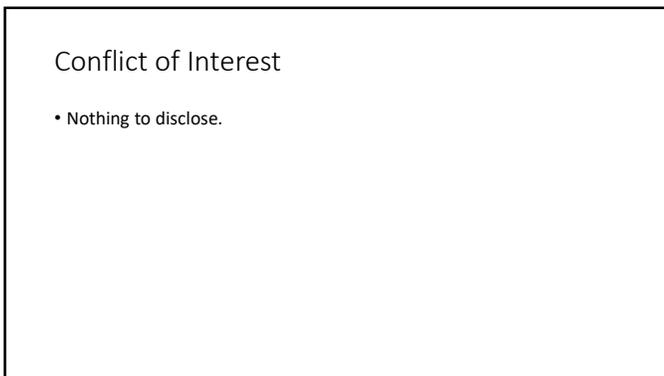
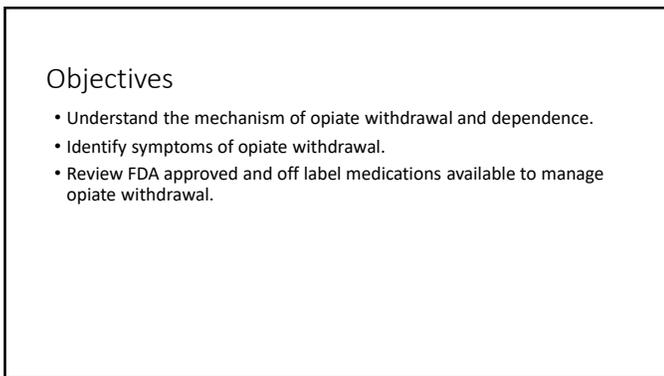


1



2



3

Clinical scenario

- 78 y/o male patient with lumbar post laminectomy syndrome, COPD and anxiety is being admitted to the skilled nursing facility. Discharge report from acute hospital describes that the patient underwent an admission to the acute medical hospital related to uncontrolled pain and failure to thrive for 3 days after discharged to SNF for skilled services.
- VS on admission: HR 115 RR 18 BP 178/99 Pulse Ox. 98% Pain scale: 10/10
- PE: Rhinorrhea, piloerection, diarrhea, tremors, irritable, restless and referring that "everything hurts"
- On further history the patient refers that he used to be on Fentanyl 200 mcg/hr and Hydromorphone 8 mg 6 times a day as needed for pain. Recently moved to Florida from Michigan and was unable to obtain a pain management physician that will prescribe his prior pain regimen recommended by his physician in Michigan

4

CLINICAL SCENARIO

- 35 y/o female patient that is admitted to hospital for diffuse abdominal pain. On exam she appears restless, anxious and complaining of having goosebumps, abdominal pain, diarrhea, chills and multiple joint pain.
- Contrast enhanced CT scan was negative. Labwork is unremarkable.
- She refers that prior to her hospital stay she was snorting oxycodone multiple times a day.

5

OPIATE WITHDRAWAL

- Generalized CNS suppression that occurs with opioid use is replaced by CNS hyperactivity.
- Severity of withdrawal and time to onset of withdrawal depends on the drug/route/half-life of the drug.
- Less likely to produce severe morbidity or mortality.

6

OPIATE WITHDRAWAL

- Spontaneous opioid withdrawal
 - Patient who is physiologically dependent upon opioids reduces or stops opioid use abruptly.

7

OPIATE WITHDRAWAL

- Precipitated opioid withdrawal
 - Physiological dependence upon opioids and who has or recently had opioids in his/her system is administered an opioid antagonist (e.g. naloxone) or an opioid partial agonist (buprenorphine).

8

OPIATE WITHDRAWAL DIAGNOSIS CRITERIA
IV V NSDUH

Opioid		IV	V	NSDUH
Three or more symptoms		✓	✓	✓ ¹ ✓ ²
Dysmorphic mood		✓	✓	✓ ¹ ✓ ²
Nausea or vomiting		✓	✓	✓ ¹ ✓ ²
Muscle aches		✓	✓	✓ ¹ ✓ ²
Lacrimation or rhinorrhea		✓	✓	✓ ¹ ✓ ²
Yawning		✓	✓	✓ ¹ ✓ ²
Pupillary dilation, piloerection, or sweating		✓	✓	✓ ¹ ✓ ²
Diarrhea		✓	✓	✓ ¹ ✓ ²
Fever		✓	✓	✓ ¹ ✓ ²
Insomnia		✓	✓	✓ ¹ ✓ ²

9

OPIATE WITHDRAWAL

According to *DSM-5*, the following disorders must be ruled out first when treating a patient with opioid withdrawal.

- **Opioid-Induced Mental Disorders**
- **Other Substance Intoxication**
- **Other Withdrawal Disorders**

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Opiate withdrawal

- Initial phase-acute withdrawal
- Chronic and Protracted Abstinence

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DSMV IV vs DSMV 5

	DSM-IV Abuse ^a		DSM-IV Dependence ^b		DSM-5 Substance Use Disorders ^c	
Hazardous use	X	} ≥1 criterion	-	} ≥3 criteria	X	} ≥2 criteria
Social/interpersonal problems related to use	X		-		X	
Neglected major roles to use	X		-		X	
Legal problems	X		-		-	
Withdrawal ^d	-	X	X	X		
Tolerance	-	X	X	X		
Used larger amounts/longer	-	X	X	X		
Repeated attempts to quit/control use	-	X	X	X		
Much time spent using	-	X	X	X		
Physical/psychological problems related to use	-	X	X	X		
Activities given up to use	-	X	X	X		
Craving	-	-	-	X		

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OPIATE WITHDRAWAL

- Moderate-Advanced
- Abdominal cramps
 - Hot or cold flashes
 - Increased pulse and BP
 - Insomnia
 - Low-grade fever
 - Muscle and bone pain
 - Muscle spasms
 - Mydriasis
 - Nausea and vomiting

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OPIATE WITHDRAWAL

- EARLY TO MODERATE
- Anxiety
 - Craving
 - Dysphoria
 - Mydriasis
 - Perspiration
 - Piloerection
 - Restlessness
 - Rhinorrhea
 - Yawning

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Table 1. Typical Withdrawal Characteristics of Various Opioids

Opioid	Half-Life (Adults)	Onset of Withdrawal Symptoms After Exposure	Onset of Withdrawal Symptoms After Prenatal Exposure	Typical Duration of Withdrawal
Heroin	2-6 min ^a	6 h	24-48 h	8-10 days
Methadone	8-150 h (mean 35 h)	24-96 h	48-72 h	10-14 days, secondary withdrawal as long as 6 mo
Buprenorphine	Mean 37 h	6-24 h	36-60 h	Milder withdrawal than other opioids. Usually resolves within 7 days, but may be prolonged in neonates
Morphine	1.5-7 h	8-12 h	ND	7-10 days
Oxycodone	3-5 h	6-12 h	36-72 h	7-14 days, secondary withdrawal as long as 6 mo
Hydrocodone	7-9 h	8-12 h	24-96 h	5-14 days, secondary withdrawal as long as 6 mo
Fentanyl ^b	11-36 h (mean 21 h)	3-5 h	ND	4-5 days

^a Heroin is metabolized to morphine-6-glucuronide and morphine.
^b min: minute; ND: no data available.
 Source: References 4, 5, 11, 12, 14, 16, 18, 25.

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CLINICAL OPIATE WITHDRAWAL
SCALE (COWS)

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Patient's Name: _____ Date and Time ____/____/____:____	
Reason for this assessment: _____	
Resting Pulse Rate: _____beats/minute <i>Measured after patient is sitting or lying for one minute</i> 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

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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 <i>If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored</i> 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 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection
Runny nose or tearing <i>Not accounted for by cold symptoms or allergies</i> 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
 This version may be copied and used clinically

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OPIATE WITHDRAWAL

Pharmacological management of opioid withdrawal is done via one of the following:

- Gradual cessation of an opioid agonist (methadone)
- Short-term use of a partial mu-opioid agonist (buprenorphine)
- Detoxification using opioid antagonists (naltrexone and naloxone)

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OPIATE AGONIST TREATMENT (OAT)

METHADONE

- Mu-agonist
- Synthetic opioid analgesic
- Principal therapeutic uses: analgesia and for detoxification or maintenance in opioid addiction

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OPIATE AGONIST TREATMENT (OAT)

Regulatory Exceptions To The General Requirement For Certification To Provide Opioid Agonist Treatment:

- During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis).
- During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21CFR 1306.07(b)).

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OPIATE AGONIST TREATMENT (OAT)

Methadone

- Inhibits cardiac potassium channels and prolongs the QT interval.
- QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed.
- More commonly associated with, but not limited to, higher dose treatment (> 200 mg/day).

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OPIATE AGONIST TREATMENT (OAT)

- Initial dose for methadone: 10 to 30 mg, with reassessment in 3–4 hours, and a second dose not to exceed 10 mg on day 1.
- The usual daily dosage of methadone ranges from 60 to 120 mg.
- Dosage increase in 5–10-mg increments applied no more frequently than every 7 days.

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OPIATE AGONIST TREATMENT (OAT)

BUPRENORPHINE

- Semi-synthetic opioid.
- Buprenorphine is a partial mu receptor agonist
- Buprenorphine is a DEA Schedule III medication.

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OPIATE AGONIST TREATMENT (OAT)

Buprenorphine has three FDA indications:

- Opioid detoxification
- Opioid maintenance

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BUPRENORPHINE

- Induction when opiate withdrawal present and in divided dose.
- Short-acting opioid: on Day 1, up to 8 mg/2 mg buprenorphine-naloxone sublingual film (in divided doses). On Day 2, up to 16 mg/4 mg of Buprenorphine sublingual film as a single dose.
- Long-acting opioid product: induction recommended on Days 1-2 of treatment.

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BUPRENOPRHINE

- Maintenance: the target dosage 16 mg/4 mg as a single daily dose.
- Precipitation of Opioid Withdrawal Signs and Symptoms:
 - IV use of buprenorphine-naloxone
 - Sublingual or buccal administration before the agonist effects of other opioids have subsided.

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OPIATE AGONIST THERAPY (OAT)

- The US FDA approves dosing to a limit of 24 mg per day.
- Methadone to buprenorphine: methadone (≤ 30 mg per day).
- Switch from buprenorphine to naltrexone, 7–14 days should elapse between the last dose of buprenorphine and the start of naltrexone.

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OPIATE WITHDRAWAL

- Detoxification without effective relapse prevention treatment is usually not successful intervention for opioid dependence.
- Most effective relapse prevention strategies include agonist substitution and maintenance treatment.

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NALOXONE

- Prevents or reverses the effects of opioids including respiratory depression, sedation and hypotension.
- Can reverse the psychotomimetic and dysphoric effects of agonist-antagonists, such as pentazocine.
- Naloxone is an essentially pure opioid antagonist.

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NALOXONE

- Mechanism of action of naloxone is not fully understood,
- *In vitro* evidence suggests it antagonizes opioid effects by competing for the mu, kappa, and sigma opiate receptor sites in the CNS, with the greatest affinity for the mu receptor.

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NALOXONE

- Initial dose of 0.4 mg to 2 mg of naloxone hydrochloride may be administered intravenously. Repeated at 2 to 3 minute intervals PRN
- If no response is observed after 10 mg of naloxone hydrochloride have been administered, the diagnosis of opioid induced or partial opioid induced toxicity should be questioned.

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Symptomatic treatment

- Benzodiazepines
- NSAIDs
- Anti-emetics
- Anti-diarrheal agents
- Hypnotic agents

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CLONIDINE: Not US FDA approved.

- Alpha adrenergic agonist.
- Orally or transdermally at doses of 0.1–0.3 mg every 6–8 hours, with a maximum dose of 1.2 mg daily.
- Its hypotensive effects often limit the amount that can be used.

34

LOFEXADINE

- Alpha2-adrenergic receptor agonist.
- Chronic opiate use there is a compensatory mechanism of continuous negative feedback. Thus chronic opiate use translates into an exacerbated production of cAMP and norepinephrine release.
- Lofexidine replaces the opioid driven inhibition of cAMP production by activating the alpha2-adrenergic receptor and moderating the symptoms of opiate withdrawal.

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LOFEXADINE

- **DOSAGE:** (3) 0.18 mg tablets taken orally 4 times daily at 5- to 6-hour intervals.
- **DURATION:** up to 14 days with dosing guided by symptoms.
- **DISCONTINUATION:** gradual dose reduction over 2 to 4 days.

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LOFEXADINE

- DRUG INTERACTIONS:
- Methadone
- Oral Naltrexone
- CYP2D6 Inhibitors

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ALPHA ADRENERGIC AGONIST

Cochrane Review:

- Clonidine and lofexidine are more effective than placebo for the management of withdrawal from heroin or methadone.
- No significant difference in efficacy between treatment regimens based on clonidine or lofexidine and those based on reducing doses of methadone over a period of around 10 days.
- Methadone was associated with fewer adverse effects than clonidine, and lofexidine has a better safety profile than clonidine.

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Opiate agonist vs alpha adrenergic agonist

- Very low to moderate evidence for the comparison of buprenorphine vs clonidine or lofexidine.
- Low to moderate evidence for buprenorphine versus methadone
- Very low to low for the comparison of different rates of dose reduction.

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ALPHA ADRENERGIC AGENTS

- Clonidine and lofexidine are more effective than placebo for the management of withdrawal from heroin or methadone.
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- Methadone was associated with fewer adverse effects than clonidine, and lofexidine has a better safety profile than clonidine.

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BACLOFEN

- GABA_B receptor agonist baclofen may be useful in treatment of opioid dependence.
- Significant superiority over placebo in terms of opiate withdrawal syndrome and depressive symptoms.
- Evidence still lacking.

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Bibliography

- Kampman, K., & Jarvis, M. (2015). American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. *Journal of addiction medicine*, 9(5), 358–367. doi:10.1097/ADM.0000000000000166
- Gowing L, Farrell M, Ali R, White JM. Alpha-adrenergic agonists for the management of opioid withdrawal. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD002024. DOI: 10.1002/14651858.CD002024.pub5
- Diaper, A. M., Law, F. D., & Melichar, J. K. (2014). Pharmacological strategies for detoxification. *British journal of clinical pharmacology*, 77(2), 302–314. doi:10.1111/bcp.12245
- Gowing L, Ali R, White JM, Mbwewe D. Buprenorphine for managing opioid withdrawal. Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD002025. DOI: 10.1002/14651858.CD002025.pub5
- Gowing L, Farrell M, Ali R, White JM. Alpha-adrenergic agonists for the management of opioid withdrawal. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD002024. DOI: 10.1002/14651858.CD002024.pub5.
- National Center for Biotechnology Information, PubChem Database. Lofexidine. CID=30668. <https://pubchem.ncbi.nlm.nih.gov/compound/Lofexidine> (accessed on Aug. 19, 2019)
- Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253–9.
- Scherbaum N, Klein S, Kaube H, Kienbaum P, Peters J, Gastpar M. (1998). Alternative strategies of opiate detoxification: evaluation of the so-called ultra-rapid detoxification. *Pharmacopsychiatry*, 31(6):205-9.
- Shah M, Huecker MR. Opioid Withdrawal. [Updated 2019 Jun 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK526017>

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Bibliography

- Behnam, B., Semnani, V., Saghafi, N., Ghorbani, R., Dianak Shori, M., & Ghooshchian Choobmasjedi, S. (2012). Gabapentin Effect on Pain Associated with Heroin Withdrawal in Iranian Crack: a Randomized Double-blind Clinical Trial. *Iranian journal of pharmaceutical research: IJPR*, 11(5), 979–983.
- Stotts, A. L., Dodrill, C. L., & Kosten, T. R. (2009). Opioid dependence treatment: options in pharmacotherapy. *Expert opinion on pharmacotherapy*, 10(11), 1727–1740. doi:10.1517/14656569093037168
- Ayman Fareed, Sreedevi Viyatapalli, Jennifer Casarelli, Richard Amar & Karen Drexler (2010) Heroin antitraging medications: A systematic review, *The American Journal of Drug and Alcohol Abuse*, 36:6, 332-341, DOI: 10.3109/10552990.2010.569991
- Mendelson J, Flower K, Pletcher MJ, Galloway GP. (2008). Addiction to prescription opioids: characteristics of the emerging epidemic and treatment with buprenorphine. *Experimental and clinical psychopharmacology*, 16(5):435-41
- National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. *Effective Medical Treatment of Opiate Addiction. JAMA*, 1998;280(2):1936–1943. doi:10.1001/jama.280.17.1936
- Mattick, RP, Breen, C, Kimber, J, Davoli, M. (2003) *Methodone maintenance therapy versus no opioid replacement therapy for opioid dependence*. The COCHRANE database of systematic reviews, 2 (2). CD002209. ISSN 1469-493X
DOI: <https://doi.org/10.1002/14651858.CD002209>
- American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, Washington, DC, American Psychiatric Association page 541.

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Thank You!

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