Community Response and Best Practices for Opioid Antagonists

Advancing Compassionate Overdose Response Strategies in Nevada

Nevada Opioid Center of Excellence
School of Public Health

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- Dr. Wagner is funded by multiple research grants from the National Institutes of Health to study opioid overdose substance use harm reduction.
- In 2024 Dr. Wagner participated in the Compassionate Opioid Overdose Response Summit, hosted by Health Management Associates. She received no funding or support for that participation.
- Dr. Wagner is a former member of the Advisory Committee for a Resilient Nevada, the Multidisciplinary Prevention Advisory Committee, and the Governor's Substance Use Response workgroup; and has provided testimony as a subject matter expert for the Nevada Legislature.

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- Mr. Delise is funded by a SAMHSA grant related to substance use, opioids, and naloxone. He also contributes in-kind under several grants in these areas.
- Mr. Delise is a member of the Clark County Opioid Task Force.

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Webinar Roadmap

- Evolution of the opioid overdose death crisis in the US and Nevada
- History of naloxone distribution as a community-based response to prevent opioid overdose deaths
- Naloxone product options
- Significance of rescue breathing and opioid withdrawal
- Data on naloxone dosing
- Implications and next steps

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Learning Objectives:

By the end of this webinar, attendees will know:

1. **The history of overdose prevention and opioid antagonist distribution for community members, including available formulations of antagonists**
2. **State of the research on opioid antagonist distribution, utilization, and outcomes in the community**
3. **Evidence-based practices for overdose response and opioid antagonist administration**

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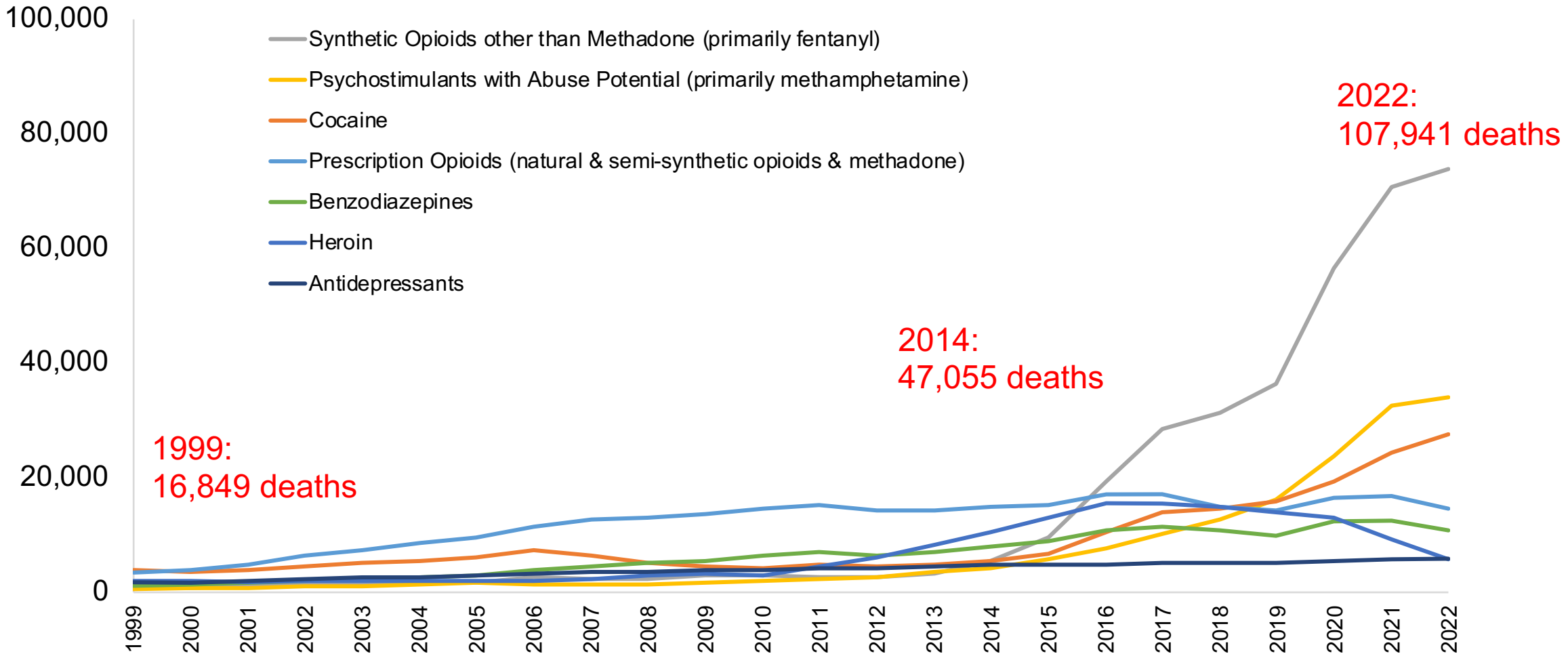
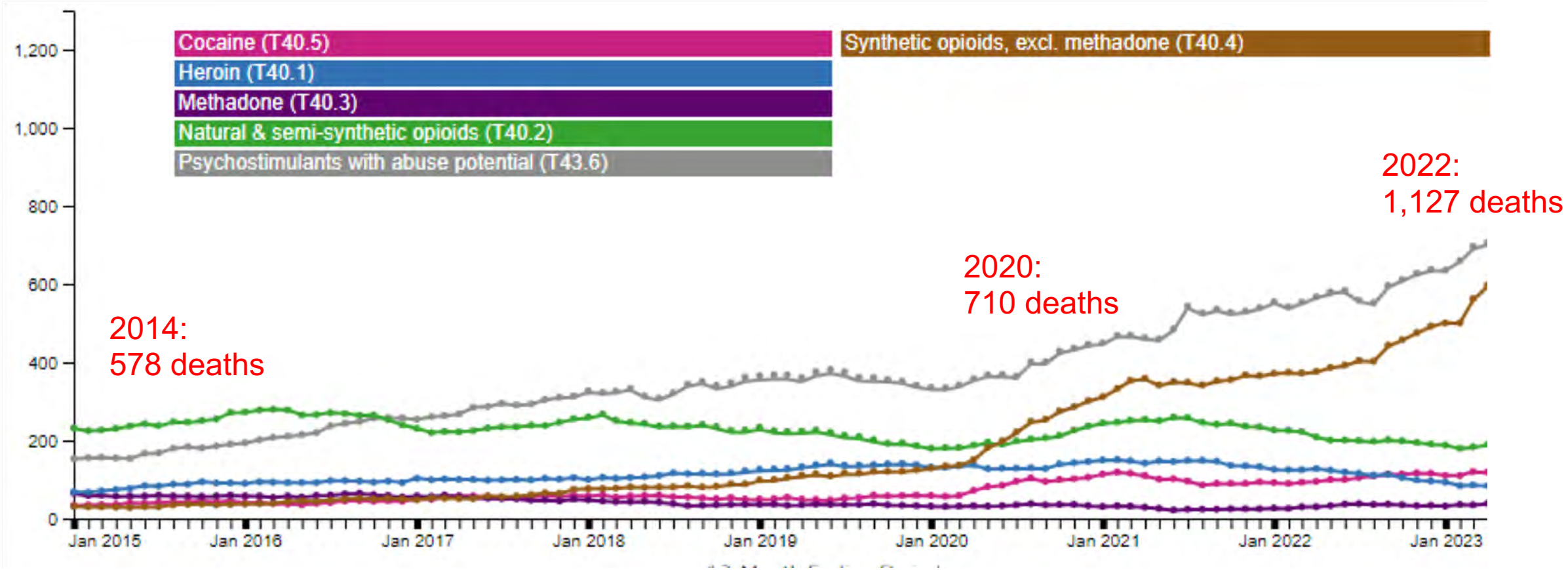
Fentanyl made an already bad problem worse

National Drug Overdose Deaths*, Number Among All Ages, 1999-2022



Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2022 on CDC WONDER Online Database, released 4/2024.

Nevada Drug Overdose Deaths*: Number among all ages, (2015-2022)



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Source: Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics Program, based on data available 6/2024..

The Facts About Fentanyl

- **Synthetic opioid that causes respiratory depression**
- **Partly responsible for the current opioid crisis in the US**
- **More potent than morphine or heroin (so you need less to have the same effect)**
- **Used routinely in clinical practice (e.g., to treat pain), in setting where respiration can be monitored and supported**

Common Fentanyl Myths

Myth	Truth
Touching, handling, or being in the same room as fentanyl can cause an overdose	Fentanyl cannot be absorbed through the skin by touching powder, or touching something like a doorknob or dollar bill
All illicit drugs have fentanyl in them	Fentanyl has been detected in many illicit drugs, including fake pills, opioids, and simulants. But studies show only about 20% of stimulant samples are positive for fentanyl.
People are being ‘tricked’ into using fentanyl	Some people use fentanyl deliberately, while others are exposed accidentally through unregulated drugs
Fentanyl overdoses are “naloxone resistant”	Opioid antagonists like naloxone *can* reverse fentanyl overdoses

History of naloxone distribution in the US

- **Used since the 1970s in clinical settings to reverse acute opioid intoxication**
- **1996, Dan Bigg and the Chicago Recovery Alliance started community-based distribution**
- **Naloxone access laws passed by states to facilitate access:**
  - 2001 New Mexico
  - 2015 Nevada
  - 2017 Every state in the US

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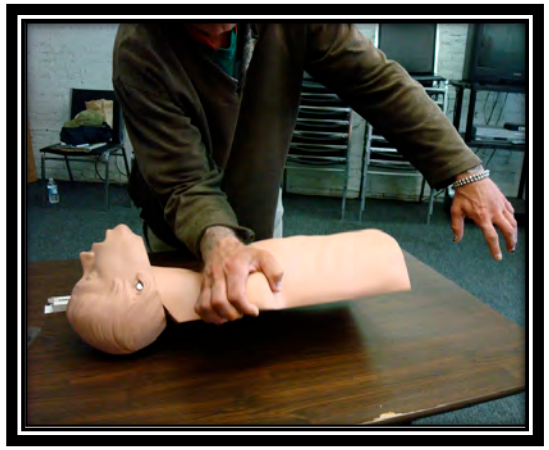
Overdose Response Training Should Teach People to:

- ***Prevent***
  - Avoid mixing drug
  - Use less after periods of abstinence
- ***Recognize***
  - Slow/stopped breathing
  - Unresponsive
  - Blue lips/nails
- ***Respond***
  - Call 911
  - Give rescue breathing
  - Give naloxone
  - Support breathing until help arrives



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Early research showed that giving naloxone to people who use drugs:

- **Improves knowledge about overdose risks and symptoms**
- **Improves overdose response**
- **Improves confidence in ability to give naloxone**
- **Does NOT increase drug use**

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Citations: Dettmer 2001, Seal 2005, Galea 2006, Green 2008, Strang 2008, Doe-Simkins 2009, Tobin 2009, Enteen 2010, Wagner 2010, Bennet and Holloway 2012, Dwyer 2013, Lankenau 2013, Jones 2014, Ashrafioun 2016, Jones 2017)

Early public health experience and data showed:

- **People who use drugs report more naloxone use than anyone else**
- **Achieving "saturation" of communities with naloxone is effective when targeted to people who use drugs**
- **Harm Reduction programs research the most people who use drugs in the country**

Citations: Seal 2005, Tobin 2009, Bird 2015, Behar 2015, Siegler 2017, Keane 2018

Rescue breathing is a critical step in overdose response

Mechanism of opioid overdose death = respiratory depression

- Opioids (no matter what kind) suppress the spontaneous drive to breathe

Therefore, an effective opioid overdose response MUST support respiration

- Administering an opioid antagonist is one way to restore respiration
- Rescue breathing or supportive oxygen is another
- Goal is to restore breathing, which may happen BEFORE the person “wakes up”

Rescue breathing is hard to teach and training is rare, but critical. This is complicated by:

- Lack of training opportunities
- COVID-19 concerns
- Conflict with AMA “hands only chest compressions” for CPR training

Opioid withdrawal is painful and can cause harm

Historically, we have minimized the risk – "you can't give someone too much naloxone"

Experience now shows us that inducing severe and painful withdrawal symptoms by giving too much naloxone:

- May cause people to use alone (a risk factor for death) to avoid being overmedicated next time
- May cause people to avoid calling 911 and getting emergency medical help or refuse care
- Can cause people to use more opioids to alleviate the symptoms
- Makes people feel punished and stigmatized
- Can cause agitation directed towards the first responder

When he awoke, he began vomiting so much he reported he could not breathe and experienced extreme anxiety. “I tried to re-dose with heroin every 15 minutes to feel anything other than this horrible feeling.

Mr. Visnich reported: “For months after that bad overdose, I was super hesitant to use around others. I mostly wanted to use alone to avoid something like that from happening again which put me at great risk.”

Malcolm Visnich, Prevention Point Pittsburgh

Research On Opioid Withdrawal

- Anger and withdrawal are not always reported together
- Withdrawal can be avoided
- Titrating opioid antagonist to lowest effective dose can help avoid withdrawal
- Gentle communication can prevent anger/agitation

Addiction
SSA
RESEARCH REPORT
doi:10.1111/add.13(

Naloxone—does over-antagonism matter? Evidence of iatrogenic harm after emergency treatment of heroin/opioid overdose

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Factors associated with withdrawal symptoms and anger among people resuscitated from an opioid overdose by take-home naloxone: Exploratory mixed methods analysis

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Currently Available Formulations

	Injectable				One-step Nasal					
	Generic			Branded	Over-the-Counter			Single step		
Brand name	Generic injectable	Generic luer-lock for injectable or nasal		Zimhi Injection	ReVive Nasal Spray	Narcan Nasal Spray	Amneal Nasal Spray	Generic nasal	Kloxxado Nasal Spray	Opvee Nasal Spray
Image										
Assembly required	X	X	X							
Can titrate dose	X	X	X							
Concentration	Naloxone 0.4 mg/mL	Naloxone 1 mg/mL	Naloxone 1 mg/mL	Naloxone 5 mg/0.5 mL	Naloxone 3mg/0.1 mL	Naloxone 4 mg/0.1 mL	Naloxone 4 mg/0.1 mL	Naloxone 4 mg/0.1 mL	Naloxone 8mg/0.1mL	Nalmafene 0.27mg/0.1mL
Cost/kit[1]	$	$$	$	$$$	$	$		$$	$$$	$$

Price as of February 2024:
$ = $0-$50
$$ = $50.01 - $100
$$$ = above $100.01

"Standard dose" is
4mg Intranasal or 0.4/1ml Injectable

May 2024 update: https://prescribetoprevent.org/wp2015/wp-content/uploads/May-2024-Naloxone-comparison.pdf

Comparison of 8mg and 4mg intranasal naloxone administration by law enforcement

8mg IN naloxone has twice the amount of the standard 4mg dose

Law enforcement officers in New York responded to 354 overdoses between March 2022 and August 2023

Researchers examined differences in:

- Average number of doses administered per patient
- Rate of survival
- Post-naloxone withdrawal, vomiting lethargy, disorientation, anger or combativeness, hospital transport refusal

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Citation: Payne et al. (2024) MMWR Morb Mortal Wkly Rep 2024;73:110–113.
DOI: http://dx.doi.org/10.15585/mmwr.mm7305a4.

What did they find from the study of law enforcement administration?

No differences between those who got 4mg and 8mg in:

- Survival
- Number of doses received
- Most withdrawal symptoms
- Combativeness
- Hospital transport refusal

Implication: using the higher dose opioid antagonist did provide any additional benefit

Observational study of naloxone dosing by people who use drugs after introduction of fentanyl

- **Prevention Point Pittsburgh has been distributing naloxone since 2005**
  - Kits contained either 2 single-dose of injectable 0.4mg/1mL naloxone or 2 single-dose of intranasal 4mg nasal spray
- **Started seeing fentanyl deaths increase in 2013**
- **Compared naloxone doses given by program participants to determine if more doses were needed over time**

What did they find from the study of naloxone dosing among people who use drugs?

2013 - 3% of deaths in the county involved fentanyl

- 89.3% of overdoses were reversed with 1-2 doses
- Average number of naloxone doses used was 1.62 (i.e., between 1 and two doses of naloxone per person)

2016 - 68% of deaths in the county involved fentanyl

- 92.6% of overdoses were reversed with 1-2 doses
- Average number of naloxone doses used was 1.52 (i.e., between 1 and two doses of naloxone per person)

Implication: the average number of doses needed to reverse overdoses did not increase as fentanyl became more common (this has persisted through 2023)

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Citation: Bell, A., et al. (2019). Substance Abuse, 40(1), 52-55.

NALOXONE ADMINISTRATION ANALYSIS

Brandon Delise

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Southern Nevada Health District

Data Sources

- ***SNHD Naloxone Administration Survey (Alchemer)***
- Uniformed first responders & lay responders
- ***SNHD's Linkage to Action (L2A) Naloxone Administration Survey (Excel)***
- People who use drugs / substance users
- ***ESO - Emergency Medical Services (EMS) Data***
- EMS providers

SNHD NALOXONE ADMINISTRATION SURVEY
(UNIFORMED FIRST RESPONDERS & LAY RESPONDERS)

	1 Dose (Survival Rate)	2 Dose (Survival Rate)	3 Dose (Survival Rate)	4 Dose (Survival Rate)	5+ Doses (Survival Rate)	All Dose Survival Rate	Proportion 1 2 Doses 4Mg
2021	15/15 (100%)	7/7 (100%)	0	0	0	100% (22/22)	100%
	22/23 (95.7%)	8/8 (100%)	3/3 (100%)	0	0	97.10% (33/34)	88.24%
2023	69/71 (97.1%)	41/43 (95.3%)	11/12 (91.7%)	4/4 (100%)	3/3 (100%)	96.20% (125/130)	84.62%
	29/29 (100%)	36/37 (97.3%)	11/12 (91.7%)	4/4 (100%)	1/1 (100%)	97.60% (80/82)	79.27%

Data retrieved on 06/25/2024.
Data source: SNHD Naloxone Administration Survey (Alchemer)
2024 data are preliminary and subject to change

SNHD Naloxone Administration Survey Limitations

- Low Response Rate
- Recall Bias
- Incomplete Data
- Self-Reporting Inaccuracies
- Lack of Standardization
- Time Constraints
- Data Entry Errors
- Limited Context
- Responder Fatigue
- Privacy Concerns

L2A NALOXONE ADMINISTRATION LOG (PEOPLE WHO USE DRUGS)

			3 Dose (Survival Rate)	4 Dose (Survival Rate)	5+ Doses (Survival Rate)	All Dose Survival Rate	Proportion 1 2 Doses 4Mg
	58/59 (98.3%)		16/17 (94.1%)	8/8 (100%)	4/4 (100%)	97.65% (166/170)	
2024	95/96 (99.0%)	104/105 (99.0%)	16/16 (100%)	7/7 (100%)	2/2 (100%)	99.11% (222/224)	88.84%

Data retrieved on 06/25/2024.
Data source: L2A Naloxone Administration Log
2024 data are preliminary and subject to change

L2A Naloxone Administration Log Limitations

- Low Response Rate
- Recall Bias
- Incomplete Data
- Self-Reporting Inaccuracies
- Lack of Standardization
- Time Constraints
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Mg	2021	% of Total	2022	% of Total	2023	% of Total	2024	% of Total
0.1	5	0.12		0.00	2	0.02		0.00
0.2		0.00	6	0.10	30	0.37	1	0.03
0.25	12	0.28	7	0.12	7	0.09	18	0.61
0.3	1	0.02	5	0.09	2	0.02		0.00
0.4	44	1.02	41	0.71	78	0.95	34	1.14
0.5	427	9.87	539	9.34	811	9.90	365	12.28
0.6	2	0.05	4	0.07	9	0.11		0.00
0.75		0.00		0.00	1	0.01	1	0.03
0.8	2	0.05	2	0.03	6	0.07	3	0.10
1	1011	23.36	1144	19.83	1551	18.93	650	21.86
1.2	4	0.09	1	0.02	2	0.02		0.00
1.5	26	0.60	52	0.90	29	0.35	14	0.47
1.6	1	0.02	2	0.03	1	0.01		0.00
2	2404	55.56	3393	58.82	4932	60.18	1539	51.77
2.5	24	0.55	27	0.47	21	0.26	22	0.74
3	9	0.21	9	0.16	55	0.67	4	0.13
3.5		0.00		0.00	4	0.05		0.00
4	272	6.29	418	7.25	503	6.14	238	8.01
5	27	0.62	45	0.78	35	0.43	29	0.98
6	5	0.12	10	0.17	11	0.13	1	0.03
8	2	0.05	13	0.23	32	0.39	20	0.67
10	3	0.07	4	0.07	10	0.12		0.00
12		0.00	5	0.09	11	0.13	2	0.07
16		0.00	1	0.02	17	0.21	2	0.07
20	2	0.05	4	0.07	5	0.06	5	0.17
>20	44	1.02	36	0.62	30	0.37	25	0.84
Total	4327		5768		8195		2973	

Data retrieved on 06/25/2024.
Data source: ESO

EMS DATA (EMS PROVIDERS)

EMS DATA (CONT.)

	2021	2022	2023	2024
<=4mg	98.08%	97.95%	98.16%	97.17%
<=8mg	98.87%	99.13%	99.11%	98.86%
> 8mg	1.13%	0.87%	0.89%	1.14%

	% Change 2021-2023
<=4mg	0.082%
<=8mg	0.243%
>8mg	-21.239%

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Data retrieved on 06/25/2024.
Data source: ESO

Considerations: IM and IV Vs. IN

Intramuscular (IM) and Intravenous (IV) Administration:

- *Naloxone administered IM or IV (compared to intranasal) is directly delivered into the bloodstream.*
- *Results in higher bioavailability and a quicker onset of action.*
- *Smaller doses are generally effective.*
- *Typical starting dose: 0.4 mg to 2 mg.*

Intranasal (IN) Administration:

- *Naloxone administered intranasally is absorbed through the nasal mucosa into the bloodstream.*
- *Results in lower bioavailability compared to IM or IV routes.*
- *Higher doses are usually required to achieve the same therapeutic effect.*
- *Typical starting dose: 2 mg to 4 mg.*

Withdrawal Symptoms:

Withdrawal symptoms induced by naloxone are more likely to be pronounced with IM or IV administration compared to IN administration.

EMS Limitations

- ***No survival outcome (captured but not complete)***
- ***Use different formulations (including different doses) of naloxone***
- ***Only used milligram's (Mg) for analysis***
- Mg made up the largest proportion of naloxone administration (roughly 71%)

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Conclusion

- **SNHD Survey Findings**: Our survey data suggest that 1-2 doses of 4mg IN naloxone is sufficient for reversing opioid overdoses, which is supported by high survival rates.

- **EMS Data**: EMS data indicate that *a very high proportion of naloxone administrations by providers consist of* doses of 8mg or less. However, multiple factors such as different naloxone formulations (IM, IV, and IN) and varying dosing methods should be taken into account.

References

- *Jones, H. E., O'Grady, K. E., Malfi, D., Tuten, M., & Svikis, D. S. (2020). Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in patients with opioid use disorder. Addiction, 115(11), 2100-2108. https://doi.org/10.1111/add.15806*
- *Lynch, K. L., & Yellig, S. A. (2008). Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in healthy volunteers. Journal of Drug Monitoring, 30(4), 421-428. https://journals.lww.com/drug-monitoring/abstract/2008/08000/population_pharmacokinetics_of_intravenous,.13.aspx*
- *Zedler, B. K., Mann, A. L., Kim, M. M., Amick, H. R., Joyce, A. R., Murrelle, E. L., & Jones, H. E. (2019). Naloxone dose for reversing opioid overdose: A systematic review. JAMA Network Open, 2(11), e1912900. https://jamanetwork.com/journals/jamanetworkopen/article-abstract/2755306*

Naloxone in its lowest dose is effective

Generic intramuscular 0.4mg/1ml naloxone is effective in reversing opioid overdoses– including fentanyl overdoses

Type	Amount	Comparison to lower dose products
Narcan & generic nasal sprays	4mg (nasal)	Roughly equivalent to 1 dose of 0.4mg/mL injectable naloxone
Kloxxado nasal spray	8mg (nasal)	2x a standard 4mg nasal or 0.4mg injectable
Zimhi injectable	5mg (injected)	12.5 vials of 0.4mg injectable naloxone

So why are people talking about needing more/higher dose naloxone?

Not waiting long enough between doses

- *Naloxone can take 2-5 minutes to work, but one study showed that law enforcement officers waited only 53 seconds between doses (White 2022).*
- *Recommendation: Wait 2-5 minutes between doses, keep giving rescue breathing*

Xylazine complicates overdose response

- *If someone has taken xylazine, they might not "wake up" even though their breathing is restored*
- *Recommendation: Look for restored breathing, even if they don't wake up – keep giving rescue breathing and give additional doses after waiting 2-5 minutes*

People think that giving more naloxone or higher doses will speed up the reversal process

- *Overmedication with naloxone may cause more serious and painful withdrawal*
- *Recommendation: give the lowest dose needed to restore breathing*

Citation: White et al. (2022). *American journal of public health*, *112*(9), 1326-1332.

What do we do with this information?

New synthetic drugs like fentanyl and xylazine are complicating overdose response, but the basics still apply:

- Give rescue breathing until spontaneous breathing is restored (1 breath ~ every 5 seconds)
- Overdoses may take longer to reverse and people may not “wake up” – breathing is most important
- Give lowest effective does of naloxone required to restore breathing
- Wait 3 minutes for naloxone to work, keep breathing for them and give additional doses as needed

Overmedication with too much opioid antagonist can cause harms

What do we do for people who are using alone?

- **Using drugs alone without someone to respond is the most significant predictor of overdose death.**
- **In 2022 59.4% of overdose deaths in Nevada occurred inside, and 56.5% had no bystander present (OD2A)**
- **Naloxone is only effective if there is someone there to give it.**
- **People use alone for many reasons: stigma, criminalization, lack of social support, fear.**
- **How do we reduce risk for people who use alone?**

For more information & access to naloxone:

CASAT-Outside of Southern Nevada

- **Where to get naloxone?**

www.nvopioidresponse.org

- **To become a naloxone distribution site or schedule overdose education please reach out to: noce@casat.org**

Southern Nevada Health District

- ***Where to get naloxone?***

Email: OD@SNHD.ORG

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