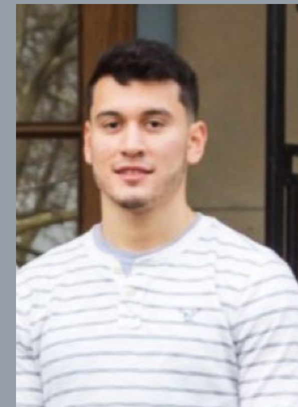
OPIOID WITHDRAWAL & USE OF A PATIENT SCORING TOOL

JOSE LAZO JR., PHARMD

PGY1 PHARMACY RESIDENT

ROBERT WOOD JOHNSON UNIVERSITY HOSPITAL



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- The presenter has no financial relationships with any commercial interests pertinent to this presentation.
- This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand or drug.

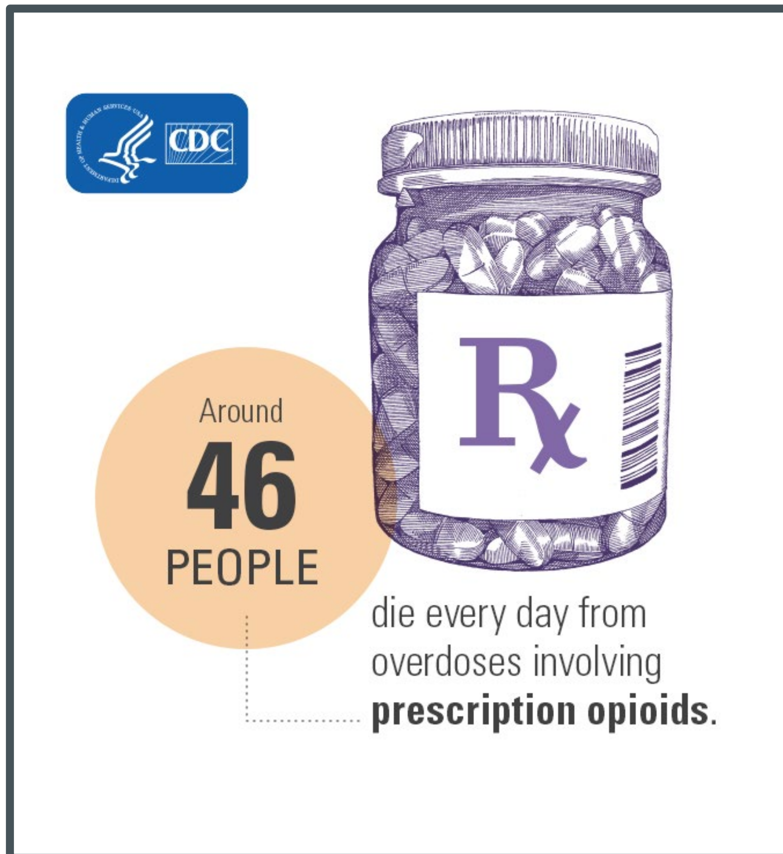
PHARMACIST OBJECTIVES

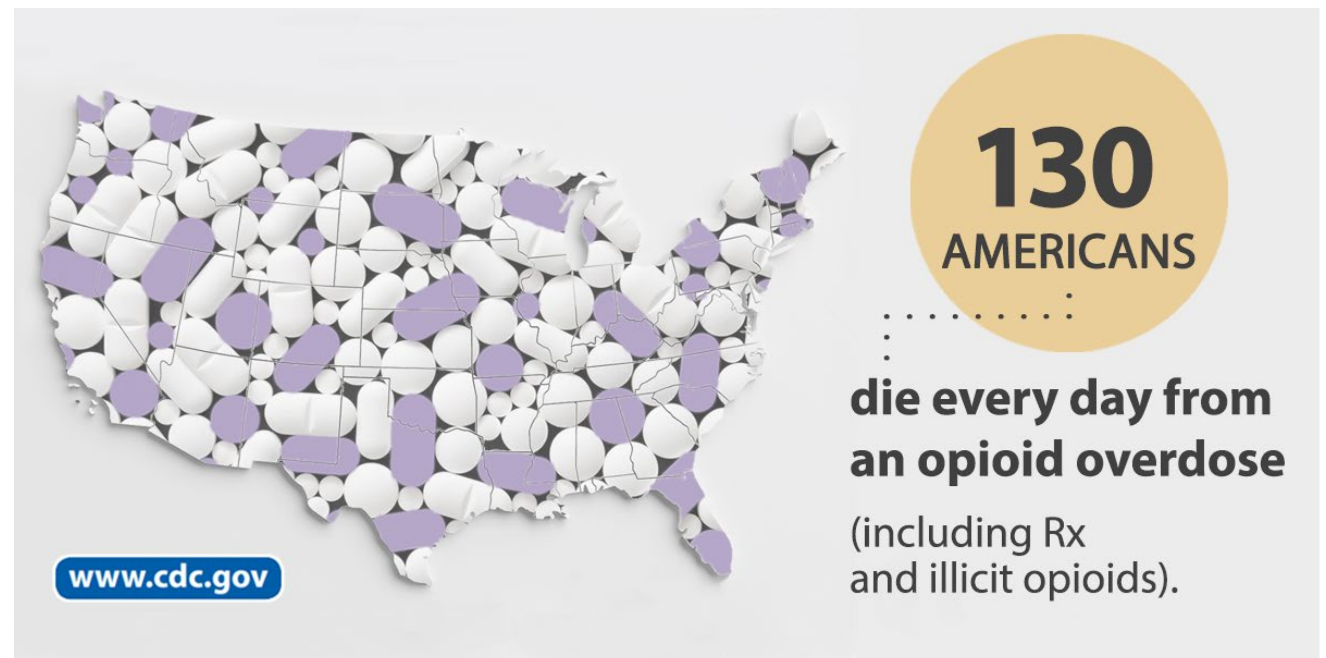
- Identify the signs and symptoms of opioid overdose and withdrawal
- Employ a treatment plan for opioid overdoses
- Interpret a clinical opiate withdrawal scale (COWS) score and formulate a treatment plan for opioid withdrawal

PHARMACY TECHNICIAN OBJECTIVES

- Differentiate between the different types of opioids
- Compare and contrast the clinical presentations of opioid overdose and opioid withdrawal

BACKGROUND

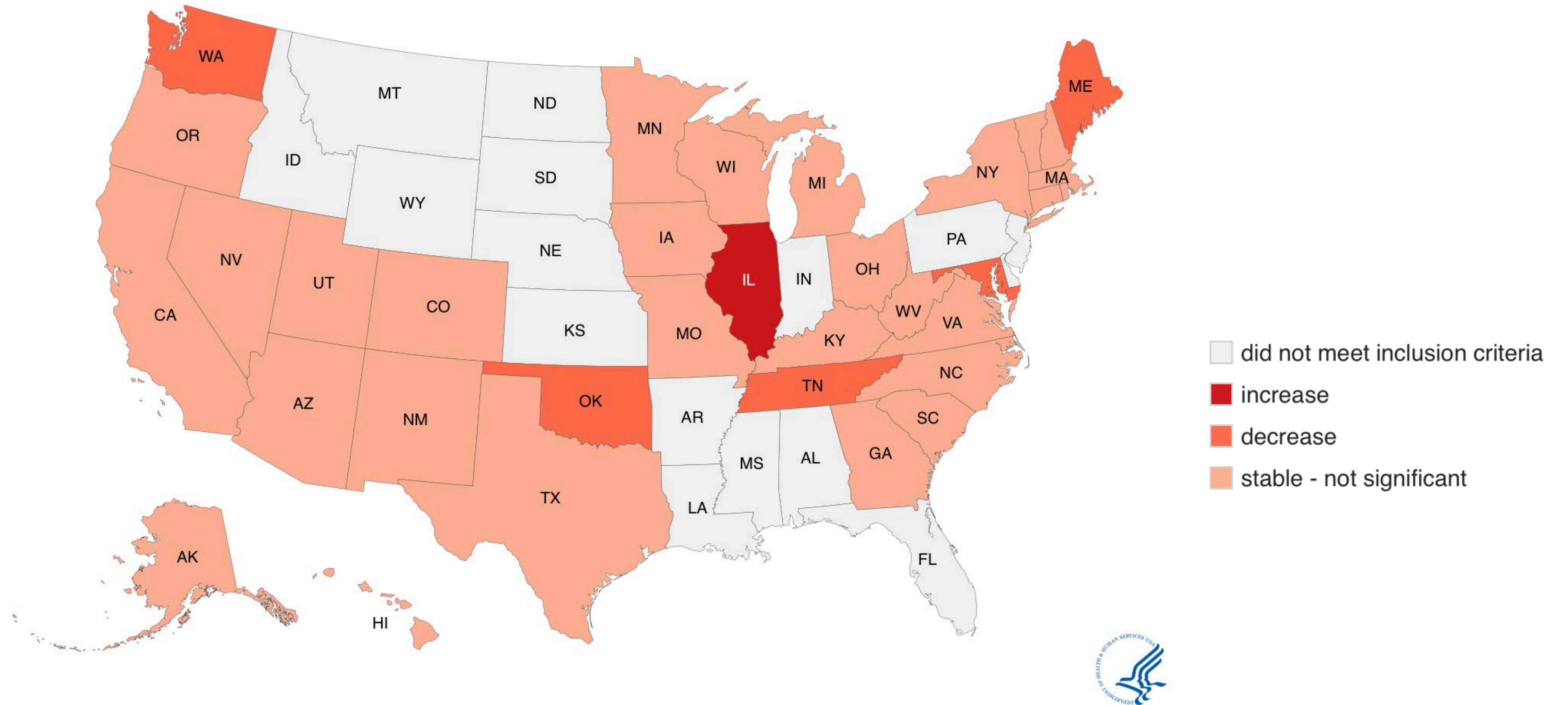




- From 1999 to 2017, almost 400,000 people died from an overdose involving any opioid, including prescription and illicit opioids

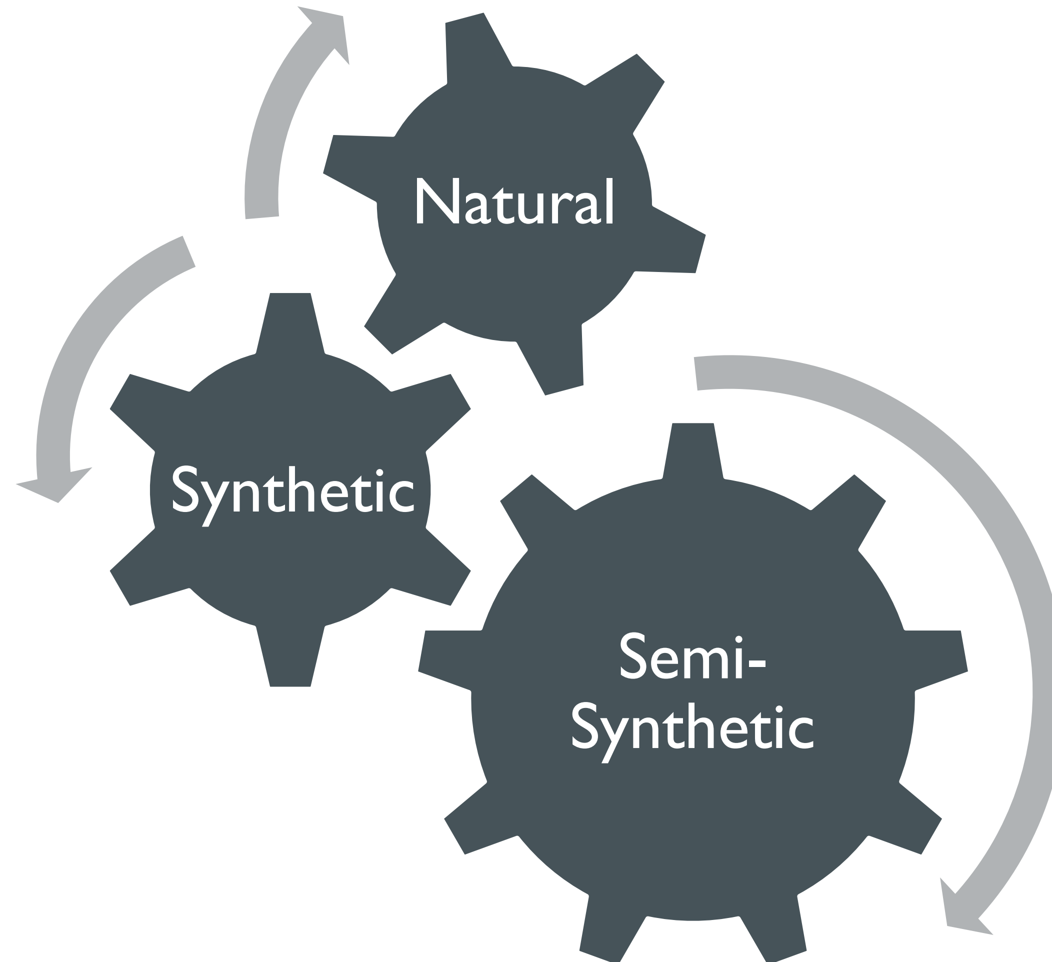
Source: Scholl L, et al.. WR Morb Mortal Wkly Rep. ePub: 21 December 2018.

CHANGES IN DRUG OVERDOSE RATES INVOLVING PRESCRIPTION OPIOIDS

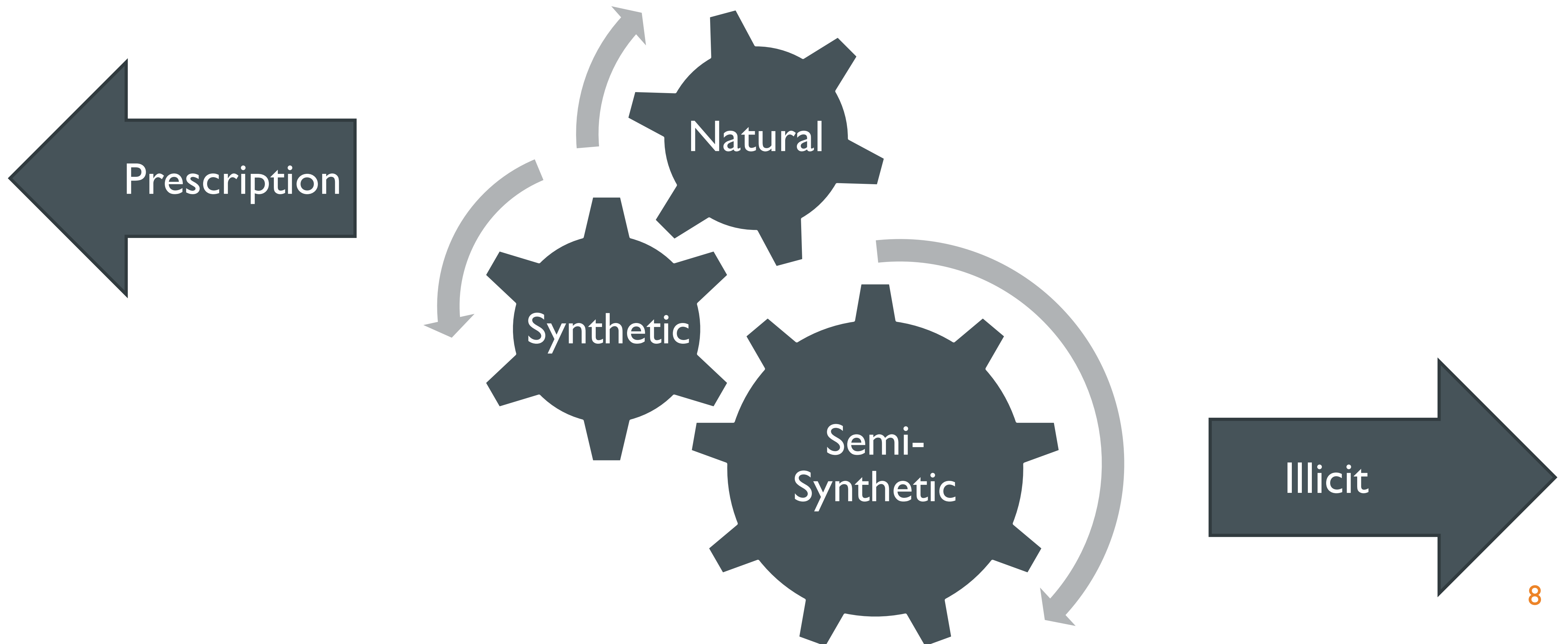


Source: CDC/NCHS, National Vital Statistics System, Mortality. 2018. https://wonder.cdc.gov/.

CATEGORIES OF OPIOIDS



CATEGORIES OF OPIOIDS



MORPHINE

Formulation	Oral (PO) Intravenous (IV)
Duration of Action	Immediate release: 3 to 5 hours Extended release: 8 to 24 hours
Metabolism	Hepatic via glucuronidation to an active metabolite and inactive metabolites
Excretion	Urine as metabolites, caution in renal insufficiency due to accumulation of active metabolites

Source: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

OXYCODONE

Formulation	PO Available in combination with acetaminophen
Duration of Action	Immediate release: 3 to 6 hours Extended release: ≤ 12 hours
Metabolism	Hepatic via CYP3A4 and CYP2D6
Excretion	Urine, mostly as metabolites

Source: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

HYDROCODONE

Formulation	PO Available in combination with acetaminophen
Duration of Action	Immediate release: 4 to 6 hours
Metabolism	Hepatic via CYP2D6 and CYP3A4
Excretion	Urine

Source: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

HYDROMORPHONE

Formulation	PO, IV
Duration of Action	Immediate release: 3 to 4 hours Extended release: ~ 13 hours
Metabolism	Hepatic via glucuronidation to inactive metabolites
Excretion	Urine, primarily as metabolites

Source: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

FENTANYL

Formulation	PO, IV Transdermal
Duration of Action	IV: 0.5 to 1 hour Transdermal: 72 to 96 hours
Metabolism	Hepatic via CYP3A4
Excretion	Urine as metabolites

Source: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

RELATIVE OPIOID POTENCIES

Agent	Route	Equivalent dose (mg)
Morphine	PO IM/IV	30 10
Hydromorphone	PO IM/IV	7.5 1.5
Hydrocodone	PO	30
Oxycodone	PO	20
Fentanyl	IM/IV	0.1
Methadone	PO	Variable

Source: Adapted from Table 44-4 in: Dipiro JT, et al. Pharmacotherapy: A Pathophysiologic Approach. 9th Edition, 2014.

RELATIVE OPIOID POTENCIES: METHADONE

Morphine (PO) Equivalent (total daily dose)	PO Morphine: PO Methadone
<100 mg	3:1
101–300 mg	5:1
301–600 mg	10:1
601–1000 mg	15:1
>1000 mg	20:1

Source: Adapted from Table 44-4 in: Dipiro JT, et al. Pharmacotherapy: A Pathophysiologic Approach. 9th Edition, 2014.

ASSESSMENT QUESTION 1

1. Which of the following opioids is not used in the healthcare setting?

   A. Morphine

   B. Heroin

   C. Hydromorphone

   D. Fentanyl

ASSESSMENT RESPONSE 1

1. Which of the following opioids is not used in the healthcare setting?

A. Morphine

B. Heroin

C. Hydromorphone

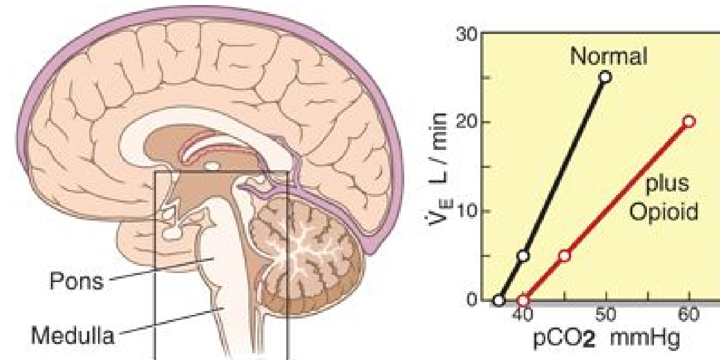
D. Fentanyl

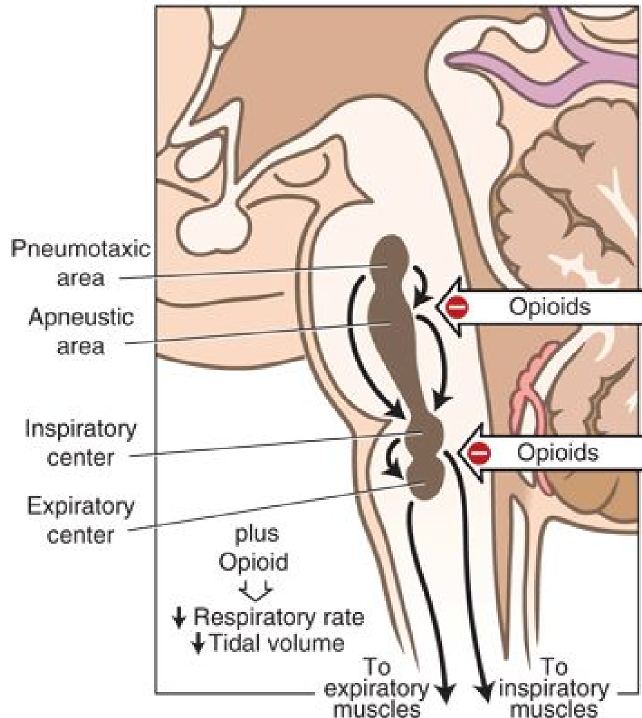
OPIOID ADVERSE EFFECTS

- **Respiratory depression**
- Cardiovascular
  - Hypotension, bradycardia
- Central nervous system effects
  - Depressed level of consciousness
- Gastrointestinal hypomotility
- **Dependence and withdrawal**

Source: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

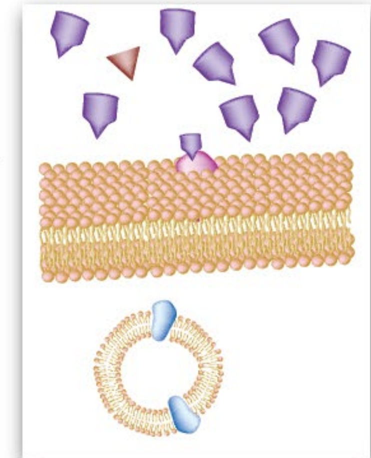
MECHANISM OF OPIOID ADVERSE EFFECTS





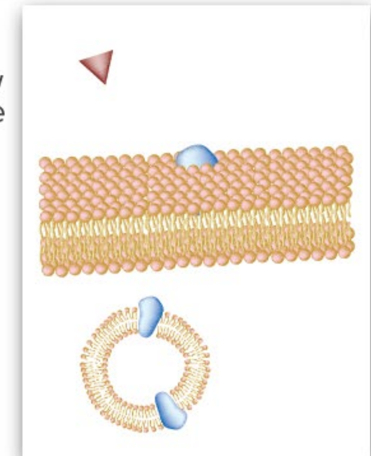
Opioid Tolerance & Opioid Dependence

With few receptors left, regardless of dose opioids, only a few receptors will be activated. The few receptors also require continuing opioids to maintain activity,



Opioid Withdrawal

If opioids are stopped suddenly, the few receptors that are left are also turned off. This causes opioid withdrawal symptoms.



Sources: Accessed from: https://aneskey.com/complications-associated-with-chronic-opioid-therapy/
Accessed from: https://medium.com/dr-ming-kao/opioid-tolerance-dependence-and-withdrawal-821ef0ec7dd7

OPIOID OVERDOSE: CLINICAL PRESENTATION

- Respiratory depression
- Miosis
- Stupor
- Hepatic injury from acetaminophen or hypoxemia
- Absent or hypoactive bowel sounds
- Compartment syndrome
- Hypothermia

Source: Boyer EW. N Engl J Med. 2012 Jul 12;367(2):146-55.

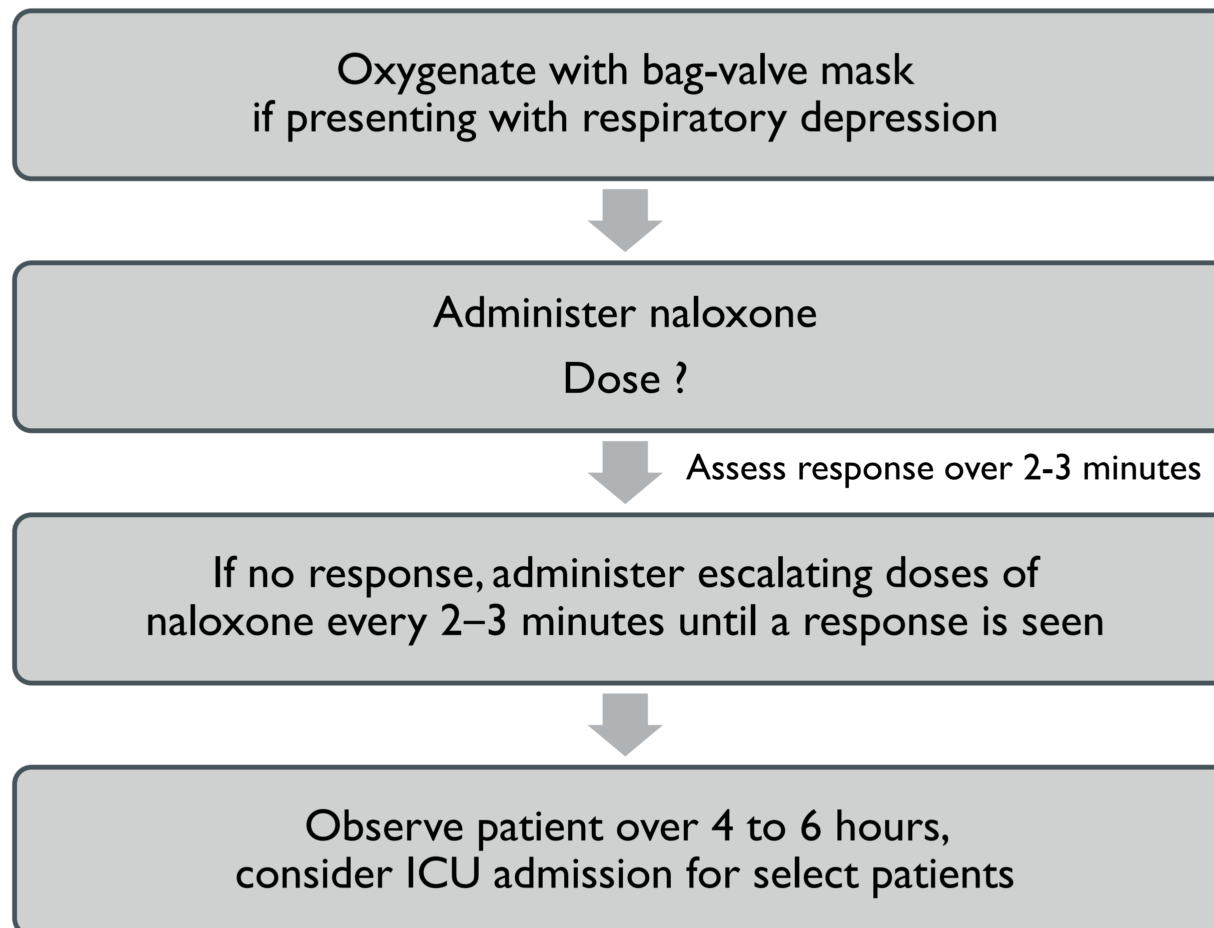
OPIOID OVERDOSE: DIAGNOSIS

DSM-V Diagnostic Criteria for Opioid Intoxication
A. Recent opioid use
B. Clinically significant problematic behavioral or psychological changes that developed during, or shortly after, opioid use • e.g., initial euphoria followed by apathy, dysphoria, psychomotor agitation or retardation, impaired judgement
C. Pupillary constriction (or pupillary dilation due to anoxia from severe overdose) and ≥ 1 of the following signs or symptoms developing during, or shortly after, opioid use: • Drowsiness or coma • Slurred speech • Impairment in attention or memory
D. Signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance

DSM = The Diagnostic and Statistical Manual of Mental Disorders

Source: American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.)2013.

ACUTE MANAGEMENT OF OPIOID OVERDOSE



Source: Boyer EW. N Engl J Med. 2012 Jul 12;367(2):146-55.

NALOXONE

Mechanism of Action	Pure μ-opioid receptor antagonist that competes and displaces opioids at receptor binding sites
Dosing	Variable based on route of administration and clinical scenario
Contraindications	Hypersensitivity
Interactions	Avoid combination with opioid antagonists
Safety Concerns	Acute opioid withdrawal Pulmonary edema and cardiovascular instability have been reported Not recommended for use in pregnant women

Source: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

NALOXONE DOSAGE FOR OPIOID REVERSAL

- Naloxone bolus dose
  - IV: 0.04 mg–2mg
  - IM/SQ: 0.4–2 mg
  - Intranasal: 4mg in one nostril

- Naloxone continuous IV infusion
  - 2.5 to 5 μg/kg/h following a bolus dose
  - Calculated dosage/hour based on effective bolus dose used and duration of adequate response seen

Sources: Rzasa Lynn R, Galinkin JL. Ther Adv Drug Saf. 2018 Jan;9(1):63-88.
Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

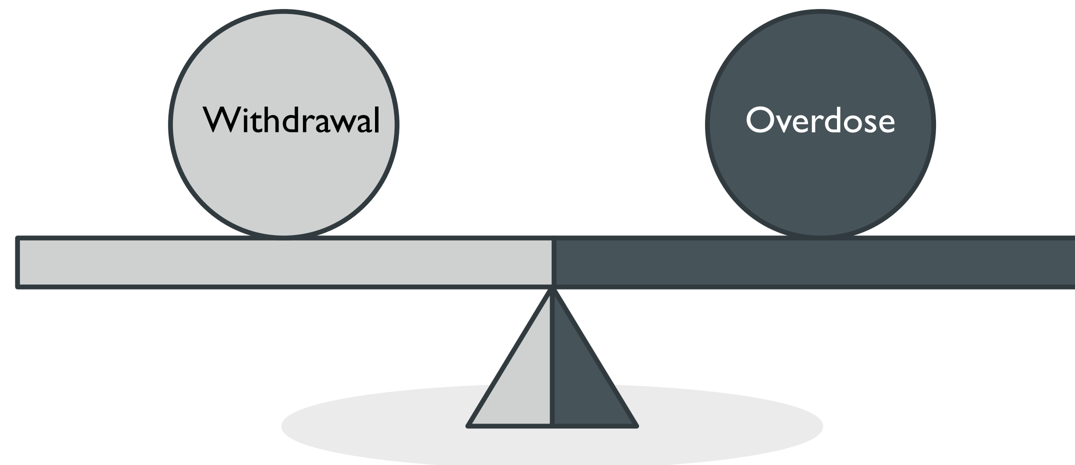
NALOXONE PRODUCT AVAILABILITY

Narcan® nasal spray	4 mg / 0.1mL
Evzio® auto-injector, solution	0.4 mg / 0.4 mL 2 mg / 0.4 mL
Naloxone injection	0.4 mg / mL 2 mg / 2 mL

Sources: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.
Accessed from: https://www.statnews.com/2015/11/18/fda-nasal-spray-overdose/
Accessed from: https://evzio.com/hcp/

BALANCING OVERDOSE AND WITHDRAWAL

- During 2017, over 15,000 people died from drug overdoses involving heroin in the United States
- Heroin was associated with opioid withdrawal in up to 60% in individuals using heroin at least once in prior 12 months
- Reversal of opioid overdose with naloxone may precipitate withdrawal



Sources: Accessed from: https://www.cdc.gov/drugoverdose/data/heroin.html
Hasin DS, et al. Drug Alcohol Depend. 2012 Apr 1;122(1-2):28-37.

OPIOID WITHDRAWAL

DSM-V Diagnostic Criteria for Opioid Withdrawal
A. Presence of either of the following 1. Cessation of (or reduction in) opioid use that has been heavy and prolonged (i.e., several weeks or longer) 2. Administration of an opioid antagonist after a period of opioid use
B. Three (or more) of the following developing within minutes to several days after Criterion A: 1. Dysphoric mood 2. Nausea or vomiting 3. Muscle aches 4. Lacrimation or rhinorrhea 5. Pupillary dilation, piloerection or sweating 6. Diarrhea 7. Yawning 8. Fever 9. Insomnia
C. The signs or symptoms in criterion B cause clinically significant distress or impairment in social, occupational or other important areas of functioning
D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance

Source: American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.)2013.

PROGRESSION OF SIGNS AND SYMPTOMS

- Symptoms usually begin two to three half-lives after the last opioid dose and can last for weeks depending on the agent used and duration of regular use

	Half-lives (hours)	Onset (hours)	Resolution (days)
Buprenorphine	2.2–3	4–48	14–21
Fentanyl (IV)	2–4	2–5	4–5
Heroin	0.5	6–12	7–10
Short acting opioids	-	24–72	14–21
Long acting opioids	-	12–23	10–14
Methadone	8–59	24–72	14–21

Sources: Herring AA, Perrone J, et al. Ann Emerg Med. 2019 Jan 5.
Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

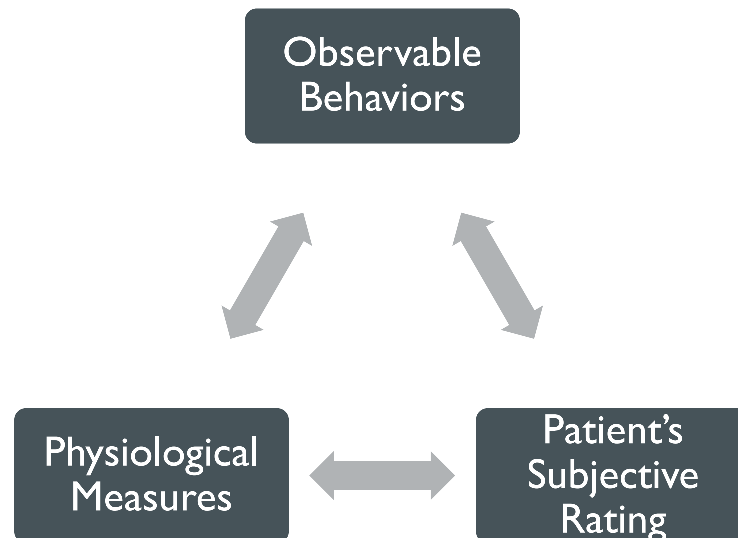
OPIOID WITHDRAWAL SCALES

OOWS	*Objective Opioid Withdrawal Scale* Relies on clinical observation
SOWS	*Subjective Opioid Withdrawal Scale* Patient's rating of opioid withdrawal on a 16-item scale
COWS	*Clinical Opiate Withdrawal Scale* Signs and symptoms of opioid withdrawal, which are both subjective and objective
CINA	*Clinical Institute Narcotic Assessment* Signs and symptoms of opiate withdrawal

Source: Kampman K, Jarvis M. J Addict Med. 2015 Sep-Oct;9(5):358-67.

CLINICAL OPIOID WITHDRAWAL SCALE (COWS)

- An 11-item scale designed to be administered by a clinician



- Opioid withdrawal intensity is a function of: (1) the severity of physical dependence, and (2) the relative occupancy of the µ opiate receptor at a point in time

Source: Wesson DR, Ling W. J Psychoactive Drugs. 2003 Apr-Jun;35(2):253-9.

COWS (1 OF 2)

Resting Pulse Rate: __________beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset:** *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute

Source: Wesson DR, Ling W. J Psychoactive Drugs. 2003 Apr-Jun;35(2):253-9.

COWS (2 OF 2)

Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score ________ The total score is the sum of all 11 items Initials of person completing assessment: ____________

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

Source: Wesson DR, Ling W. J Psychoactive Drugs. 2003 Apr-Jun;35(2):253-9.

INTERPRETATION OF COWS SCORE

- Scores
  - 5 to 12: Mild
  - 13 to 24: Moderate
  - 25 to 36: Moderately Severe
  - > 36: Severe Withdrawal

Source: Wesson DR, Ling W. J Psychoactive Drugs. 2003 Apr-Jun;35(2):253-9.

ASSESSMENT QUESTION 2

- Patient LH is an 80-year-old female with a PMH pertinent for osteosarcoma and severe cancer-related pain and uses fentanyl patches to help control her pain. LH received a visit from her family where they found her to be unresponsive. Upon EMS arrival, LH has a pulse, pinpoint pupils, and is apneic. It is noted that LH has a fentanyl patch on her upper right arm.
- Vital Signs: HR: 60 bpm BP: 110/80 mmHg RR: unmeasurable
- What is LH presenting with?

A. Cardiac arrest

B. Opioid withdrawal

C. Opioid overdose

D. Benzodiazepine withdrawal

ASSESSMENT RESPONSE 2

- Patient LH is an 80 year old female with a PMH pertinent for osteosarcoma and severe cancer-related pain and uses fentanyl patches to help control her pain. LH received a visit from her family where they found her to be unresponsive. Upon EMS arrival, LH has a pulse, pinpoint pupils, and is apneic. It is noted that LH has a fentanyl patch on her upper right arm.
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- What is LH presenting with?

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B. Opioid withdrawal

C. Opioid overdose

D. Benzodiazepine withdrawal

ASSESSMENT QUESTION 3

- What should be the first treatment strategy employed for LH?

A. Administer naloxone 0.4 mg IV

B. Administer epinephrine 1 mg IV

C. Administer flumazenil 0.2 mg IV

D. Initiate bag-mask ventilation

ASSESSMENT RESPONSE 3

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OPIOID WITHDRAWAL TREATMENT OPTIONS

Alpha$_2$-adrenergic agonists	One mechanism underlying opioid withdrawal is noradrenergic hyperactivity, alpha$_2$-adrenergic agonist act centrally to ameliorate symptoms
Gastrointestinal agents	Used for symptomatic managements of symptoms such as stomach cramps, diarrhea, nausea and vomiting
Analgesics	Non-opioid agents used for pain
Opioid Agonists	Taper to alleviate withdrawal symptoms Medication for opioid use disorder (MOUD)

Sources: Kampman K, Jarvis M. J Addict Med. 2015 Sep-Oct;9(5):358-67.
Duber HC, Barata IA, et al. Ann Emerg Med. 2018 Oct;72(4):420-431.

ALPHA$_2$-ADRENERGIC AGONISTS

Clonidine	Lofexidine	Guanfacine
• Dose: 0.1 to 0.3 mg every 6 to 8 hours (max: 1.2 mg/day) • Adverse effects: Hypotension, sedation	• Dose: 0.54 mg four times daily (max: 2.88 mg/day) • Adverse effects: Hypotension, QT prolongation	• Limited evidence • Dose: 3 to 4 mg/day

Source: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

LOFEXIDINE: PHASE III TRIAL

- Lofexidine vs. placebo in a population undergoing abrupt discontinuation from chronically administered short-acting opioids
- Patients received lofexidine 0.8 mg four times daily or matching placebo
- Primary outcome looked at the SOWS-Gossop scale on day three of treatment phase
  - 10 item scale
  - Total score ranges from 0 to 30, with higher scores indicating greater severity of withdrawal symptoms

Source: Vernon MK, Reinders S, et al. Addict Behav. 2016 Sep;60:109-16.

LOFEXIDINE: PHASE III TRIAL (CONT)

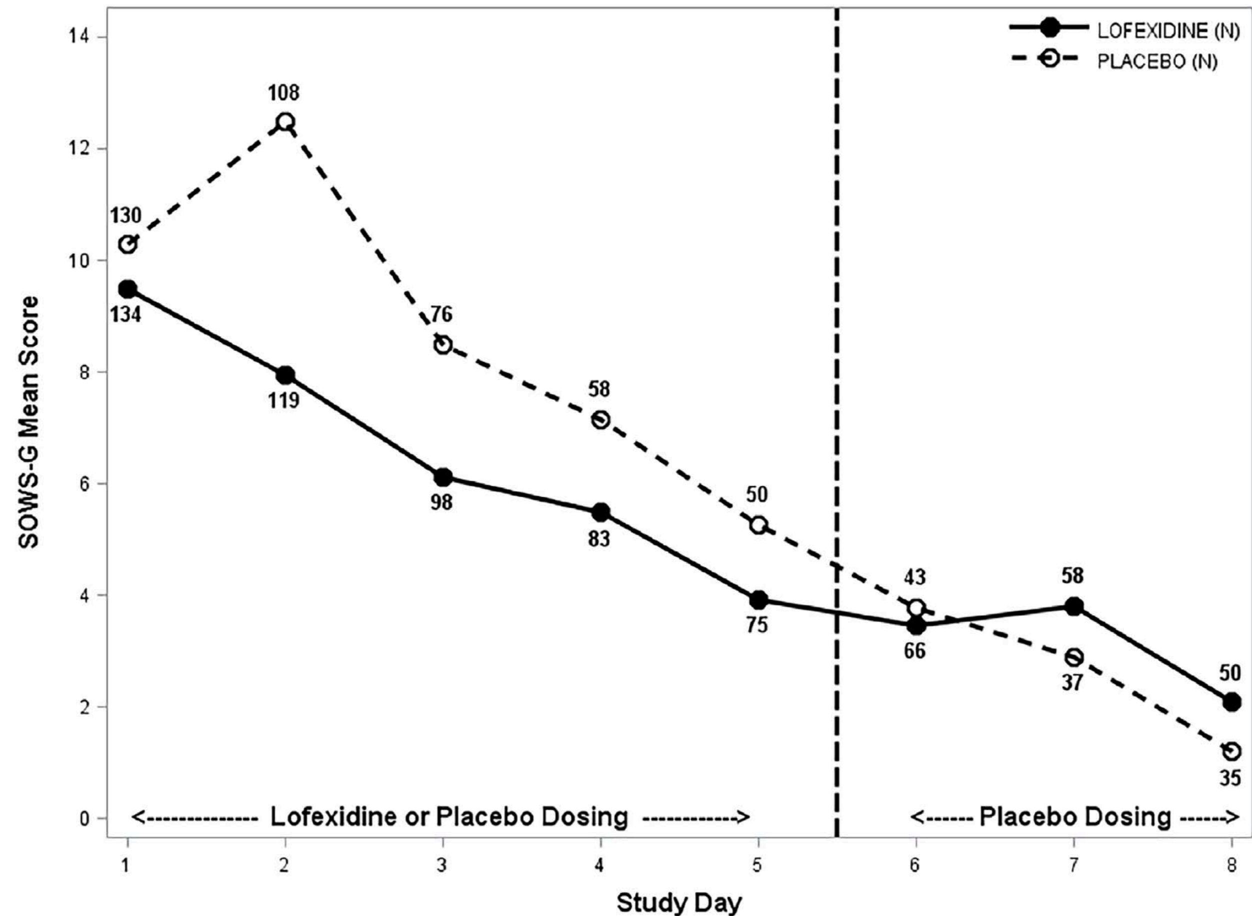


Fig. 2. Effects of lofexidine versus placebo on SOWS-Gossop scores (ITT population).

- Mean day 3 SOWS-Gossop score was approximately 2.4 points lower in the lofexidine group than the placebo group ($p = 0.0212$)
- Lofexidine significantly alleviated symptoms of opioid withdrawal

Source: Vernon MK, Reinders S, et al. Addict Behav. 2016 Sep;60:109-16.

GASTROINTESTINAL AGENTS

Agent	Dose	Alleviates	Considerations
Dicyclomine	20 mg PO q6h prn	Stomach cramps	
Loperamide	2 mg PO q4h prn	Diarrhea	Monitor QTc
Ondansetron	4 mg IV/PO q4h prn	Nausea and vomiting	Monitor QTc
Metoclopramide	10 mg IV/PO q6h prn	Nausea and vomiting	Monitor QTc May worsen diarrhea

Source: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

ANALGESICS

Acetaminophen

650 mg by mouth q6h

Avoid in pts presenting with acetaminophen overdose

Ibuprofen

400–600 mg by mouth q8h

OPIOID AGONIST: METHADONE

Mechanism of Action	Full agonist of at the µ-opioid receptor, produces higher levels of physiological dependence
Dosing	Methadone tapers generally start with doses in the range of 20-30 mg/day, and are completed in 6 to 10 days
Contraindications	Hypersensitivity Respiratory depression Acute bronchial asthma or hypercapnia Known or suspected ileus
Interactions	Extensively metabolized through CYP3A4/2B6/2C19
Safety Concerns	QTc prolongation

Source: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

OPIOID AGONIST: BUPRENORPHINE

Mechanism of Action	High affinity for μ-opioid receptors in the CNS, displays partial μ agonist and weak κ-opioid antagonist activity, with less physiological dependence
Dosing	Dose sufficient to suppress withdrawal symptoms (4 to 16 mg/day) and then dose is tapered (taper can be brief, over 3 to 5 days, or as long as 30 days)
Contraindications	Hypersensitivity Severe liver impairment
Interactions	Metabolized via CYP3A4
Safety Concerns	Precipitated withdrawal (start once a patient exhibits withdrawal symptoms)

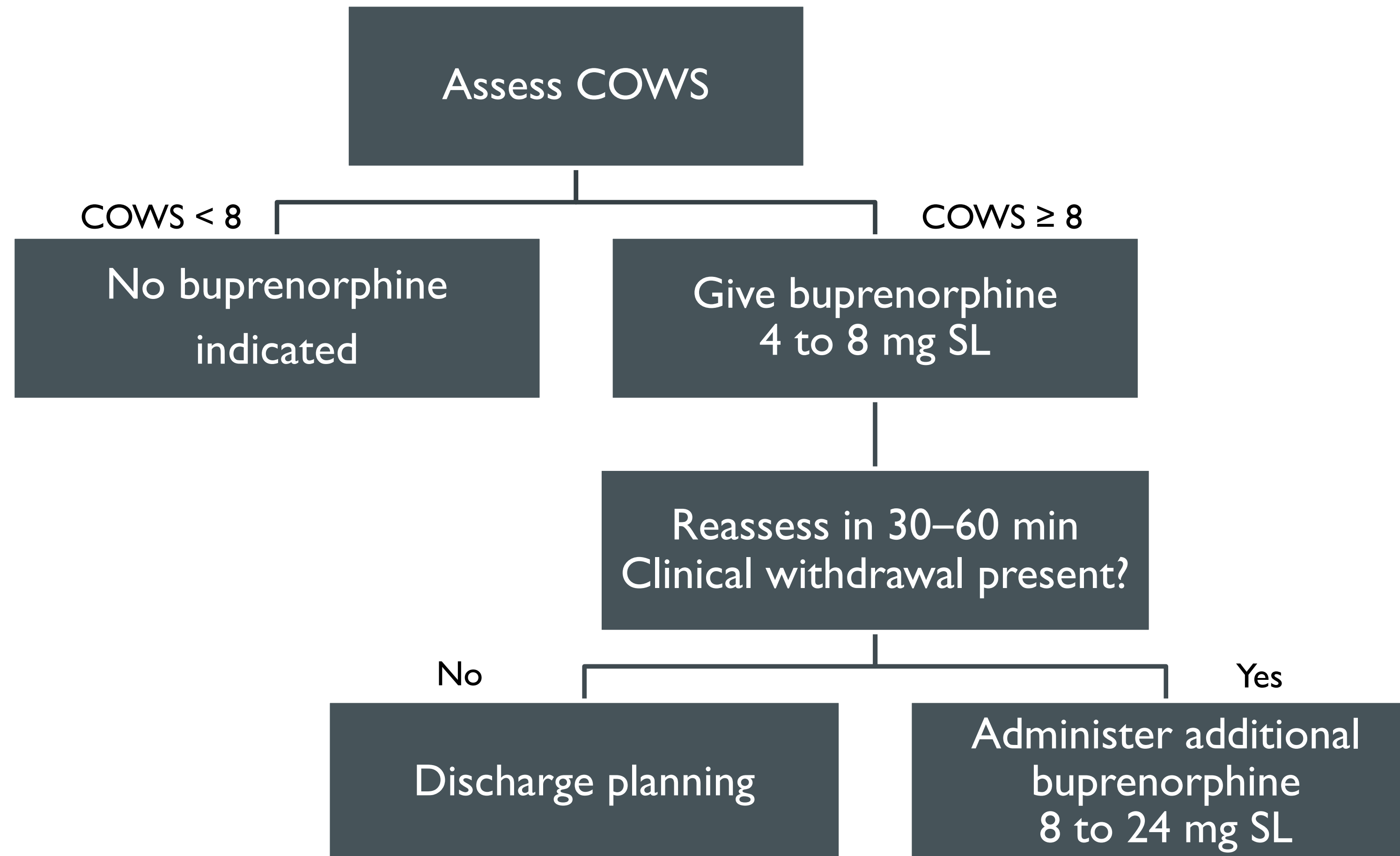
Source: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

BUPRENORPHINE PRODUCT AVAILABILITY

Subetex ® sublingual tablet, buprenorphine	2 mg 4 mg	
Suboxone ® sublingual tablet, buprenorphine/naloxone	2 mg / 0.5 mg 4 mg / 1 mg	8 mg / 2 mg 12 mg / 3 mg
Suboxone ® sublingual film, buprenorphine/naloxone	2 mg / 0.5 mg 4 mg / 1 mg	8 mg / 2 mg
Zubsolv ® sublingual tablet buprenorphine/naloxone	1.4 mg / 0.36 mg 5.7 mg / 1.4 mg	
Bunavail ® buccal film, buprenorphine/naloxone	2.1 mg / 0.3 mg 4.2 mg / 0.7 mg	6.3 mg / 1 mg

Source: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Apr 22nd, 2019.

SAMPLE STRATEGIES TO USE BUPRENORPHINE



Source: Herring AA, Perrone J, Nelson LS.. Ann Emerg Med. 2019 Jan 5.

ASSESSMENT QUESTION 4

- A 60-year-old male presents to the ED with complaints of chills, nausea and anxiousness. On physical exam, he is noted to be tachycardic and with moderately dilated pupils. Patient admits to last using heroin 24 hours ago.
- Vitals: BP 94/66 mmHg HR 120 bpm Temp 98.8 F RR 14 bpm
- The physician assesses the patient's COWS as 28.
- **What severity of opioid withdrawal is the patient experiencing?**

A. Mild

B. Moderate

C. Moderately Severe

D. Severe

ASSESSMENT RESPONSE 4

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- The physician assesses the patient's COWS as 28.
- **Which agents would be appropriate to treat the symptoms of opioid withdrawal that the patient is experiencing?**

A. Ondansetron 4 mg PO

B. Buprenorphine 8 mg SL

C. Clonidine 0.1 mg PO

D. A and B

E. A and C

ASSESSMENT RESPONSE 5

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C. Clonidine 0.1 mg PO

D. A and B

E. A and C

THANK YOU!

Jose Lazo Jr., Pharm D, PGY-1 Pharmacy Resident

jose.lazo@rwjbh.org