VALIDATED RISK ASSESSMENT TOOL TO IDENTIFY PATIENTS AT RISK FOR RESPIRATORY DEPRESSION

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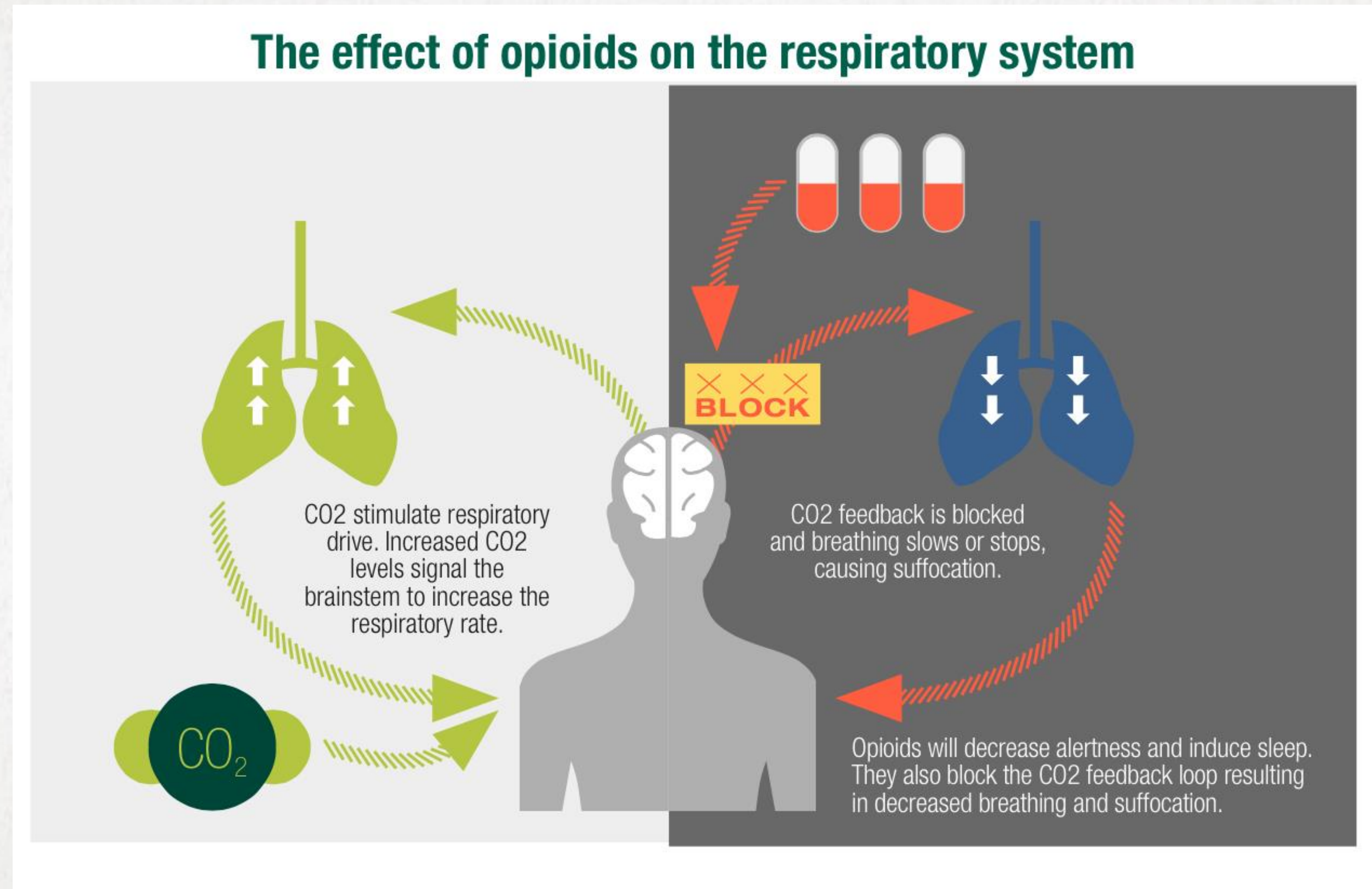
DISCLOSURES

- Kaleo pharma

OBJECTIVES

- Compare and contrast naloxone products currently available for in-home use and their supportive legislation
- Demonstrate examples of elevated 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

OPIOID INDUCED RESPIRATORY DEPRESSION (OIRD)



Teater. The Psychological and Physical Side Effects of Pain Medications; National Safety Council 2015

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

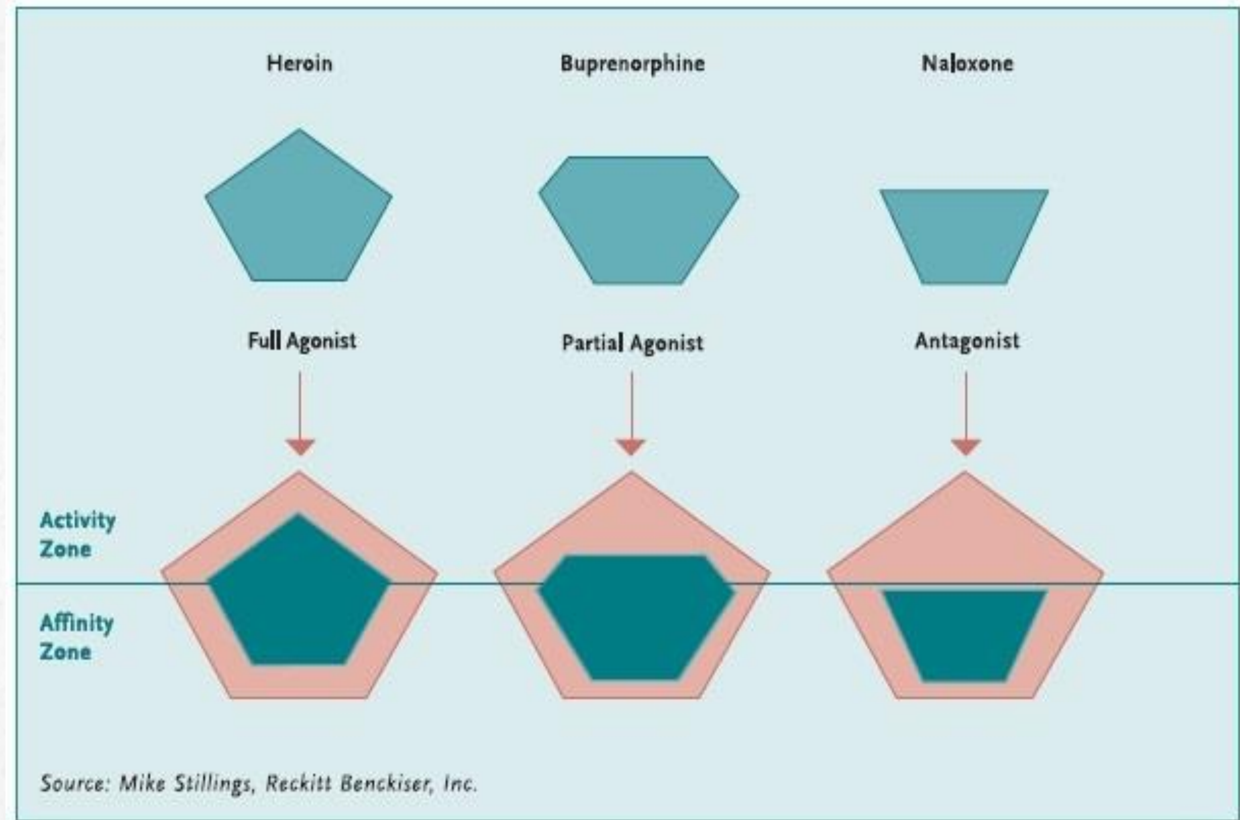
[1]Henry J, Volans G. *Br Med J*. 1984;289:990-993. [2]Substance Abuse and Mental Health Services Administration. SAMHSA Opioid Overdose Prevention Toolkit: Information for Prescribers. HHS Publication Number (SMA) 13-4742. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.

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

NALOXONE TO THE RESCUE

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

Which one do we use?

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

NCAP PROGRAM

- Naloxone Co-payment Assistance Program
- No enrollment required
- Valid prescription or standing order
- Pay up to 40$ in co-payments
- 1-800-542-2437
- https://www.health.ny.gov/diseases/aids/general/opioid_overdose_prevention/directories.htm

WHO IS A CANDIDATE FOR NALOXONE?

EVERYBODY?

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.

INITIAL THOUGHTS…

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

OTHER THOUGHTS…

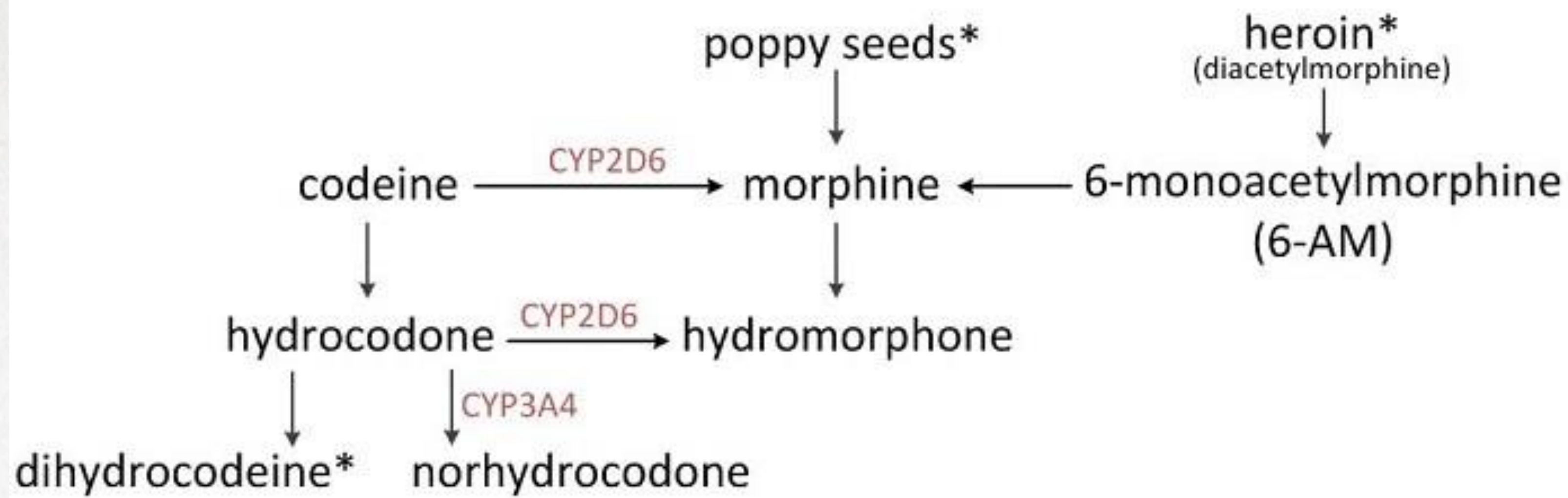
- OTC use
- Drug-drug interactions
- Drug-food interactions
- Impairment of drug excretion
- *Pharmacogenomics*

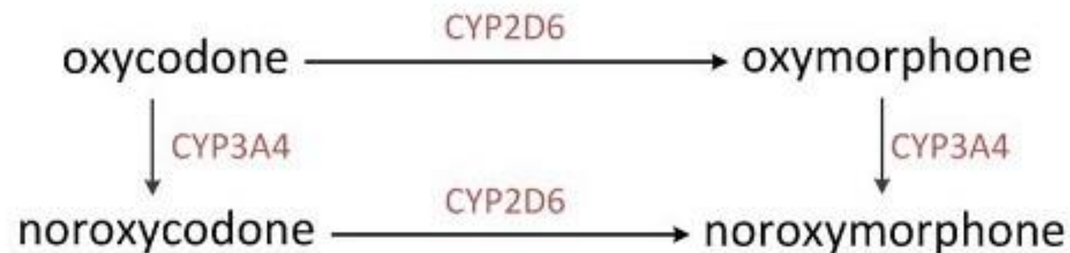
PATIENT CASE EXAMPLES

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

OPIATES AND OPIOID METABOLISM





Shown in red are the major cytochrome P450 enzymes involved in phase I metabolism; patterns of drug metabolites may reflect the metabolic phenotype of the patient. Actual proportions of individual metabolites will vary.

Pharmacogenetic testing is available for CYP2D6.

Phase II reactions (eg, glucuronide conjugation) are not shown but are prominent for most compounds.

*Not specifically detected by the *Opiates – Confirmation/Quantification, Urine,* assay

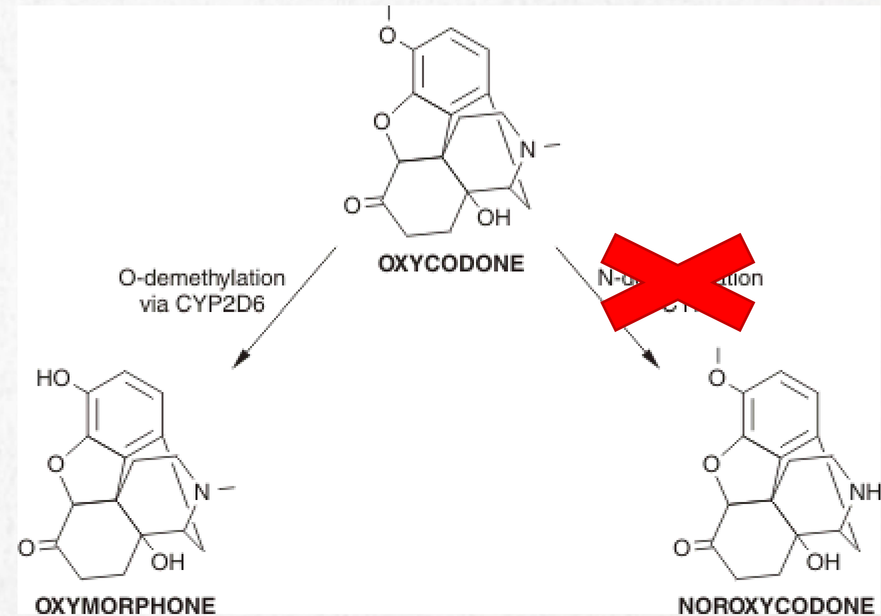
http://www.arupconsult.com/assets/graphics/OpiatesAndOpiodMetabolism.jpg

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

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?



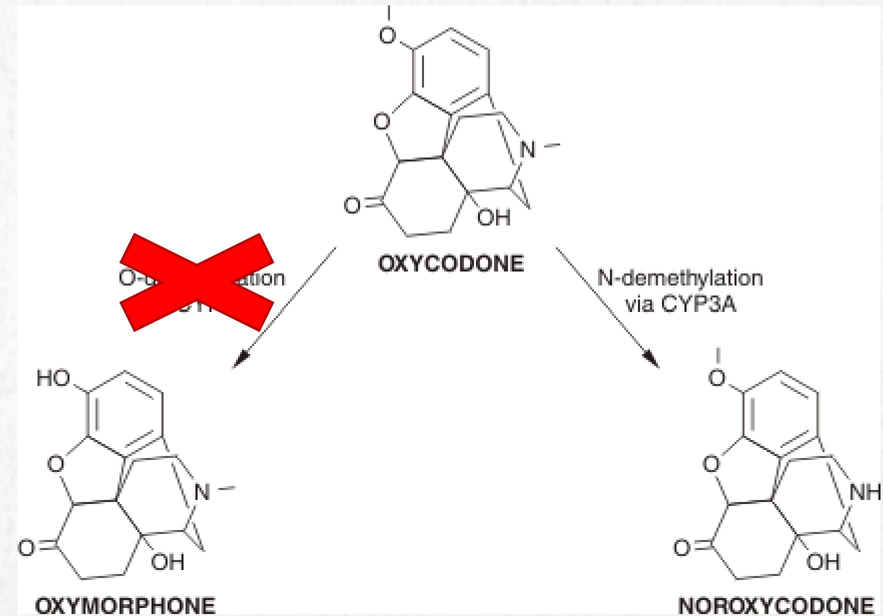
Graphic courtesy of: http://www.bioanalytical.com/library/presentations/biochem/leonard_01/index.html

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

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?



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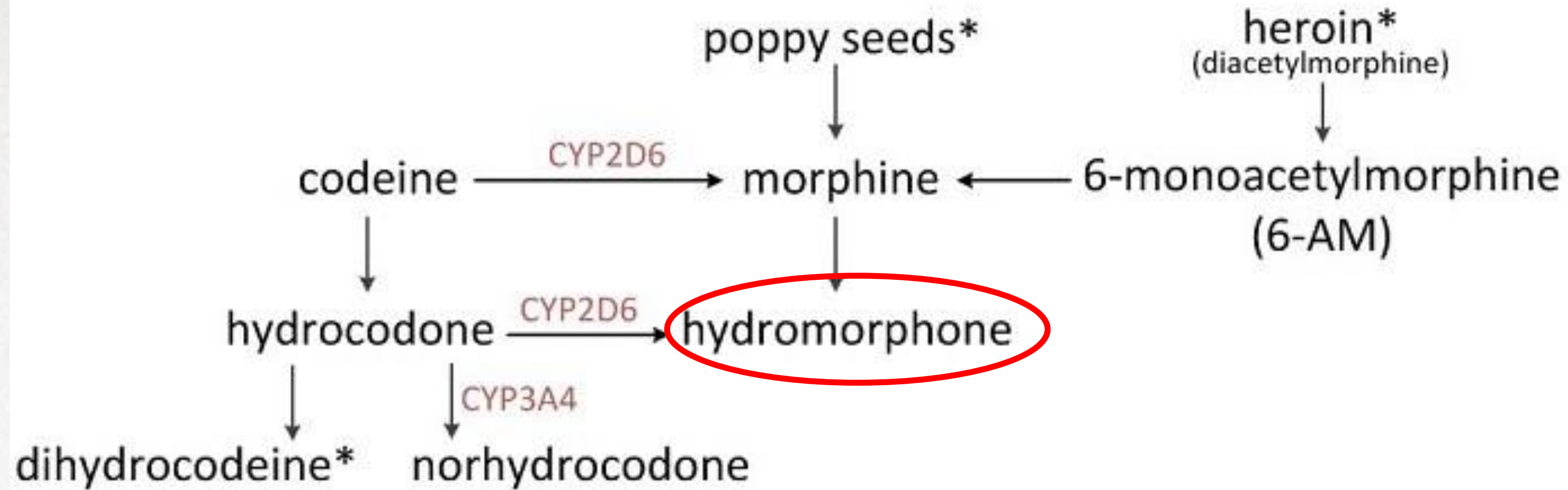

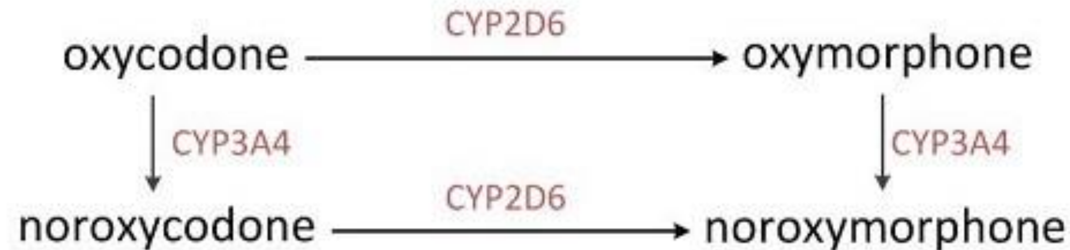

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http://www.arupconsult.com/assets/graphics/OpiatesAndOpiodMetabolism.jpg

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

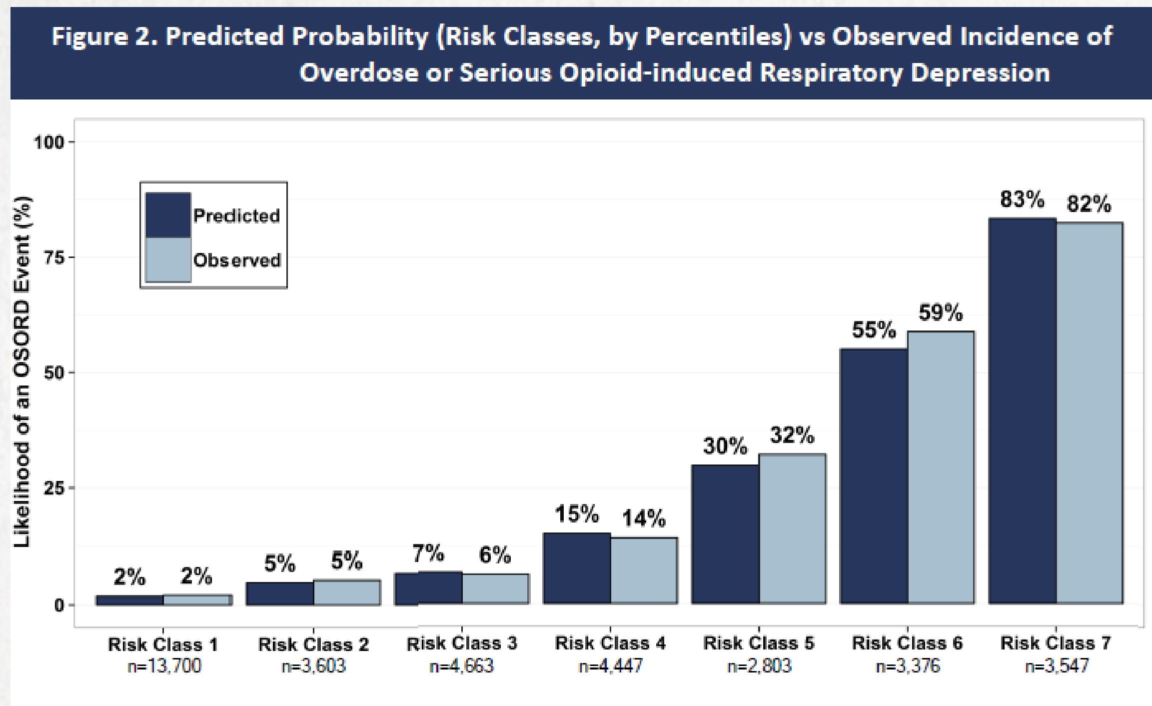
DESIGN

- 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

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 benziodiazepine (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

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

RIOSORD CONSIDERATIONS

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

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

CALCULATE THIS PATIENTS RIOSORD SCORE

PATIENT CASE EXAMPLE #3

- 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%

PATIENT CASE EXAMPLE #4

- 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

CALCULATE THIS PATIENTS RIOSORD SCORE

DID IT CHANGE?

PATIENT CASE EXAMPLE #4

- 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%

PATINET CASE #5

- B.B. 31 yo F who is a regular compliant patient at your pain clinic
- PMH: RSD, insomnia
- Current medications
  - Fentanyl 25mcg/hour transdermally q72hr for the past 3 years
  - Melatonin 5mg PO at bedtime as needed
  - Multivitamin PO daily

CALCULATE THIS PATIENTS RIOSORD SCORE

PATINET CASE #5

- CALCULATE RIOSORD SCORE: **13**
  - Fentanyl = 13 points
- CALCULATE PATIENTS PRECENT RISK: **15%**
- WOULD YOU CONSIDER NALOXONE IN THIS PATIENT?

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%

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. VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives in collaboration with the VA OEND National Support and Development Work Group.

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]
- December 7th 2015, New York Mayor Bill de Blasio and first lady Chirlane McCray announced efforts entail utilizing a physician's standing order by pharmacies to dispense naloxone to patients in more than 150 participating pharmacies[2]

1. http://www.pharmacytimes.com/news/cvs-pharmacists-can-dispense-naloxone-sans-rx-in-12-more-states
2. http://www1.nyc.gov/office-of-the-mayor/news/919-15/de-blasio-administration-launches-comprehensive-effort-reduce-opioid-misuse-overdose-deaths

Utilizing Pharmacists to Increase Naloxone Access

Based on data collected by NASPA (updated February 2016)

Legend
Statewide naloxone protocol or prescriptive authority for pharmacists
Dispensing under standing order is authorized
Broad** collaborative practice provisions
* Broad** collaborative practice provisions but need a separate agreement for each pharmacist

WA OR CA ID NV MT WY UT AZ CO NM ND SD NE KS OK TX MN IA MO AR LA WI IL MI IN OH KY TN MS AL GA FL SC NC VA WV PA NY VT ME NH MA RI CT NJ DE MD DC AK HI

NASPA

**Broad = Allow initiation of therapy, community pharmacists authorized to participate, no drug restrictions (may need to specify within the agreement), laws/regulations silent regarding the relationship between the prescriber and the patient

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**

VALIDATED RISK ASSESSMENT TOOL TO IDENTIFY PATIENTS AT RISK FOR RESPIRATORY DEPRESSION

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