Housekeeping

REAGAN-UDALL FOUNDATION FOR THE FDA

Due to the meeting size, your microphone and video will remain off during the meeting.

This public meeting is being recorded. The slides, transcript, and video recording will be available on the FDA Foundation website after the meeting.

While we won't have time to directly address audience questions during today's meeting, you may use the chat function for comments.

Today's Agenda

REAGAN-UDALL FOUNDATION FOR THE FDA

1 p.m.	Welcome & Day 1 Recap – Susan C. Winckler, RPh, Esq.
1:05 p.m.	Session 4: Novel Approaches to Preventing Overdose Deaths
2:05 p.m.	Session 5: Regulatory Considerations for Developing Opioid Overdose Management Products
2:25 p.m.	Session 6: Considerations for Opioid Overdose Management Product Development
3:40 p.m.	Session 7: Future Directions
4:45 p.m.	Adjourn

Session 4: Novel Approaches to Preventing Overdose Deaths

REAGAN-UDALL FOUNDATION FOR THE FDA

Presenter

Mary Sylla, JD, MPH
National Harm Reduction Coalition

Reactor Panel

Mark Lysyshyn, MD, MPH
Vancouver Coastal Health

Jermaine Jones, PhD
Columbia University Irving Medical Center

Emanuel Sferios, MA
DanceSafe

CAPT Jennifer Fan, PharmD, JD
Substance Abuse and Mental Health Services Administration

Novel Approaches to Overdose Prevention

March 9, 2023

Mary Sylla, JD, MPH
Director of Overdose Prevention Policy & Strategy

NATIONAL HARM REDUCTION COALITION

National Harm Reduction Coalition creates spaces for dialogue and action that help heal the harms caused by racialized drug policies.

Policy & Advocacy

National & Regional Conferences

Trainings & Technical Assistance

Overdose Prevention

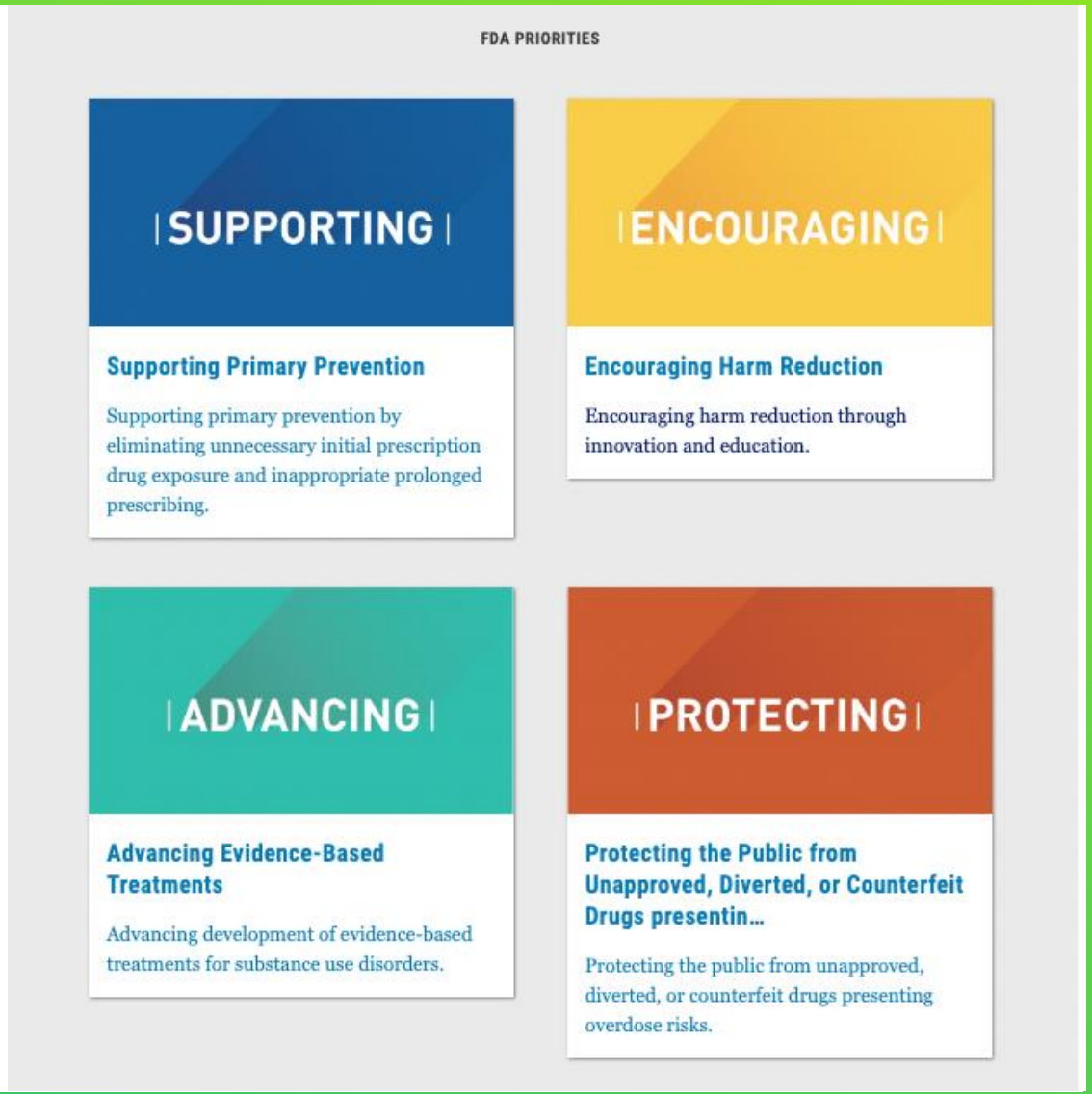
Resources & Publications

Reagan Udall Setting & Audience

NATIONAL
HARM REDUCTION
COALITION

FDA Priorities

Include “Encouraging Harm Reduction”



Ways to Increase Naloxone Access for People Who Use Drugs

NATIONAL HARM REDUCTION COALITION

Novel Low Barrier Programs

NEXT Distro

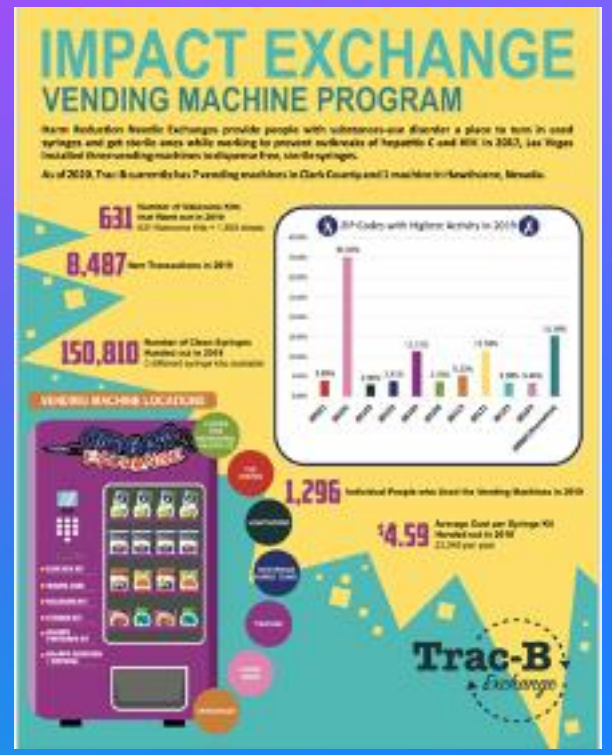
STAY ALIVE, STAY SAFE.

DRUG OVERDOSE the d.o.p.e. PROJECT PREVENTION EDUCATION

Access Point of GA

Harm Reduction Services & Recovery Resources

DANCESAFE



Vending machines dispensing free, life-saving medication

Seven county jail lobbies in NC are home to an emerging strategy for naloxone distribution at a time when drug overdoses continue to climb.

> MMWR Morb Mortal Wkly Rep. 2020 Aug 21;69(33):1117-1121. doi: 10.15585/mmwr.mm6933a2.

Overdose Education and Naloxone Distribution Within Syringe Service Programs – United States, 2019

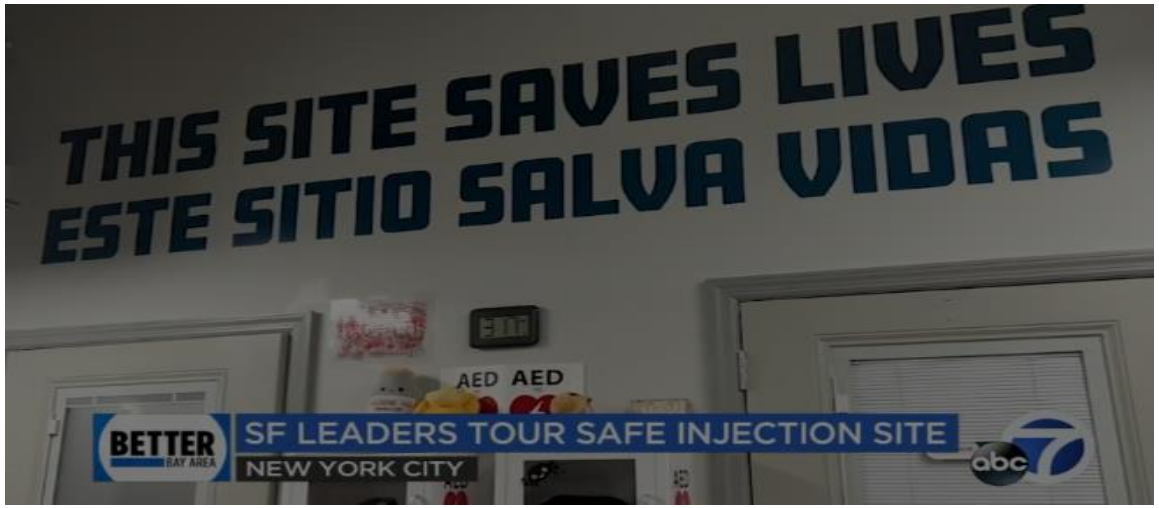
Barrot H Lambdin, Ricky N Bluthenthal, Lynn D Wenger, Eliza Wheeler, Bryan Garner, Paul Lakosky, Alex H Kral

Overdose Prevention Centers

NATIONAL
HARM REDUCTION
COALITION

Legislation pending to authorize OPCs in

Colorado, Connecticut, Illinois, Maryland, Massachusetts, New Mexico, New York and Vermont



WASHINGTON HEIGHTS CORNER PROJECT & NEW YORK HARM REDUCTION EDUCATORS
ONPOINT NYC
Serving NYC since 1992

CIVIL ACTION No. 19-0519
UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF PENNSYLVANIA

United States v. Safehouse

Decided Feb 25, 2020

PREVENT OVERDOSE RI

Ways to Reduce the Cost of Naloxone

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Remedy Alliance Model

Injectable Naloxone at very low cost

Remedy Alliance
For The People

Exemption and Exclusion From Certain Requirements of the Drug Supply Chain Security Act for the Distribution of FDA-Approved Naloxone Products During the Opioid Public Health Emergency Guidance for Industry[1]

Permitted by FDA

Allows harm reduction programs and harm reduction suppliers to buy naloxone wholesale and distribute it under an exception to tracing, licensing and reporting requirements of federal law.

Over the Counter Naloxone

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COALITION

Real World Impact Remains to be Seen

What we don’t know yet:

- Price
- Impact on Insurance Coverage
- Pharmacy Willingness to Carry

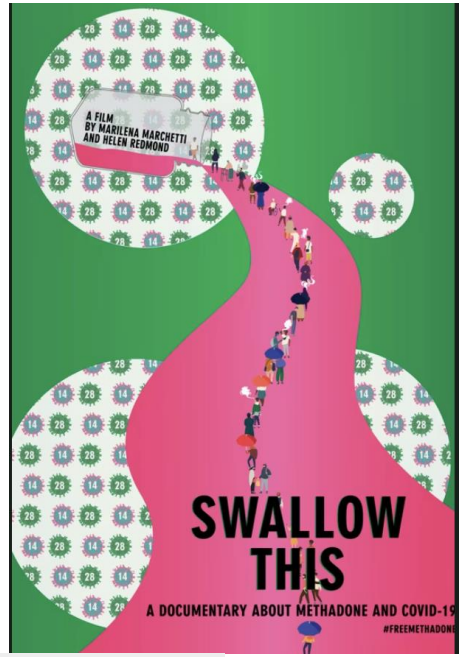
Lower Barriers to Treatment

NATIONAL
HARM REDUCTION
COALITION

Buprenorphine and Methadone

Buprenorphine: Access has been made easier by the MAT Act eliminating the X-waiver requirement for prescribers

Methadone: Highly regulated and controlled in a way that interferes with the ability of people to engage in employment, travel and other activities while in treatment



S.644 - A bill to expand the take-home prescribing of methadone through pharmacies.

118th Congress (2023-2024) | Get alerts

Drug Checking

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COALITION

Fentanyl Test Strips and Spectrometers

Drug paraphernalia laws amended to permit test strips in many places

Remain a challenging and imperfect response to the overdose crisis

CONCLUSION

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HARM REDUCTION
COALITION

THANK YOU FOR LISTENING!

Mary Sylla
sylla@harmreduction.org

harmreduction.org

NATIONAL HARM REDUCTION COALITION

Session 5: Regulatory Considerations for Developing Opioid Overdose Management Products

REAGAN-UDALL FOUNDATION FOR THE FDA

Presenter

Srikanth C. Nallani, PhD
U.S. Food and Drug Administration

Regulatory Considerations for Developing Opioid Overdose Management Products

Srikanth C. Nallani, Ph.D.

Clinical Pharmacologist

Division of Neuropsychiatric Pharmacology,

Office of Clinical Pharmacology, CDER, FDA

Outline

- Approved Opioid Antagonist Drugs
  - Naloxone, Nalmefene and Naltrexone
    - Mechanism of action
    - Indication and Usage
    - Dosage and Administration
- Clinical Pharmacology Considerations for a Bioavailability (BA) Study to Fulfill 505(b)(2) Requirements

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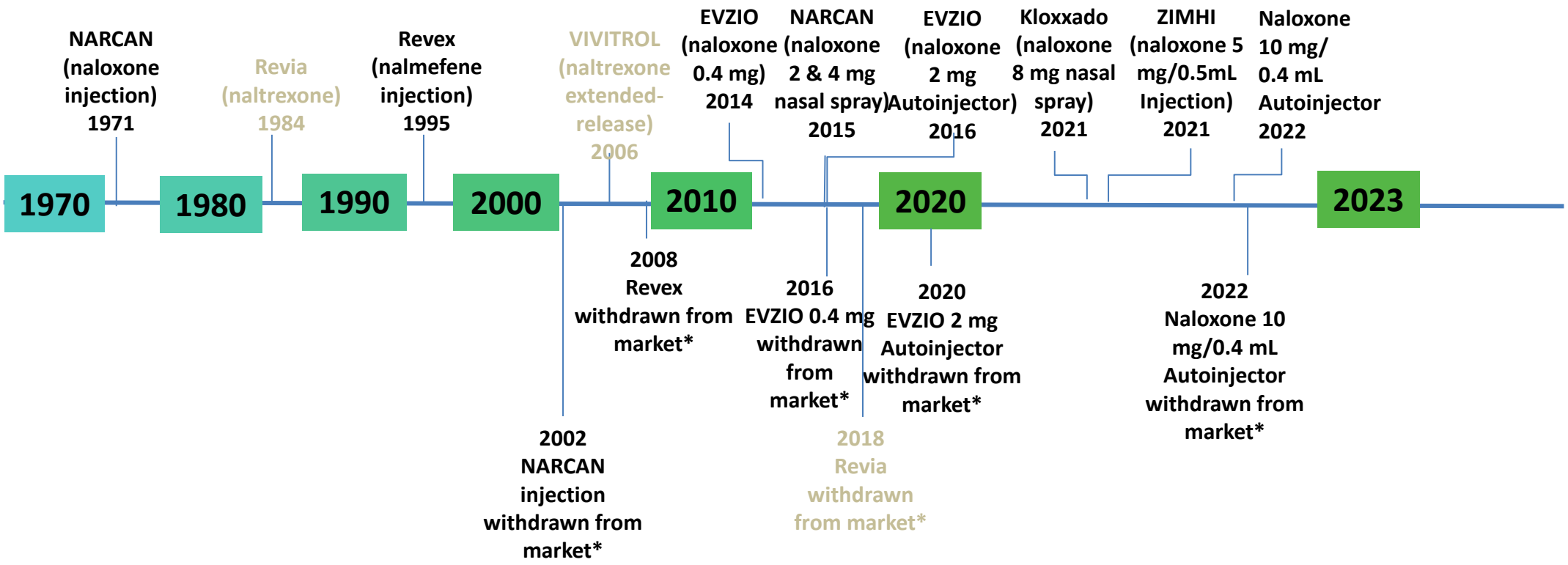
Opioid Antagonist Product Timeline



(* Withdrawn from market, not due to safety or efficacy concerns per *Federal Register/Orange book*)

Timeline is not to Scale

Opioid Antagonists
Mechanism of Action

- Naloxone
  - It is an essentially pure opioid antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists.
  - Prevents or reverses the effects of opioids including respiratory depression, sedation and hypotension.
- Nalmefene
  - It is an opioid antagonist with no agonist activity.
  - It has no demonstrated abuse potential, is not addictive, and is not a controlled substance.
- Naltrexone
  - It is an opioid antagonist with highest affinity for the mu opioid receptor. Naltrexone has little or no opioid agonist activity.

Indications and Usage

- Naloxone Injection
  - complete or partial reversal of opioid depression, including respiratory depression.
  - the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
  - is intended for immediate administration as emergency therapy in settings where opioids may be present.
  - is not a substitute for emergency medical care.
- Naloxone Nasal Sprays
  - for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
  - for immediate administration as emergency therapy in settings where opioids may be present.
  - is not a substitute for emergency medical care.

Indications and Usage

- Nalmefene Injection
  - Indicated for the complete or partial reversal of opioid drug effects, including respiratory depression, induced by natural or synthetic opioids.
  - Indicated in the management of known or suspected opioid overdose.

Dosage and Administration

- Narcan (naloxone HCl) Injection and generic products.
  - Narcan Injection (NDA 16636) is no longer on market.
  - Several generic products (ANDAs) are available.
- Naloxone Injection: Opioid Overdose–Known or Suspected: Usage in Adults
  - An initial dose of 0.4 mg to 2 mg of naloxone injection may be administered intravenously.
  - If the desired degree of counteraction and improvement in respiratory functions are not obtained, it may be repeated at two- to three-minute intervals.
  - If no response is observed after 10 mg of naloxone Injection have been administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned.
  - Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Dosage and Administration

- Revex (nalmefene HCl) Injection and generic products.
  - Revex Injection (NDA 20459) is no longer on market.
  - Generic product (ANDA) is available.
- Nalmefene Injection - Management of Known or Suspected Opioid Overdose:
  - The recommended initial dose for non-opioid dependent patients is 0.5 mg/70 kg. If needed, this may be followed by a second dose of 1.0 mg/70 kg, 2-5 minutes later.
  - If a total dose of 1.5 mg /70 kg has been administered without clinical response, additional nalmefene is unlikely to have an effect.
  - Repeated Dosing: Nalmefene is the longest acting of the currently available parenteral opioid antagonists. If recurrence of respiratory depression does occur, the dose should again be titrated to clinical effect using incremental doses to avoid over-reversal.

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Clinical Pharmacology Considerations for a Bioavailability Study to Fulfill 505(b)(2) Requirements

Clinical Development Pathway

- Agency recognizes
  - Life-threatening nature of opioid overdose.
  - Evolving nature of fentanyl-related substance use and other concomitant substances in community.
  - Ethical and logistical issues around conducting an efficacy trial.
- 505(b)(2) regulatory pathway allows for
  - Establishing a scientific bridge between new product (test) and FDA approved drug (reference) by means of a relative bioavailability study.
  - Reliance on the Agency's safety and efficacy findings as described in an approved label of the reference drug (antagonist drug).
  - Relative bioavailability study can support naloxone product safety and efficacy.
  - However, additional studies may be needed for nalmefene to support reversal of opioid overdose.
  - Specific scenarios and limitations may be discussed with the Agency.

Considerations for Drug-Device Development

- Drug-device product should be preassembled
  - Mainly for caregiver or emergency medical service personnel to administer to the patient.
  - A preassembled device avoids the need for any assembly and potential mistakes during the assembly.
- Product for use in all age groups (pediatrics included)
  - Limitations of use may be discussed with the Agency.
- Recognize that these products are a stop gap measure while waiting for arrival of emergency medical services.
  - CALL 911 after administering the first dose of the product. Additional supportive/resuscitative measures may be helpful.

Considerations Prior to a BA Study

- A pilot dose-selection study may be helpful to understand:
  - Systemic exposure at early time points, and peak exposure (Cmax and AUC).
  - Need for bracketing test product exposure (Cmax, AUC, partial AUCs) between lowest approved dose (for example, SC/IM injection) and highest approved dose (IV bolus) of antagonist drug. (See slides 7 and 8).
  - Sample size determination.

BA Study Design Considerations

- Open-label, randomized, crossover, single-dose pharmacokinetic study.
- Healthy male and female volunteers of 18 years of age or older who are capable of giving informed consent.
- Test Drug: To-be-marketed product (dose, formulation and device)
  - Focus on achieving higher exposure at early timepoints.
- Reference Drug:
  - US FDA approved Original product or Generic product as a reference drug.
  - Use label recommended dose and route (See slides 7 and 8).

BA Study Design Considerations

- Adequate sample size.
- Adequate wash-out period.
- Adequate blood samples to cover the full PK profile of drug.
  - Emphasis on early timepoints up to 30 minutes. For example, 2, 3, 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180, minutes and up to 5 half lives.
  - Analyte: Drug of interest (For example, naloxone or nalmefene).
- The study condition (e.g., dose and administration method) needs to represent the proposed labeling recommendation.
  - Nasal spray: Subjects should be in supine position.
  - Parenteral product (IM/SC routes): Impact of site of injection (upper outer arm, abdomen, thigh, etc.) on pharmacokinetics may need to be addressed.
- Limitations of use or other considerations may be discussed with the Agency.

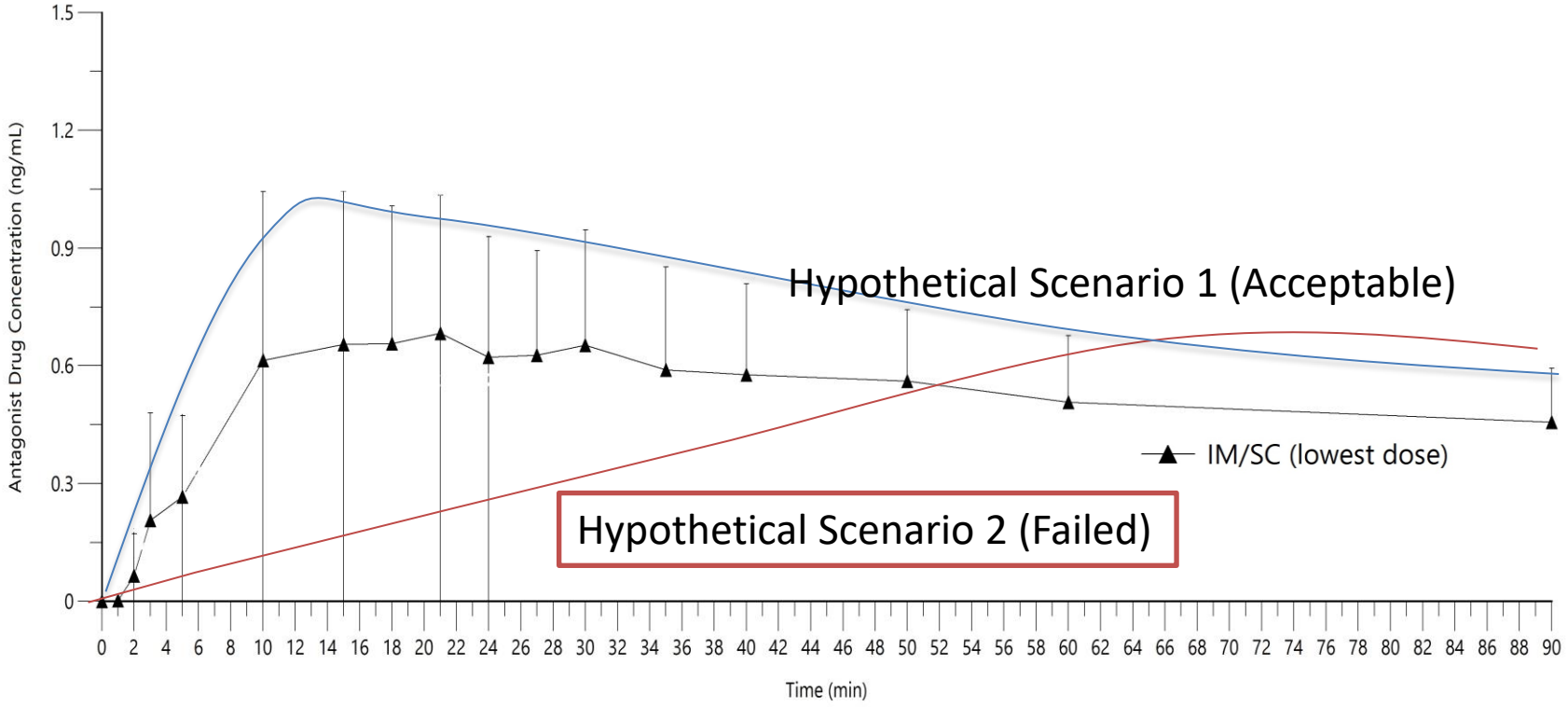
Data Analysis

- Standard PK Parameters.
  - Descriptive statistics of Cmax, AUC0-t, AUC0-inf, Tmax, half-life ($T_{1/2}$).
- Partial AUCs (pAUC) (For example, AUC0-2min, AUC0-3min, AUC0-5min, etc.).
- Bioequivalence (BE) type statistical analysis approach to analyze PK parameters.
  - BE demonstration is not required when planning to exceed exposure with labeled (IM/SC) lowest effective dose of reference drug.

Acceptance Criteria

- To support efficacy, Test product should match or exceed the systemic antagonist drug exposure compared to the label indicated lowest effective dose (IM/SC route) of reference drug.
  - Cmax, AUC0-t, AUC0-inf.
  - pAUC at early time points are important:
    - Acceptable when pAUC at early time points match or exceed reference drug.
    - Not acceptable if pAUC's of test product are lower at early time points, even if matching or exceeding Cmax or AUC.
    - May also support repeat dosing (For example, repeat every 2-3 mins)

Figure Depicting Boundaries for Single Dose (Antagonist Drug) Importance of pAUCs



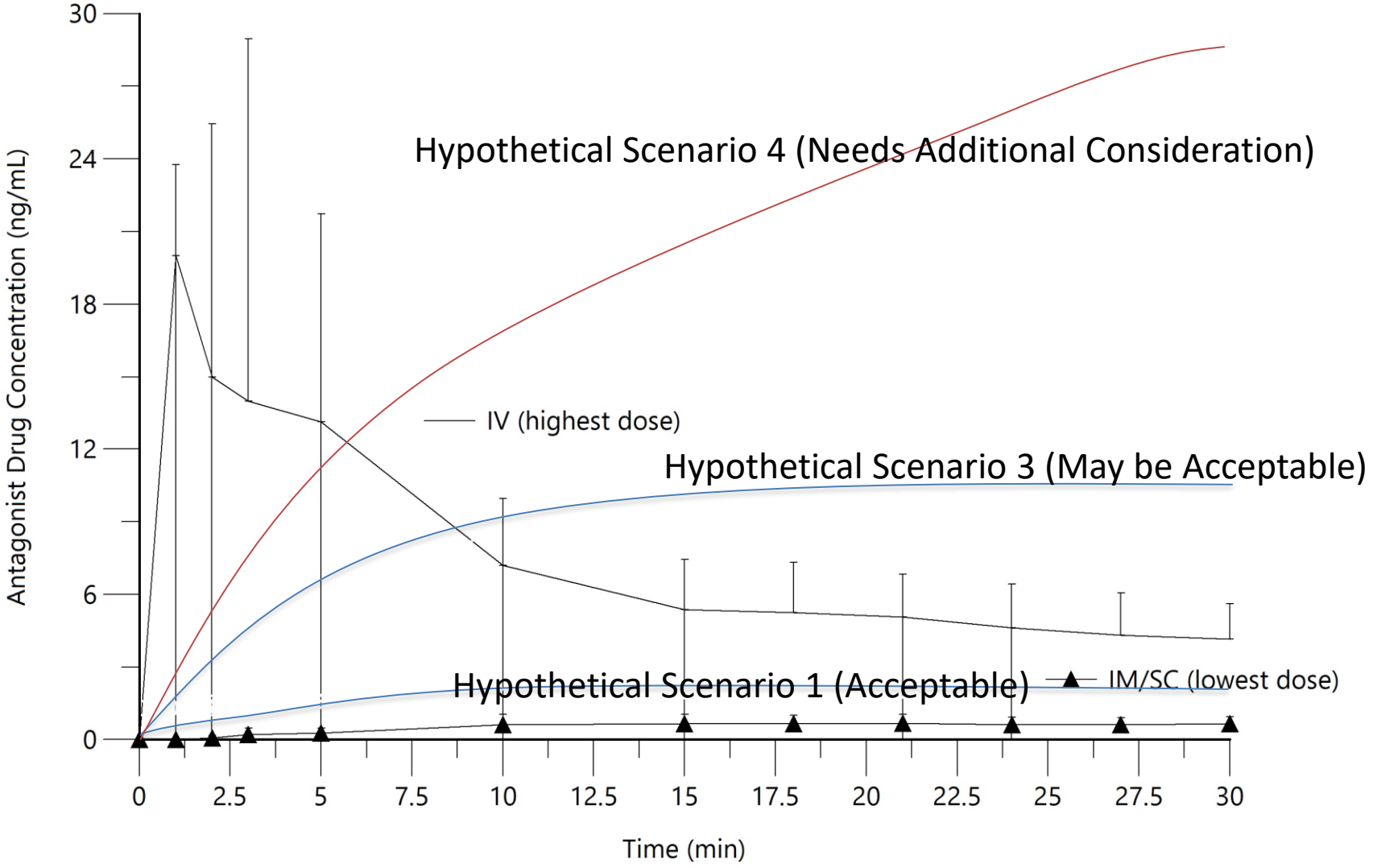
Additional Considerations

- Past approaches, based on publicly available information, included:
  - Nasal Spray volume and concentration of drug[1,2]
  - Permeation enhancers[3]
  - Antagonist drug dose (Drugs@fda)[4]
  - Route of administration (Drugs@fda)[4]

Acceptance Criteria

- To support systemic safety based on findings of the reference product, Test product should not exceed the antagonist drug systemic exposure compared to the label indicated highest safe & effective dose (IV route) of reference drug.
  - Compare Cmax, AUC0-t, AUC0-inf, and entire PK profile.
- If the new product shows higher systemic exposure, additional information or justification will be needed to support its systemic safety.
  - The highest dose of antagonist drug evaluated may be justified utilizing label described doses.
  - The sponsor may use literature information that include information from clinical trials and clinical studies.

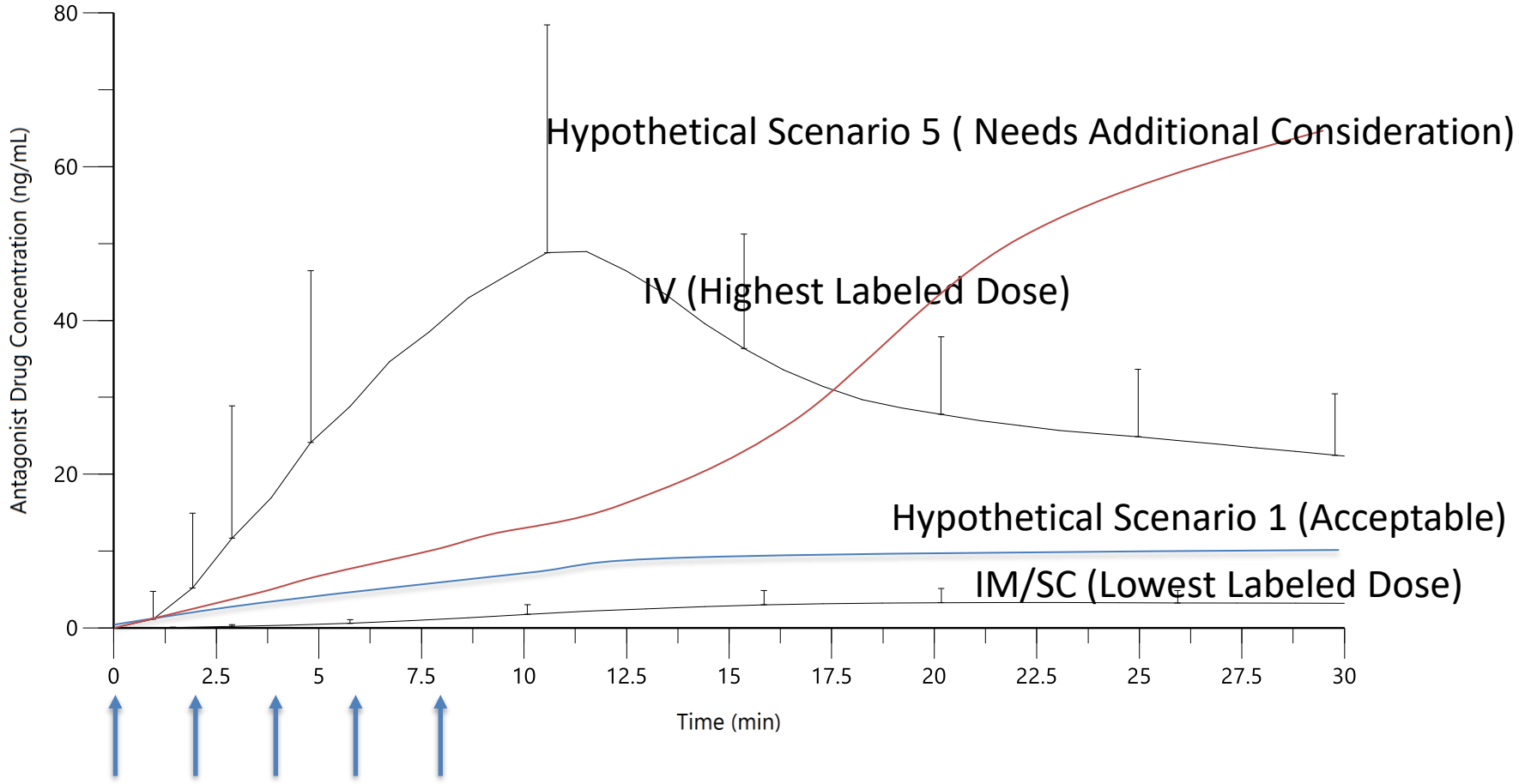
Figure Depicting Boundaries for Single Dose (Antagonist Drug)



Considerations for Repeat-Dose Administration of Antagonist Drug

- The requirement for repeat doses of antagonist drug depends upon the amount, type, and route of administration of the opioid being antagonized.
- To support systemic safety based on findings of the reference product, Test product should not exceed the Reference antagonist drug systemic exposure at the indicated highest safe & effective dose (IV route) after multiple dose administration.
- PK simulations may be conducted to understand the systemic exposure with multiple antagonist dose administration.
- Similar considerations, as before (slide 19), apply regarding justification of repeated doses of test product compared to reference drug.

Figure Depicting Boundaries for Repeated Dose (Antagonist Drug)



Relevant FDA Guidances

- Bioavailability Studies Submitted in NDAs or INDs – General Considerations (updated April 2022)
  - https://www.fda.gov/media/121311/download
- Guidance for industry: Statistical Approaches to Establishing Bioequivalence
  - https://www.fda.gov/media/70958/download
- Guidance for Industry: Bioanalytical Method Validation
  - https://www.fda.gov/media/70858/download

References

1. NIDA funded research, published by Krieter P. et al., 2016. J. Clin Pharm. 56(10):1243-1253.
2. Ryan S.A., Dunne R.B. 2018 Pain Management 8 (3): 231-245.
3. NIDA funded research, published by Krieter P. et al., 2018. J. Pharmacol. Exp. Ther. 371(2):409-415.
4. Drugs@fda https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Acknowledgements

- Colleagues at CDER
  - Division of Neuropsychiatric Pharmacology
  - Division of Applied Regulatory Science
  - Office of Clinical Pharmacology
  - Division of Anesthesiology, Addiction Medicine and Pain Medicine
  - Office of Surveillance and Epidemiology
  - Controlled Substances Program, CDER


FDA
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ADMINISTRATION

Session 6: Considerations for Opioid Overdose Management Product Development

REAGAN-UDALL FOUNDATION FOR THE FDA

Presenters

Carin King Malley, MD
University of Pittsburgh Medical Center

Iván Montoya, MD, MPH
National Institute on Drug Abuse

Reactor Panel

Jesse Pines, MD
US Acute Care Solutions

Phillip Fiuty
The Mountain Center

Nabarun Dasgupta, PhD
University of North Carolina

Jessica Paulsen
U.S. Food and Drug Administration

Srikanth C. Nallani, PhD
U.S. Food and Drug Administration

Considerations for Overdose Management Product Development: A Clinical Perspective

Carin King Malley, MD

UPMC Department of Emergency Medicine

Division of Medical Toxicology

Disclosures

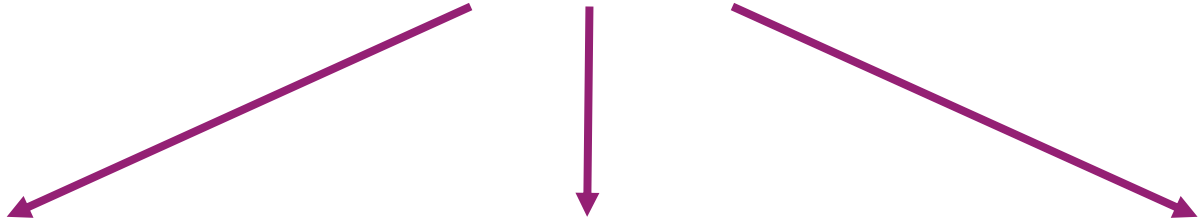
- No Financial disclosures
- Cases are based on clinical experience, but not specific patients.
  - I practice EM and Med Tox in Pittsburgh. Our illicit opioid supply is largely fentanyl and analogues. We also see “pressed” pills, and accidental opioid overdoses in people intending to use benzodiazepines, amphetamines or cocaine. We see some (but not large amounts) of xylazine.
  - I take care of people who have had an opioid overdose nearly every shift.

Outline

- Clinical Case 1: Ideal opioid reversal
- Clinical Case 2: Precipitated severe opioid withdrawal
- Clinical Case 3: Late/Ineffective reversal

Cases

- EMS is called for a 29-year-old male with a suspected overdose. Bystanders report that approximately 30 minutes ago, he went down to the basement and when he didn't come back upstairs, they went down to check on him. They report he is unresponsive and not breathing and that there are stamp bags on the ground next to him. They are administering intranasal (IN) naloxone.



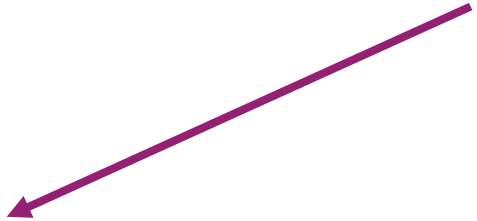
Case 1: Ideal overdose management

Case 2: severe, precipitated withdrawal

Case 3: Late/Ineffective reversal

Cases

- EMS is called for a 29-year-old male with a suspected overdose. Bystanders report that approximately 30 minutes ago, he went down to the basement and when he didn't come back upstairs, they went down to check on him. They report he is unresponsive and not breathing and that there are stamp bags on the ground next to him. They are administering intranasal (IN) naloxone.



Case 1: Ideal overdose management

Case 1:(One opinion of) ideal overdose Management

- Family administers 4 mg IN naloxone
- Paramedics arrive to find the patient breathing spontaneously but with a respiratory rate of 8 breaths per minutes (bradypnea) and pulse oxygen saturation of 80%. They administer an additional 0.2 mg IV naloxone and assist with ventilation via bag valve mask.
- Over next 5 minutes, patient's native respiratory rate rises to 16 breaths per minute (normal) and his pulse oxygen saturation rises to 98% on room air.
- Patient is drowsy but arousable to verbal stimuli.
- Patient is transported to the Emergency Department (ED) for further monitoring and treatment.

Case 1:(One opinion of) ideal overdose Management

- Reasons this worked:
  - Bystanders recognized possible overdose
  - Bystanders had naloxone
    - Knew how to administer
  - Able to connect to EMS services

Case 2

- EMS is called for a 29-year-old male with a suspected overdose. Bystanders report that approximately 30 minutes ago, he went down to the basement and when he didn't come back upstairs, they went down to check on him. They report he is unresponsive and not breathing and that there are stamp bags on the ground next to him. They are administering intranasal (IN) naloxone.

Case 2: severe,
precipitated withdrawal

Case 2: Severe precipitated withdrawal

- Family administers 4 mg IN naloxone
- Paramedics arrive and administer 2 mg intramuscular (IM) naloxone for continued respiratory insufficiency.
- Patient has rapid return of consciousness. He begins vomiting and has progressive worsening of psychomotor agitation over the next few minutes.
- Agitation worsens to the extent that he is a risk to himself and medical personnel. Verbal de-escalation is unsuccessful. 5 mg IM midazolam is administered and physical restraints applied in order to safely transport the patient to the hospital

Case 2: Severe precipitated withdrawal

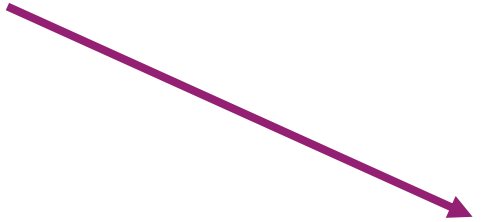
- On arrival to the ED, patient is noted to have continued severe psychomotor agitation.
- 6 security guards are required to assist in moving the patient to ED stretcher.
- ED assessment: 29-year-old male, heart rate of 140 bpm, diaphoresis, active vomiting, psychomotor agitation with a room air pulse oxygen saturation of 72% (92% on nonrebreather). Decision is made to intubate the patient for airway protection.

Case 2: Severe precipitated withdrawal

- Areas of improvement/ future areas of research
  - Use of partial opioid agonists for reversal
  - Methods/devices that allow for closer titration of opioid antagonists for patients without IV access
  - Agents that selectively reverse respiratory depression

Cases

- EMS is called for a 29-year-old male with a suspected overdose. Bystanders report that approximately 30 minutes ago, he went down to the basement and when he didn't come back upstairs, they went down to check on him. They report he is unresponsive and not breathing and that there are stamp bags on the ground next to him. They are administering intranasal (IN) naloxone.



Case 3:
Late/ineffective reversal

Case 3: Late/Ineffective reversal

- Family administers 4 mg IN naloxone. They report to 911 that patient has a weak pulse but is not breathing
- Paramedics arrive to find the patient pulseless. Advanced cardiac life support (ACLS) is initiated. Initial rhythm is asystole
- After 10 minutes of ACLS, return of spontaneous circulation (ROSC) is achieved and patient is transported to the ED.
- Initial CT head with loss of grey/white differentiation consistent with severe hypoxic/ischemic brain injury, incompatible with life

Case 3: Late/Ineffective reversal

- Areas of improvement/ future areas of research
  - Pre-use agents to prevent respiratory depression
  - Automated overdose alert system
  - Devices to more easily allow laypeople to administer assisted ventilation
  - Supervised injection sites

Thank You

- Email: malleyck@upmc.edu

National Institutes of Health
Turning Discovery Into Health

National Institute on Drug Abuse
The Science of Drug Abuse & Addiction

Expanding the Treatment Options for Opioid Overdose

Iván D. Montoya, M.D., M.P.H.

Acting Director, Division of Therapeutics and Medical Consequences
NIDA

No Disclosures
Public information

Clinical Needs

- Safe and effective OOD reversal
- Naloxone-precipitated withdrawal
- Re-narcotization
- Respiratory depression
- Fentanyl and its analogs
- “Naloxone-resistant”
- Wooden chest syndrome

Research Approaches

- Medications
  - Small molecules
    - MOR partial agonists
    - MOR antagonists
    - Drug sequestrants
    - Respiratory stimulants
  - Biologics (Monoclonal antibodies)
- Devices
- Digital Therapeutics

MOR Antagonist

Intranasal Nalmefene: OPNT003 (Opiant)

- Nalmefene + absorption enhancer dodecyl maltoside (Intravail, Neurelis, Inc.)

- Inverse agonist of the μ-opioid receptor (MOR) (Ki = 0.24 nM)
- Weak partial agonist of the κ-opioid receptor (KOR) (Ki = 0.083 nM; Emax = 20–30%)

- Healthy volunteers
- Nalmefene absorbed slowly following IN administration
- Median time to reach Cmax (Tmax) of 2 hours.
- Onset of action is comparable to an i.m. injection of nalmefene (1.5 mg), previously approved to treat opioid overdose.
- The high affinity, very rapid onset, and long half-life of IN nalmefene present distinct advantages as a rescue medication, particularly against longer-lived synthetic opioids

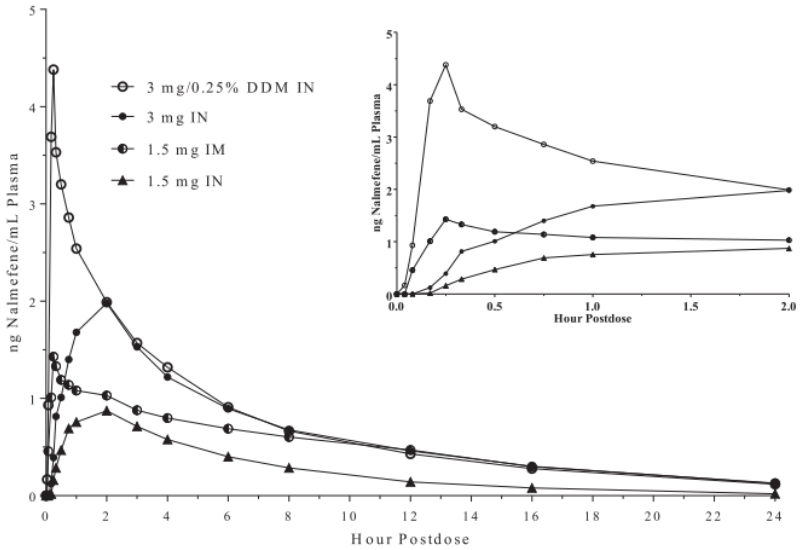


Fig. 1. Mean plasma concentrations of nalmefene following single intranasal and intramuscular administration. Doses were as follows: 3 mg IN (closed circles), 3 mg plus 0.25% (w/v) DDM IN (open circles), 1.5 mg IN (triangles), and 1.5 mg i.m. (half-filled circles). Inset: mean plasma concentrations of nalmefene between 2.5 minutes and 2 hours postdose.

Development of a novel OTC naloxone product to be affordably priced and widely accessible

Project Number	Former Number	Contact PI/Project Leader	Awardee Organization
1UF1DA053806-01A1	1U01DA053806-01A1	MATHAI, ASHANTHI	POCKET NALOXONE CORP.

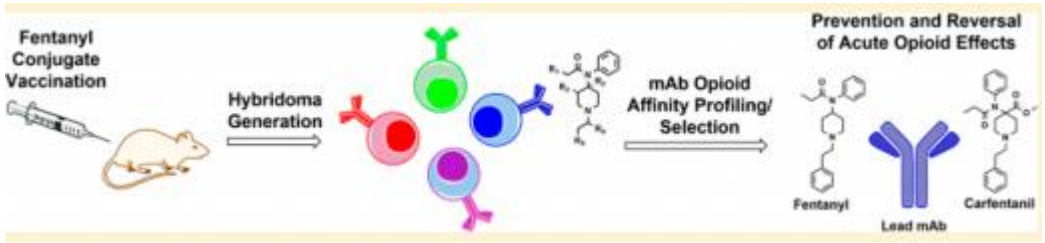
- Pocket Naloxone Corp. (PNC) has developed a novel intranasal swab delivery method for naloxone intended to be affordable and used in OTC settings ($10 per dose).
- A first-in-human pilot clinical study has been completed and the second part of the pilot program will refine dosing and administration.
- Followed by a final pivotal comparative bioequivalence study.
- Submit an NDA to the FDA and apply for Priority Review status for the OTC naloxone nasal swab.

Immunotherapy to Counteract Lethal Doses of Carfentanil

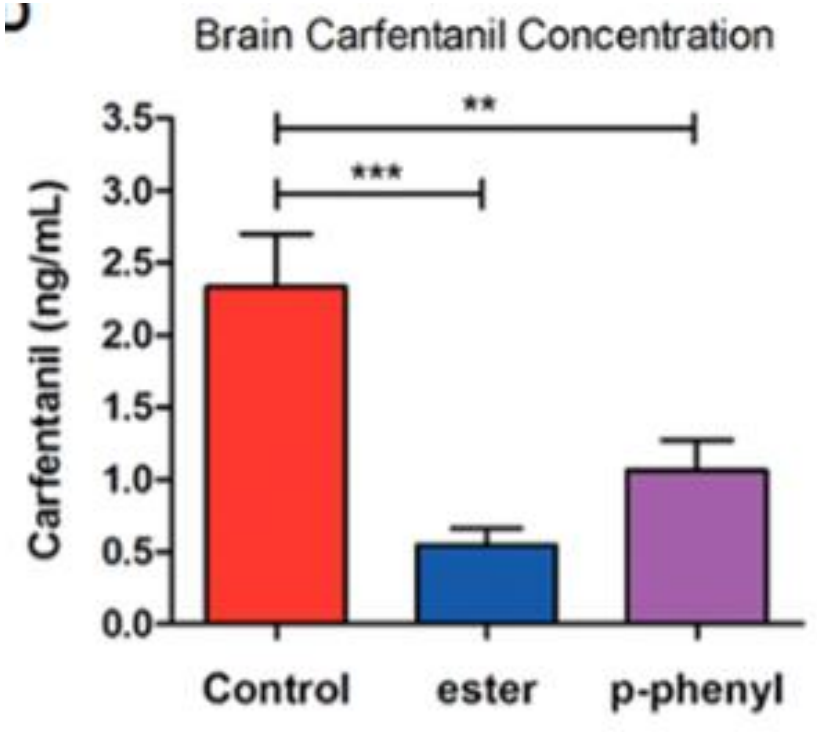
Project Number	Contact PI/Project Leader	Awardee Organization
5U01DA046323-03	JANDA, KIM	SCRIPPS RESEARCH INSTITUTE, THE

Monoclonal Antibodies for Combating Synthetic Opioid Intoxication

Lauren C. Smith,[†] Paul T. Bremer,[†,‡] Candy S. Hwang,[†,§] Bin Zhou,[†] Beverly Ellis,[†] Mark S. Hixon,[†,∥] and Kim D. Janda*[,†]



Half-life of 6A4 to be approximately 6 days in mice
Useful in preventing renarcotization

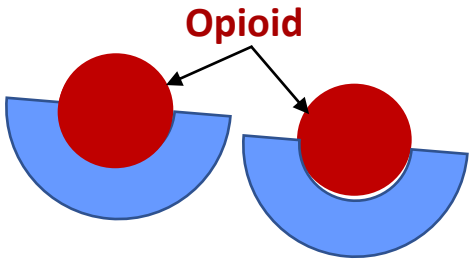


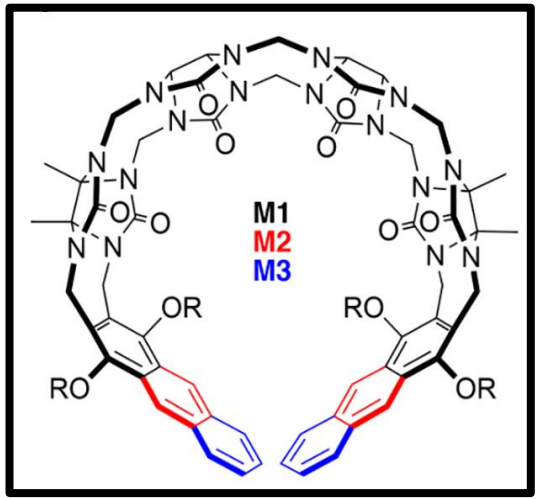
Evaluation of the drug-drug interactions of fentanyl with stimulants in the context of overdose

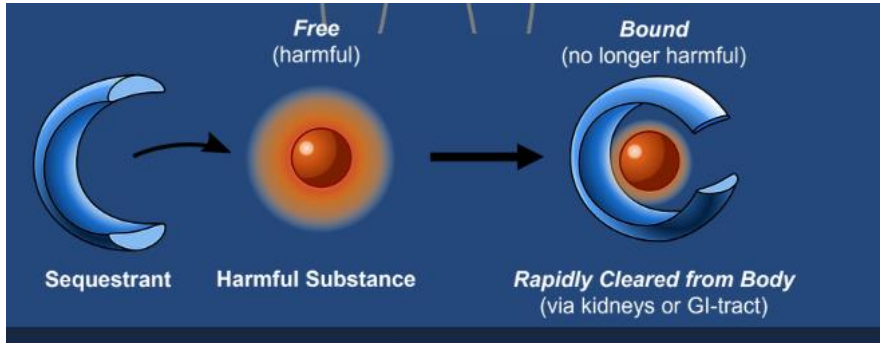
Project Number	Former Number	Contact PI/Project Leader	Awardee Organization
3U01DA053054-02S1	5U01DA053054-02	LI, XINHUA	CLEAR SCIENTIFIC, LLC

CS-1131

- Acyclic Cucurbiturils
- novel scrubber/sequestrant
- Potential to directly eliminate threat agent and prevent renarcotization





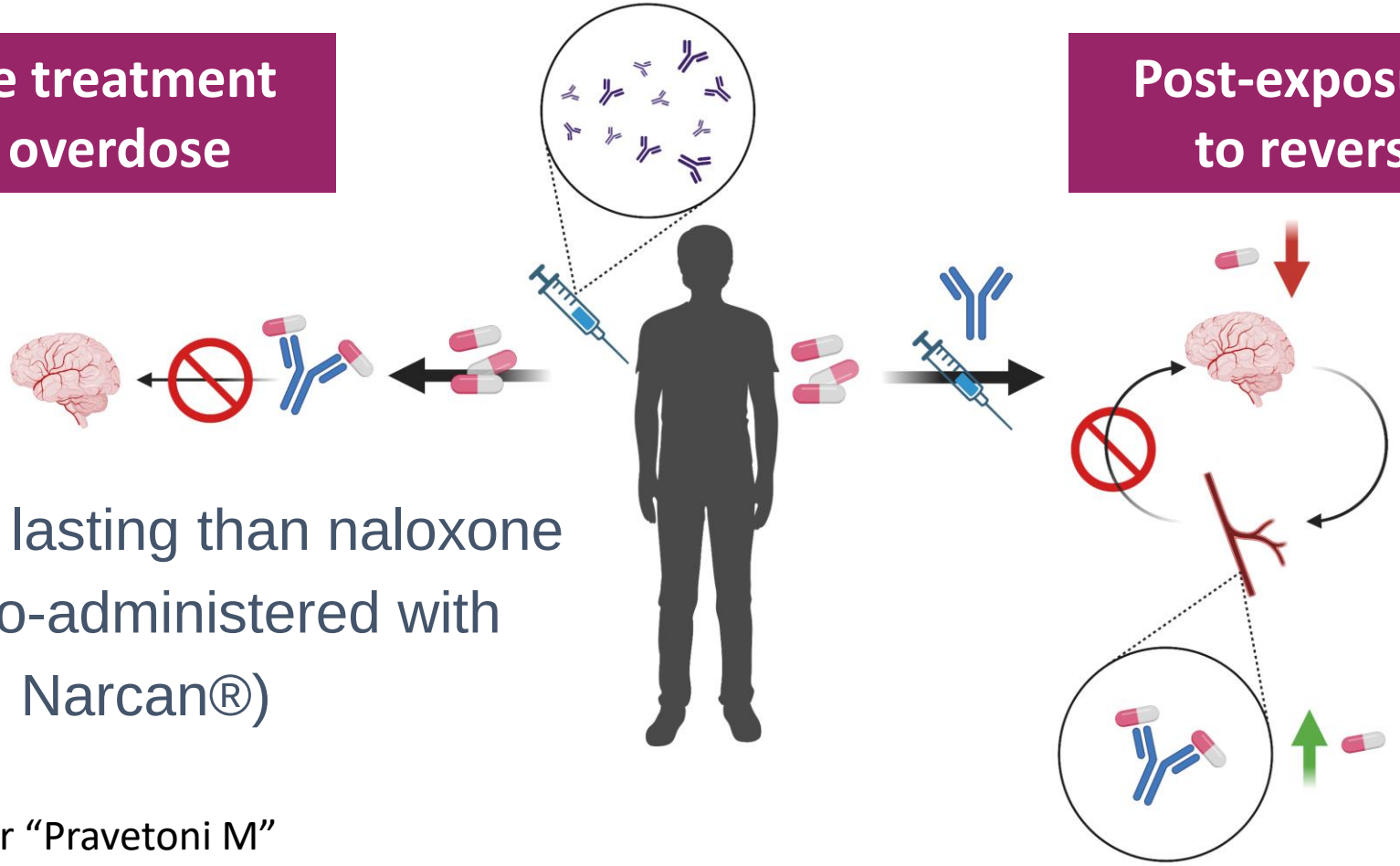


Scrubber molecules sequester opioids *in vivo*. The complexes are cleared via renal elimination.

Monoclonal antibodies (mAb)

Pre-exposure treatment to prevent overdose

Post-exposure treatment to reverse overdose



- mAb is longer lasting than naloxone
- mAb can be co-administered with naloxone (i.e., Narcan®)

References @ PubMed for “Pravetoni M”

Development of a monoclonal antibody to reverse overdose from fentanyl and its analogs: from manufa to clinical trials

Project Number	Contact PI/Project Leader	Awardee Organization
1UG3DA057850-01	PRAVETONI, MARCO	UNIVERSITY OF WASHINGTON

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 6, e2122507 (15 pages)
https://doi.org/10.1080/21645515.2022.2122507

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RESEARCH ARTICLE

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Advancing humanized monoclonal antibody for counteracting fentanyl toxicity towards clinical development

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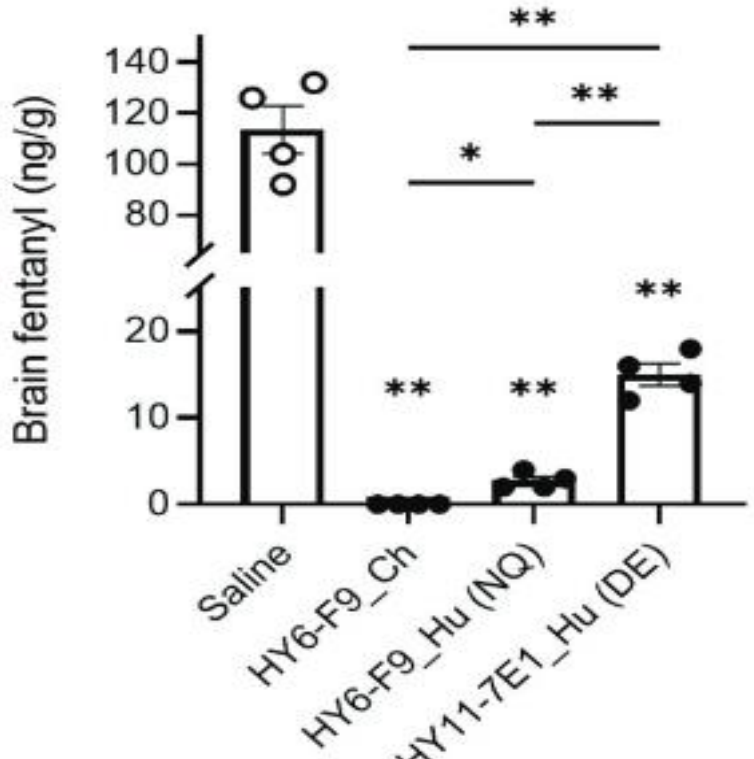
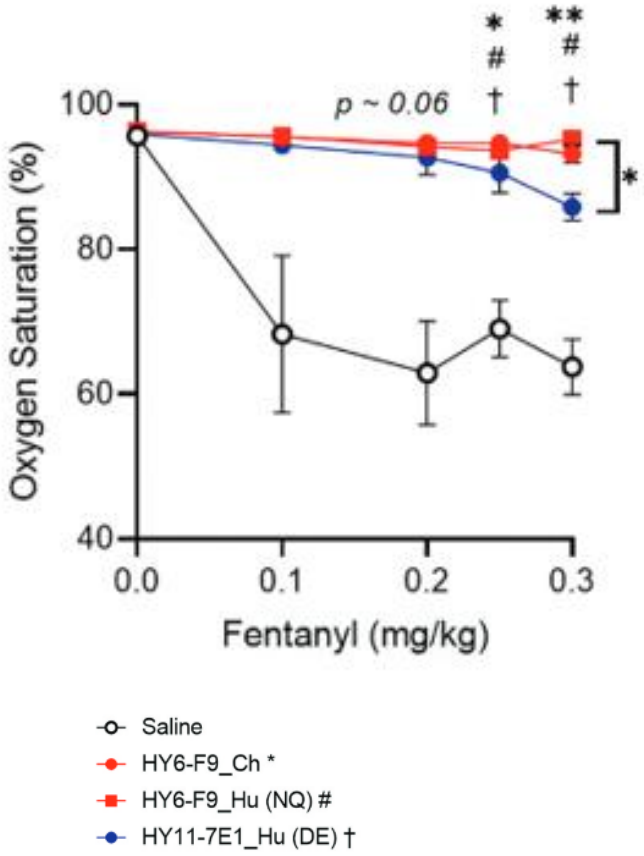
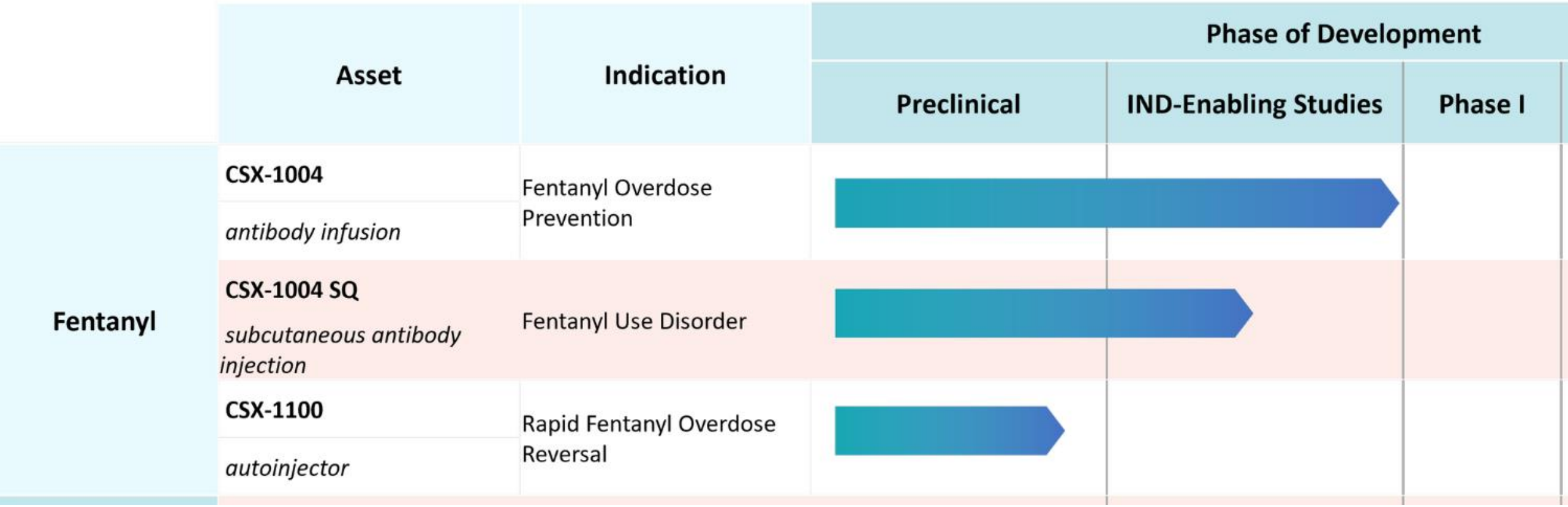




Process Development, Manufacturing, and Preclinical Evaluation of a Monoclonal Antibody for Fentanyl Overdose

Project Number	Former Number	Contact PI/Project Leader	Awardee Organization
5U01DA051071-02	1U01DA051071-01	BREMER, PAUL T	CESSATION THERAPEUTICS, LLC

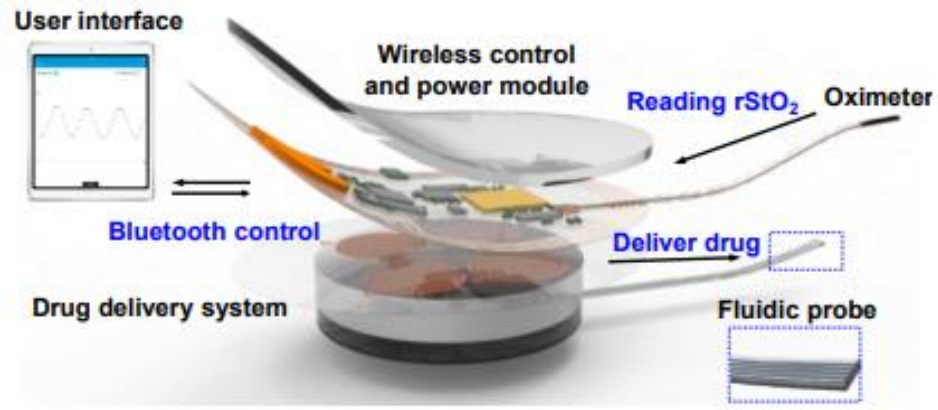
CESSATION THERAPEUTICS



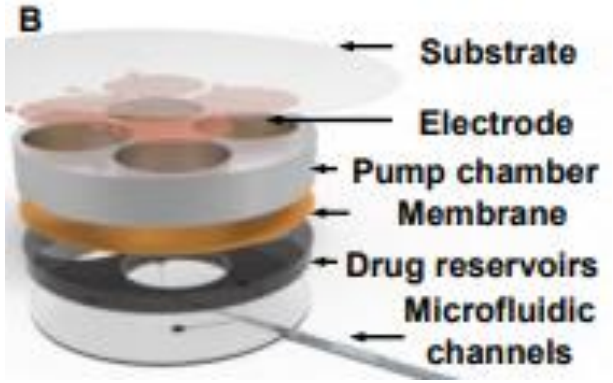
Implantable closed-loop system for delivery of naloxone

UH3 DA050303, PI: Robert Gereau, Wash. U.

- Implantable, closed-loop system that senses the presence of an opioid overdose
- Automatically administers a bolus injection of naloxone
- Simultaneously alerts first responders.



Schematic illustration of a fully implantable, system for closed-loop pharmacological intervention, based on a miniaturized oximeter, drug delivery platform, and power/control module.



Microfluidic system for programmable pharmacology

- *In vivo* rat model: deliver a dose of naloxone upon detection of low tissue oxygen levels and send an emergency signal through a smart phone.
- Current effort: device scale-up to determine appropriate doses of fentanyl and naloxone to use in a pig model.

Automatic Phrenic Nerve Stimulation to Rescue Opioid Induced Respiratory Depression

Project Number	Former Number	Contact PI/Project Leader	Awardee Organization
1R43DA045442-01	1R43HL140707-01	LEVIN, HOWARD D	CORIDEA, LLC

- Implantable device for rescuing opioid overdose
- Automatically sensing and reversing the opioid-induced respiratory arrest
- Target individuals at the highest risk for opioid overdose: history of overdose, poor response to treatment, using high opioid doses, concomitant sedative-hypnotic and alcohol use, and mental disorders
- The system is a fully implantable pacemaker-like device that is currently used for the treatment of central sleep apnea in heart failure, and has been shown to be safe
- Consists of a transvenous pacing lead and an implantable pacemaker-like pulse generator.
- It can sense patterns of respiration and then stimulate the phrenic nerve to break disordered breathing
- Design and development of a software algorithm to automatically detect and respond to critical respiratory depression and arrest
- Device will be placed via a procedure similar to cardiac pacemakers
- Ability to automatically call 911 and provide GPS coordinates to responders to locate overdosed patient

An automated portable system for detecting and treating opioid induced respiratory depression

Project Number	Contact PI/Project Leader	Awardee Organization
1U01DA056242-01	MACKIE, KENNETH	TRUSTEES OF INDIANA UNIVERSITY

- Automated portable system to detect and treat an opioid overdose in real time
- Wearable sensors to track the variation of physiological parameters (e.g., breathing pattern, blood oxygen level, and heart rate) for the real-time detection of an opioid overdose
- Optimize novel acoustic patches to deliver naloxone for treating an opioid overdose
- A closed-loop system through integration of wearable sensor, a therapeutic patch, a machine learning-based controller driven by a cell phone
- Will be validated using a mouse model of opioid overdose

Research for OIRD

- D-CYSee: Thiol-based compounds D-Cysteine ethyl ester
- ENA-001: Functional inhibition of BK channels of the carotid bodies, thereby acting as a hypoxia-mimetic
- Inhibition of TASK-1 and TASK-3 tandem pore potassium channel function
- Ampakines: allosteric modulators of α-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid (AMPA) receptor channel kinetics that enhance glutamatergic synaptic transmission and stimulate breathing
- kappa-opioid receptor agonists 1: restore the alteration of passive respiratory mechanics and suppress the hypermetabolism produced by fentanyl induced muscle rigidity
- Dexmedetomidine: central alpha-2 agonist may increase ventilation
- Intranasal leptin: adipocyte-produced hormone may up-regulate control of breathing

Session 7: Future Directions

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Nora Volkow, MD
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Yngvild K. Olsen, MD, MPH
Substance Abuse and Mental Health Services Administration

Phillip Fiuty
The Mountain Center

Jermaine Jones, PhD
Columbia University Irving Medical Center

Thank You for joining us!

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