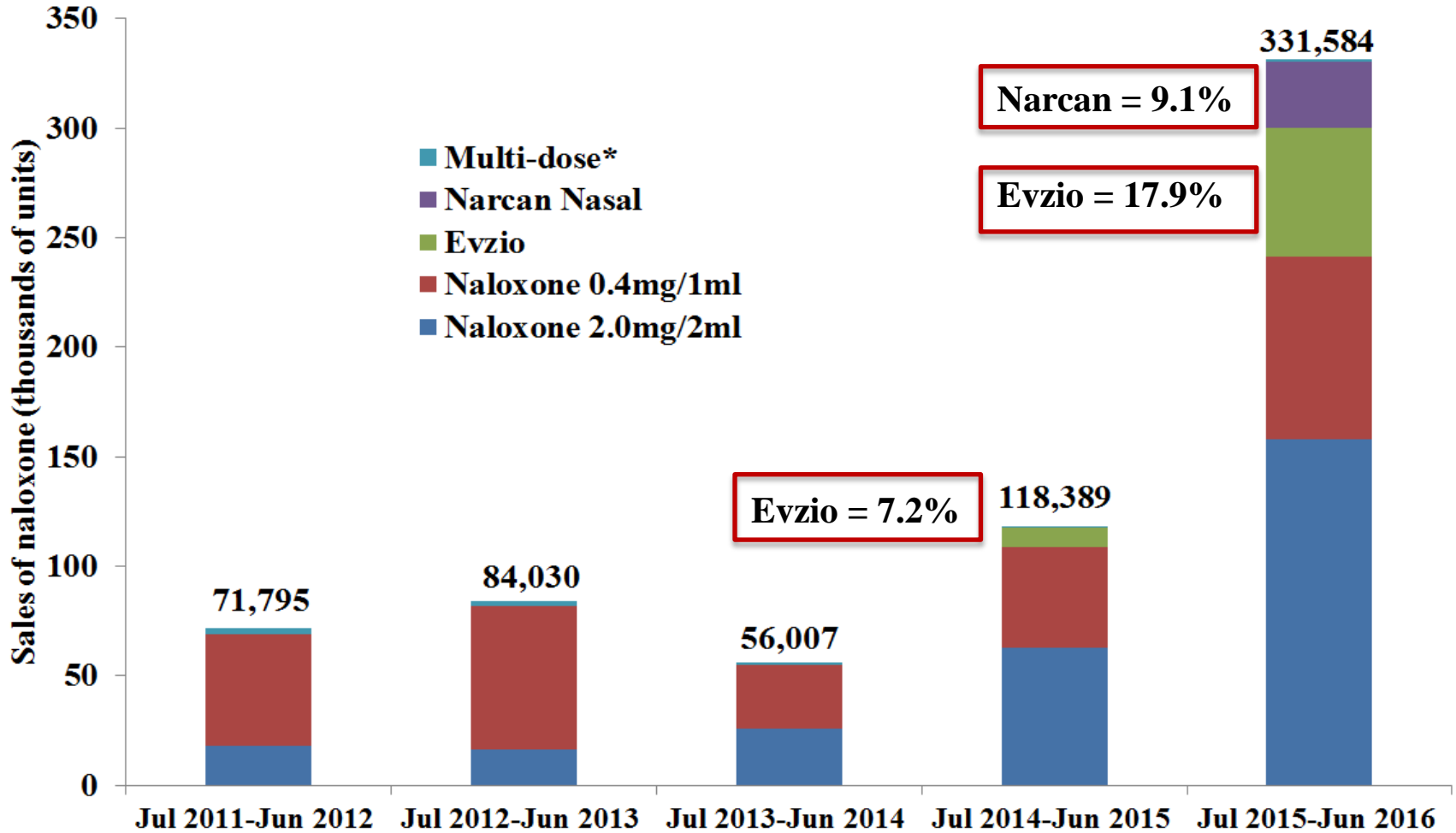


*4mg/10ml vials

Sales Data-Retail Setting



Nationally estimated number of naloxone units sold by manufacturers to the retail channel stratified by product strength and unit size, July 2011 to June 2016



*4mg/10ml vials



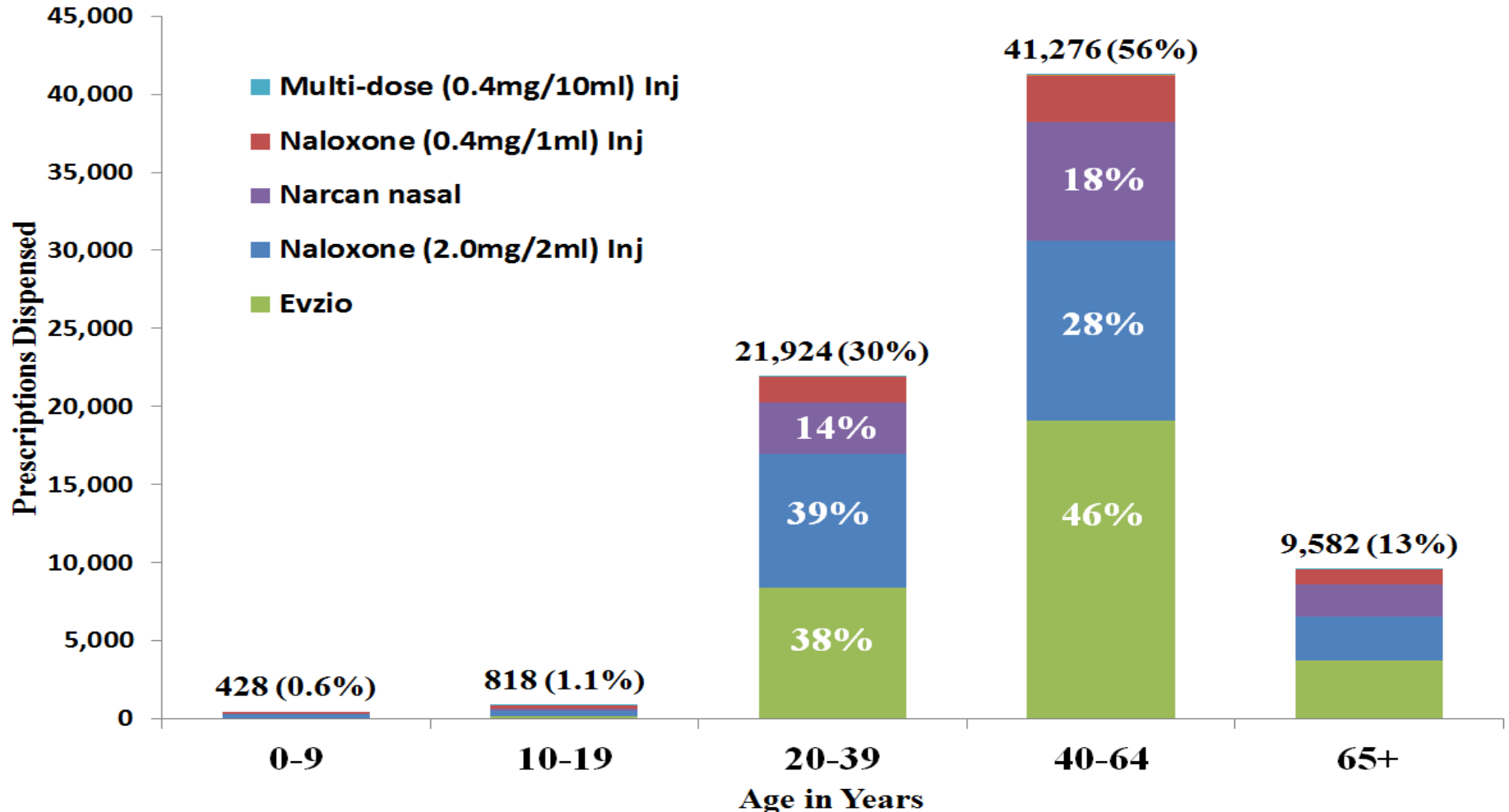
Database Description – Prescription Data

- Captures the nationally estimated number of prescriptions dispensed from U.S. outpatient settings
- Over 3.5 billion prescription claims per year, accounting for 88% of U.S. retail prescriptions

Outpatient Prescription Data



Nationally estimated number of naloxone prescriptions in the outpatient retail setting by age, August 2015 to July 2016



Source: IMS Health National Prescription Audit Extended (NPA Extended™). Extracted August 2016.
The *unspecified age group* not shown here = 95 prescriptions

Limitations

- Naloxone sales data are not all-inclusive
 - Distribution outside of typical supply chains (e.g., donations) or outside of traditional settings (e.g., first responders) not captured
- Prescription data are not a direct estimate of total use
 - Recipient of dispensed prescription may not be ultimate recipient of naloxone during overdose event (e.g., guardian)
 - Not all naloxone sold is dispensed, and not all dispensed is used; administered dose unknown
- May underestimate real-world utilization

Naloxone Donations by Manufacturers



- Kaleo (Evzio Auto-Injector)*
 - April 3, 2014 - April 3, 2015: 42,260 devices
 - April 1, 2015 - April 3, 2016: 120,466 devices
- Adapt Pharma Inc. (Narcan Nasal Spray)
 - 50,000 doses to multiple organizations**

*U.S. Food and Drug Administration. FDA Disclosure of Non-Public Information, from NDA 205787's Annual Reports. Silver Spring: Document Archiving, Reporting and Regulatory Tracking System (DARRTS) 2016. DARRTS Electronic Document Room (EDR). 24 Aug 2016.

**Jacobs H. The Price of the “antidote” to the overdose crisis is skyrocketing. *Business Insider*.
<http://www.businessinsider.com/price-of-naloxone-narcan-skyrocketing-2016-7>. Published August 1, 2016.

Summary

- Sales of naloxone products are
 - Increasing in volume
 - Shifting from non-federal hospitals to other settings
- Retail sales of naloxone products intended for use by the general public (Evzio, Narcan Nasal) are rapidly increasing
- Naloxone is being prescribed to pediatric patients

Outline

- Drug utilization databases
 - Sales Distribution Data
 - Dispensed Prescription Data
- **Other data sources**
 - NEMESIS - National Emergency Medical Information System
 - NPDS - National Poison Data System
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Other Data Sources

- National Emergency Medical Services Information System (NEMSIS)
 - Aggregated event-based data voluntarily submitted by EMS agencies from more than 40 states
 - Draft abstract of an analysis of EMS naloxone administration*
 - Naloxone was administered 214,611 times to 173,016 patients by EMS personnel in 2015

*Personal Communication: Peter Lurie , Associate Commissioner for Public Health Strategy and Analysis, FDA. July 20, 2016. Abstract submission in process.

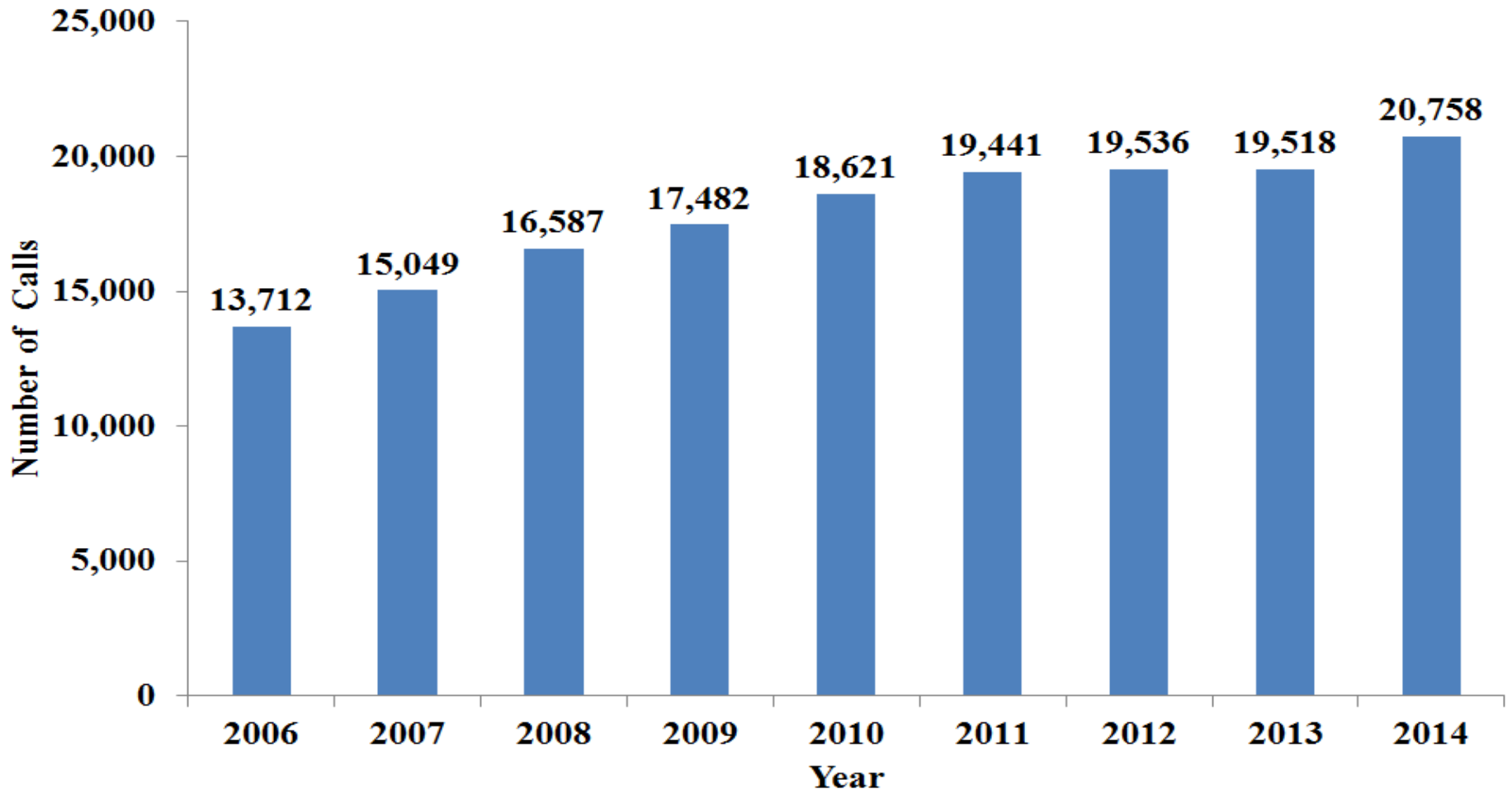
Other Data Sources

- National Poison Data System (NPDS)
 - Case records reflect human poison exposure calls received by poison centers
 - As of 2014, represents all 50 states
 - FDA examined aggregated data from annual reports of exposure calls related to naloxone administration in the U.S. from 2006 to 2014

NPDS Data



Total number of naloxone exposure calls from 2006 to 2014



Other Data Sources

National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES)

- Nationally representative probability sample of 63 hospitals with 24-hour emergency departments (ED)
- Captures Adverse Drug Events (ADEs) that led to ED visits associated with naloxone, excluding those related to abuse

****Insufficient cases involving naloxone to produce reliable national estimates**

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Literature Search Methodology



PubMed was queried for U.S. based observational and randomized studies from the last 10 years

- Focus was on naloxone distribution and utilization in the community by the general public
- Two systematic reviews were identified the larger of which evaluated 22 studies

Identified Systematic Reviews^{1,2}

- Objectives: To evaluate benefits and risks of take home naloxone (THN) programs
 - Overdose mortality in opioid users
 - Adverse events
- Methods: Searched electronic article databases with keywords associated with community distribution programs such as “opioid” and “overdose prevention”

¹McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction*. 2016;111:1177-1187

²Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. *J Addict Med*. 2014;8(3):153-163

McDonald Review Findings*

- Variability in number of THN kits
 - Distributed to participants
 - Used by participants
- Almost all studies reported nearly 100% opioid overdose reversals after THN administration
 - Most common drug to precipitate overdose was heroin
 - Eight studies reported some type of adverse event associated with naloxone administration

* McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction*. 2016;111:1177-1187

Studies Evaluated in McDonald 2016*

Table 3 Included studies: naloxone kits distributed and used, overdose reversals and adverse events.

Study	n	THN kits distributed	THN kits used (%)	Deaths	OD reversal after THN ^e	Unknown outcomes	Adverse reactions
Bennett 2011	426	426	249 (58%)	2	≥ 96%	8	NR
Bennet 2012	525	NR	28 (NR)	1	96%		NR
Dettmer 2001 ^f	101	101	5 (5%)	0	100%		Withdrawal (NR)
Dettmer 2001 ^f	124	124	29 (23%)	0	100%		Withdrawal (10)
Doe-Simkins 2009 ^d	385	385	74 (19%)	0	100%		Withdrawal (2)
Dwyer 2015 ^d	415	56	6 (11%)	0	100%		NR
Enteen 2010	1942	2962	399 (13%)	6	≥ 89%	36	Vomiting (50), agitation (36), seizures (3)
Galea 2006	25	25	10 (40%)	1 ^a	100%	1 ^a	None
Lankenau 2013 ^d	30	30	15 (50%)	0	≥ 97%	1	NR
Leece 2013	209	209	17 (8%)	0	100%		None
Lopez-Gaston 2009	70	70	0 (0%)	1 ^a	NA		NA
Markham Piper 2008	122	122	82 (67%)	0	≥ 83%	14	NR
Maxwell 2006	1120	3500	319 (9%)	1 ^c	99%		Seizures (1), vomiting (1)
McAuley 2010	41	19	2 (11%)	1 ^a	100%		NR
Rowe 2015	2500	2500	702 (28%)	10	99%		NR
Seal 2005	24	24	15 (63%)	0	100%		NR
Strang 2008	239	239	1 (5%)	1 ^a	100%		Withdrawal
Tobin 2009	250	250	22 (9%)	0	100%		NR
Tzemis 2014	692	836	85 (10%)	0	100%		Withdrawal (55), agitation (9)
Wagner 2009	66	66	28 (42%)	4 ^b	NR	5	Agitation (5), vomiting (1)
Walley 2013 [20]	2912	2912	327 (11%)	0	100%		NR
Walley 2013 [33] ^d	1553	1553	92 (6%)	0	100%		NR
Yokell 2011	120	120	5 (4%)	0	100%		NR

^aNaloxone not administered; ^bunclear if naloxone administered; ^cnon-opioids present; NA: not applicable; NR: not reported; OD = overdose; THN: take-home naloxone; ^dnot included in summary measures to avoid (partial) duplication of samples; ^ewhere applicable, unknown outcomes were counted towards unsuccessful THN administrations (as indicated by the ≥ symbol); ^fMulti-site study with two samples: Jersey (n=101) and Berlin (n=124).

*McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction*. 2016;111:1177-1187

Knowlton et al. 2013*

Route of administration and outcomes in Baltimore from 2008-2009

- EMS records evaluated and matched to dispatch records
- Naloxone administered during 1,297 incidents
- Intranasal naloxone was administered most frequently (40%), IV (27%), and IM(22%)
- 1,102 (85%) with recorded status immediately following administration
 - 62% of total incidents improved
 - 23% no change
 - 0.2% worsened
 - 91% involved transport

*Knowlton A, Weir BW, Hazzard F, et al. EMS runs for suspected opioid overdose: implications for surveillance and prevention. *Prehospital Emerg Care Off J Natl Assoc EMS Physicians Natl Assoc State EMS Dir.* 2013;17(3):317-329

Rowe et al. 2015*

Overdose reversals in San Francisco 2010 to 2013

- 702 overdose reversals reported by trained participants
- Heroin reported in 634 (90.3%) of cases
 - In 379 cases (54%) heroin was the only drug reported
 - In 255 cases (36.3%) heroin reported with other substances

*Rowe C, Santos GM, Vittinghoff E, Wheeler E, Davidson P, Coffin PO. Predictors of participant engagement and naloxone utilization in a community-based naloxone distribution program. *Addiction*. 2015;110:1301-1310.

Walley et al. 2013*

Multiple administrations of nasal naloxone from 2006 to 2009 in Massachusetts

- 327 trained participants from 19 communities
- 312 reported rescue attempts
 - 48% used one dose
 - 48% used two doses
 - 4% reported using 3 or more doses

*Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ*. 2013;346:f174

Survey of THN programs Wheeler, 2015*



Survey of 136 managers of THN programs

- In 2013, 644 local opioid overdose prevention sites contributed to the survey
 - 84 community based organizations, 18 health care facilities, 10 VA facilities, 18 state and local health departments, and 6 pharmacies
- Formulations of naloxone
 - 50% of sites provided injectable naloxone
 - 33% provided naloxone packaged in a kit with a nasal mucosal atomizer
 - 10% provided naloxone in both formulations

*Wheeler E, Jones TS, Gilbert MK, Davidson PJ. Opioid Overdose Prevention Programs Providing Naloxone to Laypersons - United States, 2014. *MMWR Morb Mortal Wkly Rep.* 2015;64:631-635.

Survey of THN Programs Wheeler, 2015*



TABLE. Reported number of laypersons receiving or prescribed naloxone kits, overdose reversals, and opioid overdose prevention programs, by survey respondent program size — United States, 1996–June 2014

Category (by size)*	Respondents		Sites		Calendar year 2013				1996—June 2014			
					Laypersons received/ prescribed kits [†]		Opioid overdose reversals [§]		Laypersons received/ prescribed kits [¶]		Opioid overdose reversals ^{**}	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Small (<100)	84	(61.8)	154	(23.9)	1,709	(4.5)	134	(1.7)	7,867	(5.2)	641	(2.4)
Medium (101–1,000)	41	(30.1)	129	(20.0)	7,607	(20.1)	1,351	(16.8)	19,239	(12.6)	4,414	(16.7)
Large (1,001–10,000)	7	(5.1)	62	(9.6)	6,117	(16.1)	4,329	(53.9)	29,099	(19.1)	11,807	(44.6)
Very large (>10,000)	4	(2.9)	299	(46.4)	22,487	(59.3)	2,218	(27.6)	96,078	(63.1)	9,601	(36.3)
Total	136	(100.0)	644	(100.0)	37,920	(100.0)	8,032	(100.0)	152,283	(100.0)	26,463	(100.0)

* Based on reported number of vials of naloxone provided during 2013.

[†] Calendar year 2013 information provided by 93 survey respondents distributing kits/prescribing naloxone during that year, with 36 estimating (6,483 [17.1%] persons) and 57 based on program data (31,437 [82.9%]).

[§] Sixty-eight of 93 respondents distributing kits/prescribing naloxone in 2013 provided information on reported reversals, with 13 estimating (659 [8.2%] reversals) and 55 based on program data (7,373 [91.8%]).

[¶] Estimated by 57 survey respondents (55,201 [36.2%] persons) and 79 based on program data (97,082 [63.8%]).

^{**} Program began in 1996; as of June 2014, 109 respondents distributing kits/prescribing naloxone provided information on reported reversals, with 28 estimating (5,245 [19.8%] reversals) and 81 based on program data (21,218 [80.2%]).

*Wheeler E, Jones TS, Gilbert MK, Davidson PJ. Opioid Overdose Prevention Programs Providing Naloxone to Laypersons - United States, 2014. *MMWR Morb Mortal Wkly Rep.* 2015;64:631-635.

Limitations of Epidemiological Analysis



- Quantity of naloxone distributed and used through non-traditional channels is unknown
- Inferences cannot be made on effectiveness of naloxone in the community
 - THN programs lack sufficient detail on the overdose event – e.g., participant retention/attrition rates, outcomes
 - Multiple administrations may be increasing but cause is unknown – e.g., error in administration, potency of drug, offending agent
- Additional data needed on: setting of overdose event, formulations/doses used, and outcomes

Summary of Epidemiological Analysis



- State and local policies are expanding access to naloxone through non-traditional channels
 - Police and EMS administer but may not obtain naloxone from traditional channels
- Multiple naloxone administrations occur, but data are limited
- Published data generally restricted to EMS and THN programs

Overall Conclusion

- National trends of naloxone sales and more granular utilization data show increasing trends in the community availability of naloxone
- More data are needed to better understand national patterns of naloxone distribution, utilization, dosing, and effectiveness

