

Worldwide problem

- Approximately 450,000 deaths in the world due to drug use in 2015 Approximately 430,000 deaths in the world divide the 76% of deaths due to Opiate use disorder (OUD)
 People who inject drugs (PWID)
 10.6 million worldwide in 2016
 Have the greatest health risks
 > 50% live with hepatitis C
 1 in 8 live with HIV

- In 2016 only 1 in 6 people with substance use disorders (SUD) got Only 79 countries have harm reduction strategies or MAT
 Only 34 countries have HIV testing for PWID

Worldwide problem

- Prisoners are at higher risks for infectious diseases but lack access to care
- Afghan opium poppy cultivation drives record opiate production
 65% increase in production between 2016-2017
 More than 75% of world opium cultivation is in Afghanistan
- Dark web closures effect was minimal





Pharmaceutical Opioids

- The misuse of pharmaceutical opioids (Tramadol) is increasing • West and North Africa
 - Near and Middle East
- Increasing misuse of opioids in Western and Central Europe (Rx pain medication)
 - Overdose deaths also from fentanyl and its analogues

Australia

- 14 million prescriptions for opiates written every year
 69% of drug-related deaths in 2015 were due to a prescription drug

- Naloxone Pilot Program offers Naloxone spray (Nyxoid) for free to certain individuals in NSW, SA, WA through Feb 2021
 Shift from heroin to prescription opiates

 Codeline has been changed from over the counter to Schedule 4 (prescription only)
 PDMPS implemented to monitor prescriptions for opiates
 Introduction of abuse deterrent formulations
- Initialization of sectors
 Initialization with Naloxone (take home naloxone or THN to reduce overdose deaths nasal spray available OTC
 Opiate substitution therapy (MAT in US)
 Only 10% of practitioners trained to prescribe

In the United States

- Almost half of Americans have a family member or close friend who's been addicted to drugs
- For the first time in 50 years, life expectancy in the USA has declined for 2 consecutive years. • A key factor was unintentional injuries, which include overdose deaths
- Over 20 million Americans over age 12 had a substance use disorder in 2016
 Opiates 2 million
 Alcohol 15 million

 - - National Survey on Drug Use and Health, 2016

















- Prescription pain relievers
 - Hydrocodone (Vicodin) dental work / injuries
 Oxycodone (Oxycontin, Percocet) for moderate severe pain
 - Oxymorphone (Opana) for moderate severe pain
 - Morphine (Kadian / Avinza) surgery pain
 Codeine for mild pain / cough / diarrhea
- Heroin
- Synthetic opioids such as Fentanyl 50-100 times more potent than morphine



















Deaths from illicit opioids

- The highest rise is from deaths associated with heroin
- 6.2 fold increase (2002-2015)







 Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response.

- response.
 Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.
 Addiction is a primary, chronic disease of brain reward, motivation, memory, (decision making) and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.



Case – Sara and Ben

- Patient is 28 y.o. white female who lives in a small mountain town in Colorado with her boyfriend of 5 years. Both have been using heroin for 3 years.
- Both are underweight, Sara has had no period for over 2 years
- They have tried to get off heroin but one or the other relapses
- Very resistant to maintenance therapy with suboxone
- Subsistence lifestyle



- Adjunctive medications for
- withdrawal Clonidine 0.1 mg every 4-6 hours
 Trazadone for sleep
- Induction protocol

• COWS score > 12-13

Medication Assisted Treatment - Benefits

- Allow reestablishment of homeostasis of the reward pathways in the brain away from substances Restore emotional and decision-making capacities
- Control symptoms of opioid withdrawal Suppress opioid cravings

- Block the reinforcing effects of ongoing opioid use Promote and facilitate patient engagement in recovery-oriented
- activities
- Coupled with behavioral interventions
- Enhance the salience of natural, healthy rewards
 Reduce stress reactivity and negative emotional state
- Improve self-regulation
 Increase avoidance of relapse triggers
- Volkow, et al, NEJM. 2016 ASAM National Practice Guideline, June 1, 2015.



	All cause	Treatment	Any Opioid	HIV or HCV	Criminal		
	Mortality	Retention	Use	Transmission	Activity		
Methadone	↓	↑	↓	↓	↓		
	(n=4) ^{a,c}	(n=6)ª	(n=6)ª	(n=34) ^b	(n=2)ª		
Buprenorphine	↓	↑	↓	↓	↓		
	(n=2) ^{8,c}	(n=4)ª	(n=2) ^a	(n=6) ^b	(n=2) ^a		
Oral Naltrexone	No data	↑ (n=3) ^d	↓ (n=3) ^d	No data	↓ (n=2) ^d		
Extended Release Naltrexone	↓ (n=1) ^e	↑ (n=6) ^{e-j}	↓ (n=6) ^{e-j}	No data	↓ (n=1)9		
				(n = number	n = number of studies)		

Methadone

- Oral preparation liquid, tablet or oral solution
 Only dispensed at SAMHSA-certified opioid treatment programs (OTP) for daily administration onsite or if stable, at home.
- Opioid agonist
- Risk of overdose during induction or if taking benzodiazepines or alcohol
 Approved for detox and maintenance of opioid addiction
- Papierover on each and maintenance supervision, frequent relapses, may need psychosocial support, need more structure
 Contraindication: patients with respiratory depression or paralytic ileus
 Use with caution in elderly and debilitated, head injury or increased intracranial pressure, renal, liver disease, or at risk for QT prolongation

Methadone

- Duration of action = 24-36 hours
 Variable, long elimination half-life = 15-150 hours
- 80-120 mg is average dose
- Has been used in pregnancy for over 40 years.
 Breastfeeding not contraindicated
 Neonatal abstinence syndrome may occur
- Cons:
- Cons: requires careful monitoring Prolongs QTc in 23% of patients by 16 weeks of treatment Multiple drug-drug interactions Increased risk of mortality in first 2 weeks of treatment due to complex pharmacokinetics

Medication Assisted Treatment -Buprenorphine

- Requires prescriber to complete special training to obtain a DATA waiver 35 / 100 / 245
- Buprenorphine is a long-acting partial opiate agonist
- It is not "substitution of one addiction for another"
- Induction on medication must be in mild to moderate withdrawal (see COWS scale)
- Average dose is 8/2 16/4 mg per day = Sublingual
- Used for detox and maintenance
- Drug interactions: Atazanavir/ritonavir: increases buprenorphine concentrations; rifampin: decreases buprenorphine concentrations

Medication assisted treatment

 Inverse relationship between heroin overdose deaths and patients treated with buprenorphine Schwartz et al AJPH 2013

В	uprenorphine	/ Naloxone	
Table 1: Available Dose	es of Buprenorphine/Naloxo	one Combination Produc	cts*
Suboxone SL Tablet	Suboxone SL Film	Zubzolv SL Tablet	Bunavail Bucca
2 mg / 0.5 mg	2 mg / 0.5 mg	1.4 mg / 0.36 mg	
4 mg / 1 mg	4 mg / 1 mg		2.1 mg / 0.3 mg
8 mg / 2 mg	8 mg / 2 mg	5.7 mg / 1.4 mg	4.2 mg / 0.7 mg
12 mg / 3 mg	8 / 2 mg + TWO 2 mg /		6.3 mg / 1 mg

Buprenorphine + Naloxone

- Naloxone is included to reduce diversion / misuse
- Contraindicated with concurrent liver impairment, use of alcohol or benzodiazepines
- Precaution: Precipitated withdrawal
- Inverse relationship between heroin overdose deaths and patients treated with buprenorphine • Schwartz et al AJPH 2013

Buprenorphine

- Subutex is a sublingual formulation of buprenorphine without Naloxone
 It is recommended for Opiate dependence and can be used for chronic pain
 Doses of 2 mg and 8 mg are available; 24 mg / day usually the highest effective dose
 Elimination half-life is 31-35 hours
 Dose adjustments needed for hepatic impairment
 Butrans -is a buprenorphine transdermal patch
 Used for chronic pain necessitating long-term opioid treatment
 For those on 30 80 mg morphine equivalents or higher, it is recommended to reduce dose to <30 mg to reduce the risk of opiate withdrawal or inadequate pain management
 Initiate with 5 mcg patch. Do not change dose for at least 72 hours



Injectable Naltrexone - Vivitrol

Consider for:

- Patients who have failed agonist treatment Patients with value tanked agoinst treatment
 Patients confined to environments that do not allow for medication treatments
 Patients who do not have access to agonist treatment
 Patients with high risk of diversion
 Patients who are highly motivated and willing to tape of folioid agonists
 Patients who do not want to be treated with an agonist
 Patients with concomitant opioid and alcohol use disorder

- Requirements
 5-7 days abstinent from short acting opioids
 7-10 days abstinent from long acting opioids Opioid abstinence – 35.7% vs. 23% with placebo. High attrition in study Krupitsky Lancet 2011
- Monitor for development of depression, suicidality

Medication	Pros	Cons
Buprenorphine	 Quick stabilization of withdrawal May also treat concomitant pain 	 Possible overdose risk with concomitant alcohol use
Methadone	 Quick stabilization of withdrawal May be more effective to treat concomitant pain 	Possible overdose risk with concomitant alcohol use
XR-Naltrexone	 Will treat concomitant alcohol use disorder No risk of withdrawal if patient is incarcerated 	 More severe withdrawal Delay in initiation of treatment



Other Considerations on MAT

- Behavioral interventions improve outcome
- Studies show implants are superior to sublingual preparations by about 10% but studies are too short
- One study on Sublocade 41-43% abstinence vs. 5% for placebo
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 Buprenorphine used for detox vs. maintenance:
 Maintenance: 75% abstinent at 1 year / 0% mortalitDetox: 0% abstinent at 1 year / 20% mortality
 Buprenorphine vs. Methadone Retention
 High dose methadone (60-100 mg/day) 73%
 Low dose methadone (50-100 mg/day) 73%
 Low dose methadone 58%
 Retrospective study in JAMA. Only treatment with buprenorphine or methadone was
 associated with or reduced risk of overdose 76% reduction in overdose at 3 mos. And
 55% reduction at 2 months (study included in your folder)
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Case - Sara and Ben

- About 4 months after being on Suboxone, Sara reports that she thinks she might be pregnant
- She wants to know whether she should continue taking her Suboxone

Special Populations – OUD in Pregnancy

1 in 3 women enrolled in Medicaid and 1 in 4 with private insurance of reproductive age filled a prescription each year for the previous 4 years for opiates

- Opioid use during pregnancy has increased
 The number of women with OUD during labor and delivery more than quadrupled between 1999-2014
- Health outcomes of OUD in pregnancy
 Maternal death
 Poor fetal growth
 Preterm birth
 Siliblirth
 Birth defects neural tube defects, gastroschisis
 Neonatal abstinence syndrome

Pregnant Women – SBIRT (Screening, Brief Intervention, Referral to Treatment)

- Screening for use of alcohol and other substance use among all pregnant women is recommended in all health-care settings (e.g., primary care, obstetrical care).
- Pregnant women reporting hazardous or harmful alcohol or other substance use should receive a brief intervention.
- Pregnant women found to be dependent on alcohol or other substances should be referred to specialist services, where such services exist.

Barriers to Care for Pregnant Women with Opiate Use Disorder

- Legal consequences that sanction pregnant women with OUD
- State laws vs. what medical provider organizations are recommending re: substance use disorder screening and treatment and reporting and involvement of child protective services can be confusing
- Shame associated with OUD during pregnancy and biases in the medical profession (shaming)

Should she remain on Suboxone? Should she breastfeed? What are the chances her baby will go through withdrawals? Should she get off Suboxone after the baby is born?



Opiate Use Disorder after Delivery

- · Patients should be encouraged to breastfeed if possible
- Monitor and treat for depression / anxiety in the postpartum period as this can trigger relapse Encouraging mother-child attachment is extremely important in this
- Population
 Breastfeeding women have lower stress hormones
- Stress is a trigger for relapse
- Relapse is common during the post partum period so close monitoring, support, treatment are necessary. World Health Organization

- Neonatal abstinence syndrome is a group of physiologic and neurobehavioral signs of withdrawal that may occur in a newborn who has been exposed to opioids in utero. Opioid use - either from prescription misuse or from illicit use – has consequences for both mother and infant.
- Between 50-80% of exposed infants develop neonatal abstinence syndrome
- From 2009-2012, the number of infants with neonatal abstinence syndrome rose from 3.4 to 5.8 per 1000 hospital births (>20,000 infant in 2012) Rates are higher in rural vs. urban areas



Neonatal Abstinence Syndrome Treatment

- Health-care facilities providing obstetric care should have a protocol in place for identifying, assessing, monitoring and intervening, using non-pharmacological and pharmacological methods, for neonates prenatally exposed to opioids.
- An opioid should be used as initial treatment for an infant with neonatal opioid withdrawal syndrome if required.
- If an infant has signs of a neonatal withdrawal syndrome due to withdrawal from sedatives or alcohol, or the substance the infant was exposed to is unknown, then phenobarbital may be a preferable initial treatment option.
- Infants should be kept 4-7 days in hospital for observation and should be assessed for exposure to other drugs of abuse
 World Health Orgnization

Neonatal Abstinence Syndrome

SYMPTOMS:

- Tremors (trembling)
- Irritability, including excessive or high-pitched crying
 Sleep problems
 Hyperactive reflexes
- Seizures
- Seizures
 Yawning, stuffy nose, or sneezing
 Poor feeding and sucking
- Vomiting
- Loose stools and dehydration
 Increased sweating

Medical Complications of Opiate Use Disorder

- Hepatitis C (HCV)

 Affects 2.7 million in US
 Affects 1/3 of IVDU age 18-30
 Over 30% of IVDU over age 30
 Baby boomers account for 75% of HCV
 % of infected people are unaware
 HCV is the leading cause of cirrhosis, hepatocellular cancer and need for liver transplants
 Most infected individuals have normal Liver function tests
- HCV Risk Factors
 People who inject drugs
 Intranasal drug use
 Multiple sexual partners
 HIV + / HBV +
 Blood transfusion or organ transplant
 before 1992
- before 1992 Groups at risk Children born to HCV+ mothers Healthcare workers Patients on hemodialysis Incarcerated persons Persons who exchange sex for money or drugs







HIV / HCV

- People living with opioid use disorders are at increased risk for HCV and HIV due to needle sharing and sexual risk behaviors
 Approximately 14, S00 with injection drug use unaware of their HIV status Testing is not routine in opioid treatment programs and decreasing: 2005 to 2011: 3% to 6%
 When treated concurrently, results are better, stay in treatment longer

 - Buprenorphine use was associated with increased likelihood of initiating and remaining on HIV treatment
- remaining on HIV treatment
 Comprehensive prevention interventions for HCV and HIV include effective addiction treatment, behavioral risk reduction, and antiviral agents (pre-exposure prophylaxis for HIV, "PrEP")
 Treatment regimens for both HCV and HIV are highly effective in this population and can be safely used with opioid agonist therapy

Opiate Use Disorders – Psychiatric Comorbidities

- Among the 19.6 million adults with a past year substance use disorder, 41% (8.4 million adults) had co-occurring mental illness in 2015 (vs. 17.9 % of adults without SUD)
- Individuals with dual diagnoses:
 - Have worse prognosis
 - Have poorer quality of life
 Have increased risk of suicide
- Treatment of psychiatric comorbidity improves the outcome of SUD

Why so common?

- Neurodevelopmental factors
- Shared risk factors
- Self-medicating theory

Treatment

- Substance use disorders + depression • Antidepressants help with depression symptoms
- Not clear if they foster improvement in drug or alcohol use • Substance use disorders + Bipolar
- Lithium or mood stabilizers have an impact on both
- Substance induced mood disorder vs. Independent mood disorder
 Does Suboxone affect mood?

CAM therapies for OUD

Acupuncture

- Acupuncture could be effective in treating OUD. Moreover, EA could effectively alleviate symptoms of craving for opioid and depression, and TEAS could be beneficial in improving symptoms of insomnia and anxiety. Nevertheless, the conclusions were limited due to the low-quality and small number of included studies.
- Chenetal, 2018
 Chenetal, 2018
 After 35 years of active research by both Asian and Western scientists, this review cannot be used to establish the efficacy of acupuncture in the treatment of opiate addiction because the majority of these studies were classified as having low quality.
 Linetal, 2012

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Treatments

- Inpatient or residential treatment
- Partial hospitalization treatment
- Intensive outpatient treatment
- Outpatient +/- Medication-assisted treatment

How lessons from the HIV Epidemic can help in the opioid crisis

• Stigma hurts

• Activism helps

• The medications can only hel when people have access to



The Rest of Billy's Story

To heal the addict, you must treat the trauma





Points to Ponder

- How can we change the question from: What's wrong with you? To What happened to you?
- If addiction is a disease, why do we lock up people who relapse?
 Does this make sense: the imprisonment of a patient with substance use disorder because of worsening condition and relapse
- Addicts do stupid things but not because of moral failing or intrinsic evil... drugs and alcohol severely affect good judgment
- Why are we punishing the victims?
 Purdue Pharma institutional antisocial behavior with severe national consequences that went unpunished



Integrative Medicine Approach



References

- Inglesby TV: et al. A prospective, community-based evaluation of liver enzymes in individuals with hepatitis C after drug use. Hepatology. 1999;29:590-596.
 Volkow 2004; Bolanso et al. 2003; Carlezon et al. 2003, NIDA Topics in Brief: Comorbid Drug Abuse and Mentailliness.
- https://ndarc.med.unsw.edu.au/blog/how-australia-responding-pharmaceutical-opioid-problem. Accessed 4/10/2020
- Campbell, G., Lintzeris, N., Gisev, N., Larance, B., Pearson, S., & Degenhardt, L. (2019), Regulatory and other responses for the pharmaceutical opioid problem. *Medical Journal of Australia*, 210(1), 6-8-e1. doi:10.5694/mj2.12047
- Kakko J, et al. Craving in opioid use disorder. Psychiatry, 30 August 2019 <u>https://doi.org/10.3389/fpsyt.2019.00592</u>

References

- World Health Organization. Guidelines for identification and management of substance use and substance use disorders in pregnancy. https://www.who.int/substance_abuse/publications/pregnancy_guidelines/gn/2014. (accessed 3/10/2020)
- Microsoft A. S. Statistics and Science and Merital Microsoft Science and Merital Microsoft Accessed (Control Science) (Contro

References

- Comer, S, Cunningham, C, et al. (2015) ASAM The National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use.
- the Treatment of Addiction Involving Opioid Use. Comer 5, Sultivan, MA. (2006) Injectable, sustained-release natrexone for the treatment of opioid dependence: a randomized, placebo: controlled trial. Arch Gen Psychiatry, 63 (2): 210-8. Fudin, J. (2016) A Brief Review of Bupernorphine Products. Pharmary Times. Gowing, L.Farrell, M. et al. (2011) Oral substitution treatment of injecting opioid users for prevention of HIV intervition. Corriane Database (2014) Oral Substitution treatment of injecting opioid users for prevention of HIV Systematic Reviews (8): CD004145

- Systematic Reviews (8): LOUG4145
 Johnson, R., Chutape, M., et al. (2000) A comparison of Levomethadyl acetate, Buprenorphine, and Methadone for Opioid Dependence. New
 England Journal of Medicine, 343: 1290-1297.
 Karkol, Svanborg, K. et al. (2003) 4-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin
 dependence in Sweden: a randomized, placebo controlled trial. Lancet, 361 (9358):662-8.
 Korthuis PT, McCarty D, Weimer M, et al. (2017) Primary Care-Based Models for the Treatment of Opioid Use Disorder: A Scoping Review

References

• Lin J-G, et al. Acupuncture for the treatment of Opiae Addiction. Evid Based Complement Alternat Med. 2012; 2012: 739045.