We Can NarCAN

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Disclosures

- Kaleo pharma
- Remitigate, LLC.
- Genomind

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OBJECTIVES

- Compare and contrast naloxone products currently available for in-home use and their supportive legislation
- Demonstrate examples of elevated opioid induced respiratory depression (OIRD) risk through drug-drug interactions, pharmacogenomics, and various disease states
- Assess a patient's need for in-home naloxone through interpretation of the Risk Index for Overdose or Serious Opioid-induced Respiratory Depression (RIOSORD) tool

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TYPES OF OPIOID CONSUMERS

- Opioid abuse disorder (know where the data is coming from!)
  - Heroin
  - Carfentanil
  - RX opioids
  - Other
- Legitimate opioid consumers (RX)
  - Long-term opioid therapy v. short-term acute pain
- A combination of #1 and #2 above

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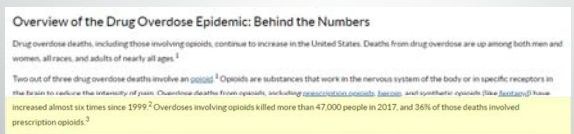

https://www.cdc.gov/drugoverdose/data/index.html

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https://www.cdc.gov/media/releases/2018/p0329-drug-overdose-deaths.html

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% CHANGE IN OPIOID PERSCRIBING PER COUNTY, U.S.

2010–2015

2016 data available at:
https://www.cdc.gov/mmwr/volumes/67/wr/pdfs/mm6712a1-H.pdf

Opioid prescribing measures	Decrease (%)	Stable (%)	Increase (%)
MEDD per capita	49.6	27.8	22.6
Overall prescribing rate	46.5	33.8	19.6
High-dose prescribing rate	86.5	6.7	6.9
Average daily MME per prescription	72.1	25.7	2.2

Guy GP, et al. MMWR Morb Mortal Wkly Rep. 2017;66:697–704

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Who is at risk for overdose?

- Any period of abstinence leading to lower tolerance
- Mixing medications
- Using alone
- Not having naloxone available
- Fentanyl or its derivatives in the drug supply
- Injecting or smoking can increase your risk

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SIGNS OF OPIOID OVERDOSE

Opioid Toxidrome Triad

- Altered mental state
  - Drowsiness or coma
- Opioid-induced respiratory depression
  - Decreased Tidal Volume
  - Decreased Respiratory Rate
- Miosis
  - "Pinpoint" pupils

Additional Signs of Overdose

- Pale and clammy face
- Limp body
- Fingernails or lips turning blue/purple
- Vomiting or gurgling noises
- Cannot be awakened from sleep or is unable to speak
- Heartbeat is very slow or stopped

[1]Henry J, Vickers G. *Ir Med J*.1984;289:990-993. [2]Substance Abuse and Mental Health Services Administration. SAMHSA Opioid Overdose Prevention Toolkit: Information for Prescribers. HHS Publication Number (SMA) 13-4742. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.

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Check to see if they respond

- Shake them and shout to wake them up
- If no response, grind your knuckles into their chest bone (sternal rub)
- If the person still does not respond, call 911 OR give naloxone
  - Whatever is quicker!

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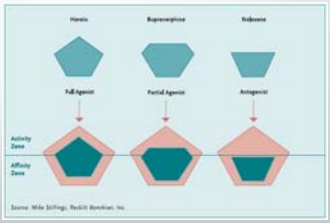
NALOXONE TO THE RESCUE

- Non-scheduled opioid antagonist proven to rapidly reverse life-threatening OIRD and other CNS depressant effects
- Higher affinity for mu receptors than traditional opioids

(exception: buprenorphine)

- Displaces and prevents binding of opioid at the receptor sites



Straus M, et al. *Subst Abuse Rehabil*. 2013;2013(4):65-72

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NALOXONE TO THE RESCUE

- Intramuscular (IM) kit
- Intranasal (IN) kit
- Auto-injector (2014)
- IN spray (11/18/2015)

Which one do we use?

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NALOXONE COMPARISONS

	NXN Auto-injector	NXN Intranasal (FDA Approved)	NXN Intranasal (Makeshift)	NXN IM Traditional
COMPLEXITY	Usability studies show 90% and 100% correct adm c/t NXN makeshift.[1]	Usability studies show >90% correct adm[3]	60-100% failure rates[1,3]	No usability studies
INSTRUCTIONS	Audio stepwise direction and written directions	Written directions	No FDA approved written directions	N/A for in-home use
CONSIDERATIONS	May inject through seam of jeans	Reduced Cmax due to altered nasal mucosa (DS, cong)	Requires sig dexterity and familiarity	Requires sig dexterity and familiarity
FDA APPROVED for in-home use	YES, Known or suspected Op OD, EVEN IF NOT TRAINED	YES, Known or suspected Op OD, ~~EVEN IF NOT TRAINED~~	NO	N/A
DOSE	~~0.4 mg/0.4 mL injection~~ 2mg/0.4mL injection	4 mg/0.1 mL spray	0.5 mg/0.5 mL	1.0 mg/mL
Tmax (median)	0.25 hour (0.4 mg dose)	0.33 hour (8 mg) (2 x 4 mg doses)	*N/A, but consider Kelly et al.[2]	0.38 hour (0.4 mg dose)
COST	170x	10.75x	2x	1x
Private 3rd Party Pay	Discussion…NCAP Program			

*Note: 2 mg IM vs 2 mg IN

1. Edwards ET, et al. Pain Ther. 2015;4:89-105.
2. Kelly A, et al. Med J Aust. 2005;182:24-27.
3. Krieter P, et al. J Clin Pharmacol. 2016. DOI: 10.1002/jcph.759

With permission from Dr. Jeffrey Fudin.
Saving Lives With Naloxone: Opportunity or Obligation? is a live continuing education activity for pharmacists developed by the American Pharmacists Association. Initial Release Date: June 15, 2016. Target Audience: Pharmacists

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PEEL, PLACE, PRESS

- https://www.youtube.com/watch?v=hGVSaO1oxpg
- Phone app: NARCAN Now
- If person does not respond within <u>2 minutes</u>, give second dose

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Who is a candidate for naloxone?

Everybody?

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RECOMMENDATIONS

SAMHSA: "With proper education, patients on long-term opioid therapy and others at risk for overdose may benefit from having a naloxone kit containing naloxone, syringes and needles or prescribing *[naloxone auto-injector]* which delivers a single dose of naloxone via a hand-held auto-injector that can be carried in a pocket or stored in a medicine cabinet to use in the event of known or suspected overdose."

"The AMA has been a longtime supporter of increasing the availability of naloxone for patients, first responders and bystanders who can help save lives."

American Medical Association. AMA Statement on Naloxone Product Approval. 2014. American Society of Addiction Medicine. Use of Naloxone for the Prevention of Drug Overdose Deaths. 2014. FDA News Release. FDA approves new hand-held auto-injector to reverse opioid overdose. 2014. Office of National Drug Control Policy. *National Drug Control Strategy*. 2014. World Health Organization. *Community Management of Opioid Overdose*. 2014. American College of Emergency Physicians. Naloxone distribution from the ER for patients at-risk for opioid overdose. 2014. Substance Abuse and Mental Health Services Administration. *SAMHSA Opioid Overdose Prevention Toolkit*. HHS Publication No. (SMA) 14-4742. Rockville, MD: SAMSHA, 2014. Substance Abuse and Mental Health Services Administration. *Federal Guidelines for Opioid Treatment Programs*. HHS Publication No. (SMA) PEP15-FEDGUIDEOTP. Rockville, MD: SAMHSA, 2015. National Association of State EMS Officials. NASEMSO Issue Brief: The Use of Naloxone in Out-of-Hospital Settings. 2014. Clinton Foundation. *Prescription Drug Abuse Reduction*. 2014.

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INITIAL THOUGHTS…

- Substance abusers
- Respiratory related chronic illness
- Pain patients
  - Opioid use

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OTHER THOUGHTS…

- OTC use
- Drug-drug interactions
- Drug-food interactions
- Impairment of drug excretion
- *Pharmacogenomics*

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PATIENT CASE EXAMPLES

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OPIOID	METABOLISM	METABOITES
Fentanyl	3A4 (N-dealkylation)	Norfentanyl, hydroxyfentanyl
Morphine	Phase II glucuronidation	Morphine-3-glucuronide; morphine-6-glucuronide; hydromorphone (<5%)
Hydromorphone	Phase II glucuronidation	hydromorphone-3-glucuronide; hydromorphone-6-glucuronide
Hydrocodone	2D6 (O-demethylation); 3A4 (N-demethylation); 6-keto reduction	Hydromorphone (active, ~5.4 times more potent); norhydrocodone (active, ~70 times less potent); 6-alpha and 6-beta hydroxymetabolites
Codeine	2D6 (O-demethylation); phase II glucuronidation; 3A4 (N-demethylation)	Morphine (active); codeine-6-glucuronide; norcodeine (inactive)
Oxycodone	2D6 (O-demethylation); 3A4 (N-demethylation)	Oxymorphone (active, 2 time more potent); noroxycodone)
Oxymorphone	Phase II glucuronidation	oxymorphone-3-glucuronide
Methadone	3A4, 2B6, 2C19 (n-demethylation)	2- ethylidene-1, 5-dimethyl-3, 3- diphenylpyrrolidene (EDDP)
Tapentadol	Phase II glucuronidation; 2C9/2C19 (methylation)	O-glucuronide; n-desmethyl-tapentadol

Courtesy of: http://paindr.com/wp-content/uploads/2012/05/Pharmacodynamic-and-Pharmacokinetic-Properties-of-Commonly-Prescribed-Opioids_Fudin-Perkins.pdf

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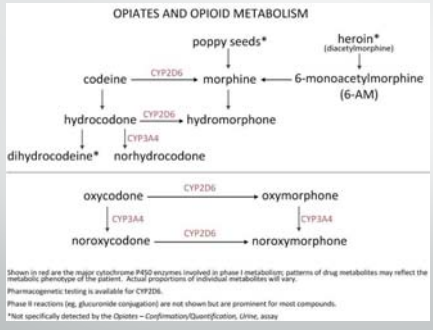

http://www.aruplaboratories.com/assets/graphics/OpiatesAndOpiodMetabolism.jpg

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PATIENT CASE EXAMPLE

- D.P. is a 55 yo M, PMHx: DM, HTN, peripheral neuropathy, and chronic low back pain
- Allergies: penicillin
- Medications include: metformin 1000mg PO BID, lisinopril 20mg PO daily, gabapentin 600mg PO TID, aspirin 81mg PO daily, atorvastatin 40mg PO daily, oxycodone 20mg ER PO q12
- D.P. develops a bronchial infection and goes to the ED for treatment
- D.P. is given an prescription for clarithromycin

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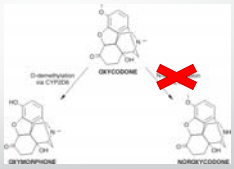
PATIENT CASE EXAMPLE

- Clarithromycin is a 3A4 inhibitor
  - Enzyme inhibition occurs within 24-48 hours
- Oxymorphone is 2X as potent as oxycodone
- Would you give this patient naloxone?



Graphic courtesy of: http://www.bioanalytical.com/library/presentations/biochem/leonard_ou/index.html

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PATIENT CASE EXAMPLE

- D.P. had a pharmacogenetic test done which revealed the following:
  - 1A2: ULTRARAPID METABOLIZER
  - 2B6: EXTENSIVE (NORMAL) METABOLIZER
  - 2C19: EXTENSIVE (NORMAL) METABOLIZER
  - 2C9: EXTENSIVE (NORMAL) METABOLIZER
  - 3A4: POOR METABOLIZER
  - 2D6: ULTRARAPID METABOLIZER

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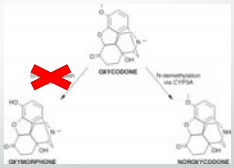
PATIENT CASE EXAMPLE

- Provider wants to switch this patient to hydrocodone as the oxycodone dose not seem to be helping
- Hydromorphone is ~4X as potent as oxycodone
- Would you give this patient naloxone?



Graphic courtesy of: http://www.bioanalytical.com/library/presentations/biochem/leonard_os/index.html

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http://www.aruplabsresult.com/assets/graphics/OpiatesAndOpioidMetabolism.jpg

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Validation of a screening risk index for serious prescription opioid-induced respiratory depression or overdose in a us commercial health plan claims database

Zedler, et al. Pain Medicine 2015

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DESIGN

- Case control analysis
- 18,365,497 patients and 7,234 cases of OIRD
- 4 controls assigned to each veteran included
- Variables were selected for the risk index model
  - Based on logistics regression modeling
- Each variable was assigned a point value
- Point values added up to scores
  - Scores were then defined by predicted probability

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RIOSORD Risk Index for Overdose or Serious Opioid-induced Respiratory Depression

DESCRIPTION	YES/NO	POINTS
In the past 6 months, has the patient had a healthcare visit (outpatient, inpatient or ED)involving any of the following health conditions?		
Substance use disorder (abuse or dependence)? *includes opioids, antidepressants, sedatives/anxiolytics, alcohol, amphetamines, cannabis, cocaine, hallucinogens	25	0
Bipolar disorder or schizophrenia?	10	0
Stroke (cerebrovascular accident, CVA) or other cerebrovascular disease?	9	0
Chronic kidney disease with clinically significant renal impairment?	8	0
Heart failure?	7	0
Non-malignant pancreatic disease (e.g., acute or chronic pancreatitis)?	7	0
Chronic pulmonary disease (e.g., emphysema, chronic bronchitis, asthma, pneumoconiosis, asbestosis)?	5	0
Chronic headache (e.g., migraine)	5	0
Does the patient consume:		
Fentanyl (e.g., transdermal or transmucosal immediate-release products)?	13	0
Morphine?	11	0
Methadone?	10	0
Hydromorphone	7	0
An extended-release or long-acting (ER/LA) formulation of any prescription opioid, including the above?	5	0
A prescription benzodiazepine (e.g., diazepam alprazolam)?	9	0
A prescription antidepressant (e.g., fluoxetine, citalopram, venlafaxine, amitriptyline)	8	0
Is the patient's current maximum prescribed opioid dose ≥ 100mg morphine equivalents per day? (include all prescription opioids consumed on a daily basis)	7	0
TOTAL:		146

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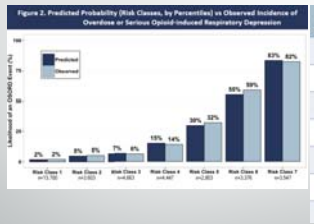
NON-VA POPULATION



Risk Class	RIOSORD Score (Points)	Average Probability of OSORD
1	0-4	2%
2	5-7	5%
3	8-9	7%
4	10-17	15%
5	18-25	30%
6	26-41	55%
7	≥42	83%

Zedler B, Saunders W, Joyce A, Vick C, Murrelle L (Venebio Group) Validation of a Screening Risk Index for Overdose orSerious Prescription Opioid-Induced Respiratory Depression. Courtesy of painmed.org Accessed: 2/9/2016

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PATIENT CASE EXAMPLE

- M.B. is a 47 yo M who is scheduled in your pain clinic for chronic low back pain
- PMH: DM, HTN, CKD (stage III), and MDD/anxiety
- Current medications:
  - Morphine SA 30mg PO TID
  - Oxycodone 5mg PO 1-2 tablets every 4-6 hours as needed
  - Lisinopril 10mg PO daily
  - Gabapentin 600mg PO QHS
  - Sertraline 150mg PO daily
  - Simvastatin 40mg PO QHS

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Calculate this patients RIOSORD score

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PATIENT CASE EXAMPLE

- CALCULATE RIOSORD SCORE: **39**
  - CKD = 8 points
  - Morphine = 11 points
  - ER/LA opioid = 5 points
  - Antidepressant = 8 points
  - Daily morphine equivalents > 100mg = 7 points
- DETERMINE PATIENTS PRECENT RISK: **55%**
- WHICH NALOXONE FORMULATION WOULD YOU PICK?

Risk Class	RIOSORD Score (Points)	Average Probability of OSORD
1	0-4	2%
2	5-7	5%
3	8-9	7%
4	10-17	15%
5	18-25	30%
6	26-41	55%
7	≥42	83%

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PATIENT CASE EXAMPLE

- M.B. is back for a follow up after your initial visit with him
- M.B. states his pain is better controlled and feels he does not need the naloxone auto-injector dispensed at the initial visit
- No change in medical conditions
- Current medications:
  - Methadone 5mg PO TID
  - Lisinopril 10mg PO daily
  - Gabapentin 600mg PO QHS
  - Sertraline 150mg PO daily
  - Simvastatin 40mg PO QHS
  - Lorazepam 1mg PO TID PRN

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Calculate this patients RIOSORD score

Did it change?

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PATIENT CASE EXAMPLE

- CALCULATE RIOSORD SCORE: **40**
  - CKD = 8 points
  - Methadone = 10 points
  - ER/LA opioid = 5 points
  - Benzodiazepine = 9 points
  - Antidepressant = 8 points
- CALCULATE PATIENTS PRECENT RISK: **55%**
- HOW WOULD YOU EDUCATE THIS PATIENT?
- ANY ADDITIONAL INTERVENTIONS TO BE MADE?

Risk Class	RIOSORD Score (Points)	Average Probability of OSORD
1	0-4	2%
2	5-7	5%
3	8-9	7%
4	10-17	15%
5	18-25	30%
6	26-41	55%
7	≥42	83%

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RIOSORD CONSIDERATIONS

- Switch from ICD-9 to ICD-10
- Visit within the past 6 months
- Morphine equivalence calculator
- Tramadol
- Buprenorphine

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POTENTIAL BARRIERS TO NALOXONE THERAPY

- Naloxone supply shortages
  - COST/reimbursement
- Concerns about increased opioid use
- Unwillingness to carry naloxone
- Difficulty assembling or administering naloxone
- Medical-legal concerns
- Patient resistant to change

Naloxone Kits and Naloxone Autoinjectors: Recommendations for Issuing Naloxone Kits and Naloxone Autoinjectors for the VA Overdose Education and Naloxone Distribution (OEND) Program. May 2015. Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives in collaboration with the VA OEND National Support and Development Workgroup.

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What have been **your** experiences with dispensing and educating on naloxone?

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NALOXONE LEGISLATION

- Two types of legislation: (1) increase access to naloxone (2) Good Samaritan regulation- reduce personal and professional liability
- Forty-two states have passed laws allowing a layperson to have access to naloxone (exceptions: AZ, IA, KS, MO, MT, SD, and WY)
  - Not always applicable to EMS, police, firefighters, etc.
- Naloxone is available with a prescription at retail pharmacies in 15 states: RI, MA, AR, CA, MN, MS, MT, NJ, ND, PA, SC, TN, UT, NM, and WI[1]
- 2017 Governor Chris Christie signed a bill for a standing order of Naloxone distribution out of pharmacies in NJ

1. http://www.pharmacytimes.com/news/cvs-pharmacists-can-dispense-naloxone-sans-rx-in-12-more-states
2. https://www.pressofatlanticcity.com/news/new-jersey-pharmacies-can-now-dispense-narcan-without-prescription/article_154bbdc6-6730-5ddc-bed5-6775f0944c68.html

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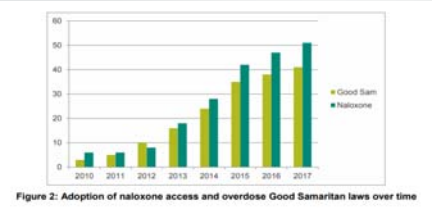

Figure 2: Adoption of naloxone access and overdose Good Samaritan laws over time

Know the laws for your state!
Know the policy where you are practicing!

Davis C. Legal Interventions to Reduce Overdose Mortality: Naloxone Access and Overdose Good Samaritan Laws. www.networkforphl.org/_asset/qrzpvn/network-naloxone-10-4.pdf. Accessed February 28, 2018.

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FINAL Naloxone THOUGHTS

- Chronic opioid patients should be evaluated for the need of in-home naloxone
- Pros and cons to each available naloxone formulation
- Proper education and training on selected naloxone product to patient, family members an/ or caregivers is crucial
- If a reversal by naloxone is needed, that patient's pain management regimen needs to be re-evaluated **immediately**

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Resources to Help

- https://nj.gov/health/integratedhealth/services-treatment/naloxone.shtml
- Email me: Jacqueline.cleary@acphs.edu
- For more information: Harm Reduction Coalition harmreduction.org/overdose

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Hope it wasn't too painful…QUESTIONS?

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5/9/2019

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