ASAM VIRTUAL

REVIEW COURSE

in Addiction Medicine

2024

COURSE SYLLABUS:
ELECTRONIC NOTE-TAKING

https://elearning.asam.org/review-course

Welcome to the 2024 ASAM Review Course!

This course is widely recognized as the essential and foundational course for physicians who are preparing for the addiction medicine exam or for a career in addiction medicine. With a comprehensive curriculum, covering everything from neurobiology and pharmacology to individual substances and ethical concerns, the course offers a streamlined overview of addiction medicine delivered by an outstanding faculty lineup.

As part of registration, attendees will receive access to:

- 15+ hours of live and on-demand lectures featuring national and international experts in addiction medicine.
- Weekly office hours with featured faculty and access to peers.
- Carefully crafted study guide offering suggestions on how to incorporate lectures and additional resources.

Letter from Committee Chair

Dear Colleague:

We are pleased to welcome you to the 2024 ASAM Virtual Review Course in Addiction Medicine! As of 2022, it is estimated that 46.8 million Americans aged 12 and older had battled a substance use disorder in the past year. Yet only 26% of those received any help for substance use disorder (NSDUH). With this alarming statistic, we appreciate each of you for taking the time to learn more about addiction, the process of becoming certified, and for working with us to help bridge this gap.

On behalf of the Program Planning Committee, I encourage you to get the most out of your experience by taking advantage of everything The ASAM Virtual Review Course has to offer. We look forward to connecting with you!

Sincerely,

Jonathan D. Avery, MD, FASAM, *Chair*

Learning Objectives

Upon completion, participants should be able to:

- Demonstrate practical knowledge on the neurobiology of addiction and articulate its activity in terms useful in a clinical setting.
- Describe the effects of alcohol, nicotine/tobacco, and other drugs in both tolerant and non-tolerant individuals.
- Describe the process for diagnosing addiction and differentiating the symptoms of addiction from those of other medical or psychiatric disorders.
- Explain the various pharmacologic and psychosocial treatments for addictive disorders and describe the factors that should be considered in selecting a treatment modality to match the needs of a specific patient.
- Describe the precipitants of relapse and current evidence-based practices to prevent and manage relapse.

Course Planning Committee

Jonathan Avery, MD, FASAM, *Chair*
Faye Chao, MD
Mashal Khan, MD
Annie Levesque, MD, MSc, FASAM
Carla Marienfeld, MD, DFAPA, FASAM
Carolyn Warner-Greer, MD, FACOG, FASAM

Addiction Medicine Certification Exam Information

There are two organizations offering addiction medicine certification exams: the American Board of Preventive Medicine (ABPM) and American Osteopathic Association (AOA). The ASAM Review Course curriculum is carefully mapped to their exam blueprints.

ABPM Addiction Medicine Exam Blueprints

CORE CONTENT AREAS	
25%	Definitions
	Genetics
	Pharmacokinetic and Pharmacodynamic Principles
	Pharmacology
	Neurobiology of Addiction
20%	Epidemiological Concepts
	Epidemiological Trends of Substance Use Disorders
	Prevention
40%	Screening, Assessment, and Brief Intervention
	Overview of Addiction Treatment
	Management of Inpatient and Outpatient Intoxication, and Withdrawal
	Pharmacologic Interventions for Addictions
	Behavioral Interventions
	Co-Occurring and Medical Disorders among Patients with Alcohol and Other Drug Use and Addiction
	Co-Occurring Psychiatric Disorders among Patients with Alcohol and Other Drug Use and Addiction
	Pain and Addiction
15%	Ethical, Legal, and Liability Issues in Addiction Practice

SUBSTANCE AREAS	
15-20%	Alcohol
7-10%	Sedatives
7-10%	Stimulants
10-15%	Opioids
7-10%	Cannabinoids
15-20%	Nicotine
0.5-3%	Hallucinogens
0.5-3%	Dissociatives
0.5-3%	Inhalants
0.5-3%	Anabolic steroids
1-3%	Other substances
1-3%	Nonsubstance addiction
1-5%	**General/All substances combined**

AOA Addiction Medicine Exam Blueprint

CORE CONTENT AREAS	
24%	Pharmacology
18%	Epidemiology and Genetics
15%	Treatment
14%	Legal Aspects
12%	Diagnosis
11%	Special Populations
6%	Prevention

Learn More

Explore ABPM's Website:
https://www.theabpm.org/become-certified/subspecialties/addiction-medicine/

Check Eligibility for ABPM Exam:
https://www.TheABPM.org/am-i-eligible

Explore AOA's Website:
https://certification.osteopathic.org/addiction-medicine/

Check Eligibility for AOA Exam:
https://certification.osteopathic.org/addiction-medicine/board-policies/

Explore ASAM's Certification Guide:
https://www.asam.org/education/addiction-medicine-certification

Claiming Credit & Certificate

Claim credit anytime between July 29, 2024, and July 29, 2025.

Review Course Registrants:

1. Type https://eLearning.ASAM.org into your web browser.
2. Log in to the eLearning Center (eLC), using your ASAM.org username and password (what you used when registering for the course).
3. After logging in, select “My Dashboard” from the top menu (on mobile devices, you will find “My Dashboard” by clicking the three horizontal lines in the header).
4. Locate “Evaluation & Certificate - Live Attendees of the 2024 Review Course in Addiction Medicine,” which will be under "Courses and Sessions.”
5. Click “Content” and find the box that says “Complete Evaluation.” Click the button that says, “Fill out Survey.”
6. After you have completed the evaluation, select the box labeled “Claim Credit & Certificate” and click the button that says, “Claim Medical Credits.”
7. Select your provider type and the number of hours you attended, then click “Submit.”
8. Print out your certificate or save it on your device.

Watching Sessions On-Demand

Relive the course or catch sessions you missed! Registrants of the ASAM 2024 Virtual Review Course in Addiction Medicine receive complimentary access to their sessions on-demand in the ASAM eLearning Center. On-demand sessions will be available from July 29, 2024 – July 29, 2027.

Did You Know?

Sessions are also available as audio-only, so you can review on-the-go.

More Information

Learn more about ASAM by visiting: https://asam.org

If you have any questions or experience any issues, please contact ASAM Staff at education@asam.org

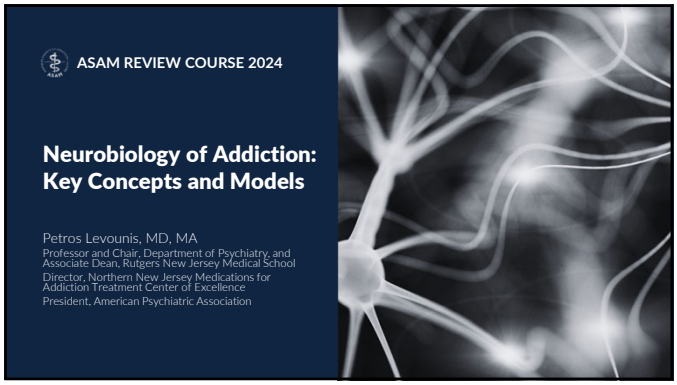
Review Course Schedule & Table of Contents

The full course schedule, including speaker information, live stream links, time changes, and more is available on the course website: https://reviewcourse.asam.org/.

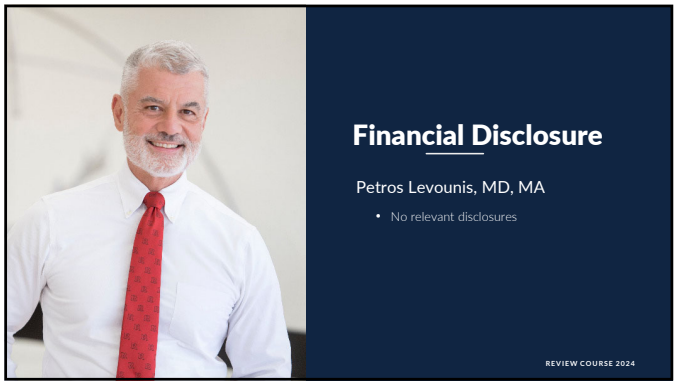
Thursday, July 25, 2024

Friday, July 26, 2024

Time	Session	Page #
9:50 am – 10:00 am	**Welcome Back & Day Two Overview** *Jonathan D. Avery, MD, FASAM*	
10:00 am - 10:35 am	**Evolution of Addiction and Treatment: History and Impact** *Paul H. Earley, MD, DFASAM*	275
10:35 am - 11:35 am	**Pharmacology and Toxicology: Principles, Applications, and Limitations** *Lewis S. Nelson, MD, MBA, DFASAM*	288
11:35 am - 11:50 am	**Break**	
11:50 am - 12:40 pm	**Epidemiology: Core Concepts and Applications** *Jeffrey J. DeVido, MD, MTS, FAPA, FASAM*	313
12:40 pm - 1:10 pm	**Interesting Cases: Applying Concepts to Unexpected Real-Life Scenarios** *Edwin A. Salsitz, MD, DFASAM*	336
1:10 pm - 1:40 pm	**Break**	
1:40 pm - 2:25 pm	**Psychiatric Co-Morbidities: Complexities of Diagnosis and Care** *Mason S. Turned, MD, DFASAM*	350
2:25 pm - 3:10 pm	**Medical Co-Morbidities: Diagnosis, Prevention and Complications** *Carolyn Warner-Greer, MD, FACOG, FASAM*	369
3:10 pm - 3:25 pm	**Break**	
3:25 pm - 3:55 pm	**Pregnancy and Newborns: Considerations from Science to Systems** *Leslie A. Hayes, MD*	380
3:55 pm - 4:25 pm	**Psychosocial Interventions: Cognitive Behavioral Therapy and Motivational Interviewing** *Carla B. Marienfeld, MD, DFAPA, FASAM*	404
4:25 pm – 4:55 pm	**Psychosocial Interventions: Mutual Help, Psychotherapy, and Social Support** *Paul H. Earley, MD, DFASAM*	414
4:55 pm - 5:10 pm	**Break**	
5:10 pm - 5:50 pm	**Ethics and the Law: Principles and Implications** *David Y. Kan, MD, DFASAM*	429
5:50 pm - 6:35 pm	**Prevention and Public Health: From Theory to Practice** *Amutha V. Rajagopal, MD, MPH*	449
6:35 pm - 7:10 pm	**Becoming Certified: Pathways, Insights and Preparation Strategies** *Michael F. Weaver, MD, DFASAM, Deborah A. Dupnik, CAE, CCSM-A, Cara A. Poland, MD, Med, FACP, DFASAM*	462


ASAM REVIEW COURSE 2024
Neurobiology of Addiction: Key Concepts and Models
Petros Levounis, MD, MA
Professor and Chair, Department of Psychiatry, and Associate Dean, Rutgers New Jersey Medical School
Director, Northern New Jersey Medications for Addiction Treatment Center of Excellence
President, American Psychiatric Association

1


Financial Disclosure
Petros Levounis, MD, MA
• No relevant disclosures
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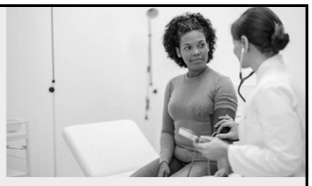
2


LEARNING OBJECTIVE
Identify key neurotransmitters, brain pathways, and brain structures implicated in addiction and addiction treatment.

3

Outline



1. Neurotransmitters
2. The Fundamental Model
3. The New and Improved Model
4. Treatments

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Neurotransmitters

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Substance	Endogenous Neurotransmitter
Alcohol	GABA / Glutamate*
Amphetamines & Cocaine	Dopamine
Benzodiazepines & GHB	GABA
Cannabis	Anandamide
Hallucinogens & MDMA	Serotonin
Nicotine	Acetylcholine
Opioids	Endorphins
Phencyclidine & Ketamine	Glutamate*

*Drug acts as an antagonist at the NMDA subtype of the glutamate receptor.

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The Fundamental Model

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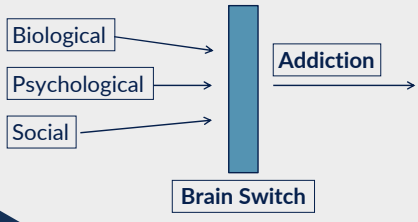
Addiction: A Biopsychosocial Illness



Olsen and Levounis, Sober Siblings, 2008.

8

The Root Cause of the Disaster

ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients[1] who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,[2] Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

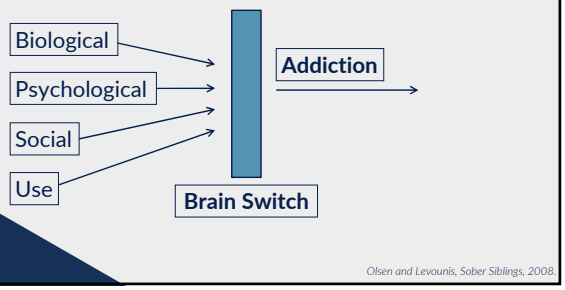
JANE PORTER
HERSHEL JICK, M.D.
Boston Collaborative Drug Surveillance Program
Waltham, MA 02154 Boston University Medical Center

1. Jick H, Miettinen OS, Shapiro S, Lewis GP, Siskind V, Slone D. Comprehensive drug surveillance. JAMA. 1970; 213:1455-60.
2. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. J Clin Pharmacol. 1978; 18:180-8.

Porter and Jick, N Engl J Med, January 10, 1980.

9

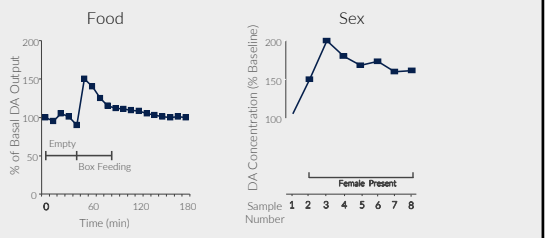
Addiction: A Biopsychosocial Illness



Olsen and Levounis, Sober Siblings, 2008.

10

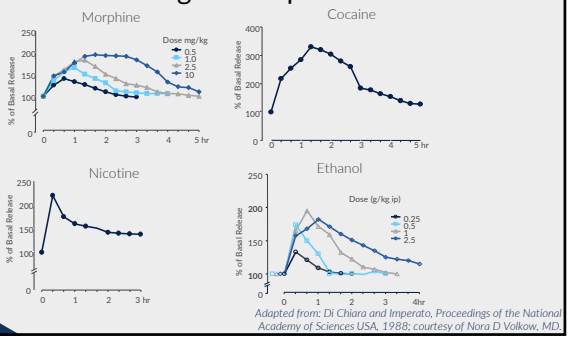
Basal Ganglia (Nucleus Accumbens) and Binge/Intoxication



Adapted from: Di Chiara et al, Neuroscience, 1999.
Adapted from: Fiorino and Phillips, J Neuroscience, 1997.

11

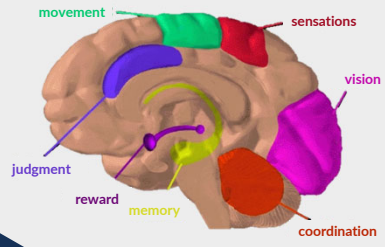
Effects of Drugs on Dopamine Levels



Adapted from: Di Chiara and Imperato, Proceedings of the National Academy of Sciences USA, 1988; courtesy of Nora D Volkow, MD.

12

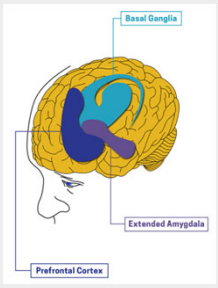
Hippocampus and Extended Amygdala



National Institute on Drug Abuse, NIDA.NIH.gov, 2000.

13

Prefrontal Cortex and Executive Function



National Institute on Drug Abuse, NIDA.NIH.gov, accessed on March 17, 2024.

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The New and Improved Model

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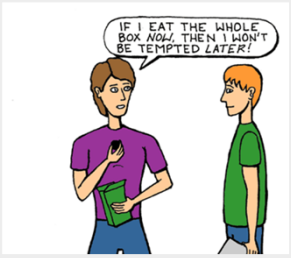
Three Novel Areas

Motivational Circuitry (Medial OFC)	Antireward Pathways (Extended Amygdala)	Interoception (Insula)

Levounis, Journal of Medical Toxicology, 2016.

16

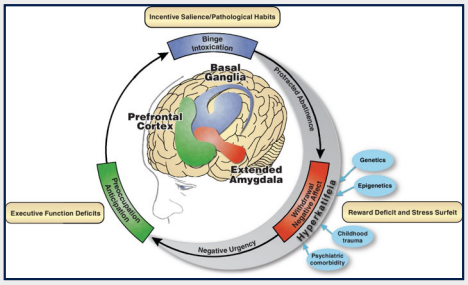
Medial Orbitofrontal Cortex (OFC) and Preoccupation/Anticipation



Levounis, Arnaout, and Marienfeld, Motivational Interviewing for Clinical Practice, 2017.

17

Extended Amygdala and Withdrawal/Negative Affect



Koob, American Journal of Psychiatry, 2020.

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Reward Systems

Game #1

A. A sure gain of $250
B. 25% chance to gain $1,000, 75% chance to gain nothing.

Adapted from: Tversky and Kahneman, Science, 1981.

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Reward Systems

Game #1

A. A sure gain of $250 **84%**
B. 25% chance to gain $1,000, 75% chance to gain nothing **16%**

Adapted from: Tversky and Kahneman, Science, 1981.

20

Anti-Reward Systems

Game #2

A. A sure loss of $750
B. 25% chance to lose nothing, 75% chance to lose $1,000.

Adapted from: Tversky and Kahneman, Science, 1981.

21

Anti-Reward Systems

Game #2

A. A sure loss of $750 **13%**

B. 25% chance to lose nothing, 75% chance to lose $1,000. **87%**

Adapted from: Tversky and Kahneman, Science, 1981.

22

Human Nature

People avoid risks to ensure gains.

People take risks to avoid definite losses.

Psychology trumps probability.

23

The Ultimate Gatekeeper: Insula

Zerbo, Schlechter, Desai, and Levounis, Becoming Mindful, 2017.

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Treatments

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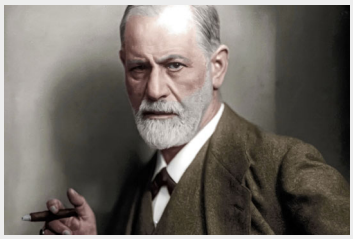
1st Wave: Psychoanalysis



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2nd Wave: Boot Camps

The prototype, synanon, was founded in California in 1958 to address heroin addiction. The goal was to:

- break down defenses,
- bust through denial, and
- reshape the individual's personality.

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3rd Wave: Current Treatments

- Medications
- Mutual Help
- Psychotherapy and Counseling

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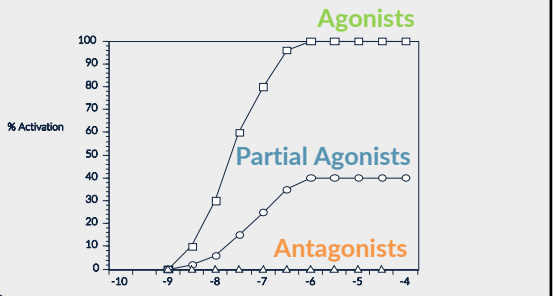
Medications (opioids and tobacco)



Renner, Levounis, LaRose, Office-Based Buprenorphine Treatment of Opioid Use Disorder, American Psychiatric Association Publishing, 2018.

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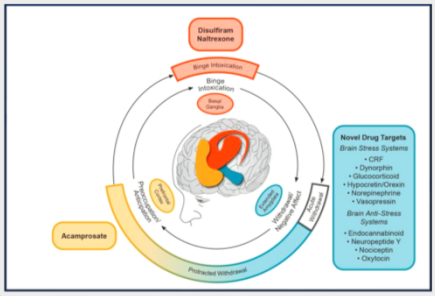
Medications (alcohol and possibly others)



Mason BJ and Heyser CJ, Alcohol use disorder: the role of medication in recovery, Alcohol Research, 2021.

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Mutual Help

MEDICAL STUDENTS	PATIENTS	WHAT MEDICAL STUD. THINK PATIENTS THINK
1. Housing	1. Inner Peace	1. Housing
2. Government	2. God	2. Outpatient Treatment
3. Medical Services	3. Medical Services	3. Medical Services
4. Outpatient Treatment	4. AA	4. Job
5. Job	5. Housing	5. Trusting People
6. Community	6. Spirituality	6. AA
7. Trusting People	7. Outpatient Treatment	7. Inner Peace
8. Inner Peace	8. Community	8. Community
9. God	9. Government	9. Government
10. Spirituality	10. Trusting People	10. Spirituality
11. AA	11. Job	11. God

Goldfarb LM, Medical student & patient attitudes toward religion and spirituality in the recovery process American Journal of Drug & Alcohol Abuse, 1996..
Fazzio L, Galanter M, Dermatis H, Levounis P, Evaluation of medical student attitudes toward Alcoholics Anonymous, Substance Abuse, 2003.

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Cognitive Behavioral Therapy & Motivational Interviewing

Levounis, Zerbo, and Aggarwal, Pocket Guide to Addiction Assessment and Treatment, 2016.

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4th Wave: Mindfulness

"Between stimulus and response there is a space. In that space is our power to choose our response. In our response lie our growth and our freedom."

Victor E. Frankl

Frankl, Man's Search for Meaning, 1959.
Zerbo, Schlechter, Desai, and Levounis, Becoming Mindful, 2017.

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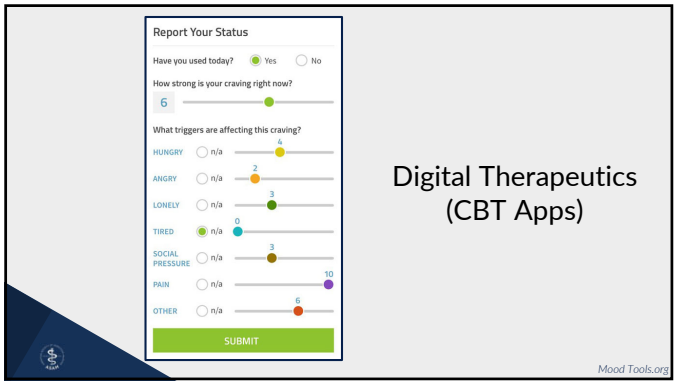
Report Your Status
Have you used today?
Yes
No
How strong is your craving right now?
6
What triggers are affecting this craving?
HUNGRY
ANGRY
LONELY
TIRED
SOCIAL PRESSURE
PAIN
OTHER
n/a
SUBMIT
Digital Therapeutics (CBT Apps)
Mood Tools.org

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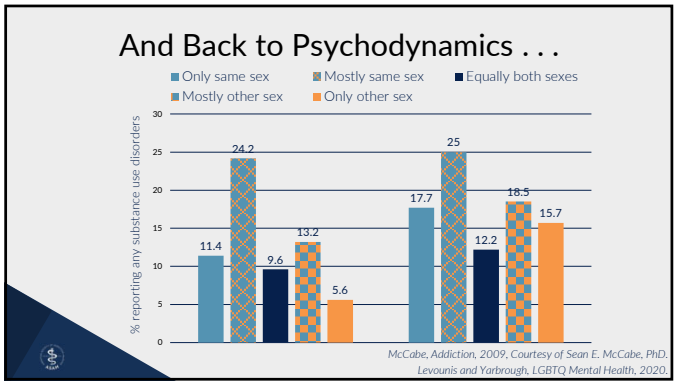
And Back to Psychodynamics . . .
Only same sex
Mostly same sex
Equally both sexes
Mostly other sex
Only other sex
% reporting any substance use disorders
30
25
20
15
10
5
0
11.4
24.2
9.6
13.2
5.6
17.7
25
12.2
18.5
15.7
McCabe, Addiction, 2009, Courtesy of Sean E. McCabe, PhD.
Levounis and Yarbrough, LGBTQ Mental Health, 2020.

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Neurotransmitters
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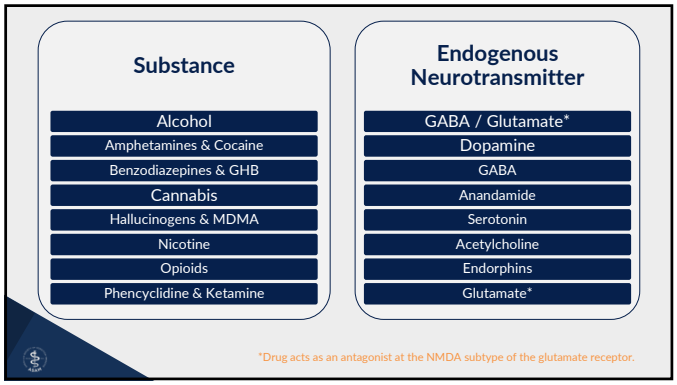
Substance
Alcohol
Amphetamines & Cocaine
Benzodiazepines & GHB
Cannabis
Hallucinogens & MDMA
Nicotine
Opioids
Phencyclidine & Ketamine
Endogenous Neurotransmitter
GABA / Glutamate*
Dopamine
GABA
Anandamide
Serotonin
Acetylcholine
Endorphins
Glutamate*
*Drug acts as an antagonist at the NMDA subtype of the glutamate receptor.

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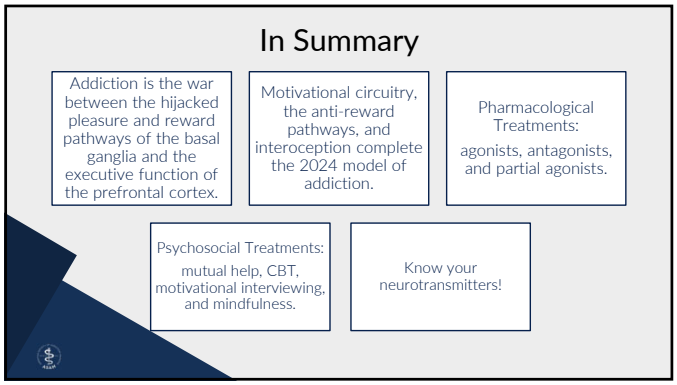
In Summary
Addiction is the war between the hijacked pleasure and reward pathways of the basal ganglia and the executive function of the prefrontal cortex.
Motivational circuitry, the anti-reward pathways, and interoception complete the 2024 model of addiction.
Pharmacological Treatments:
agonists, antagonists, and partial agonists.
Psychosocial Treatments:
mutual help, CBT, motivational interviewing, and mindfulness.
Know your neurotransmitters!

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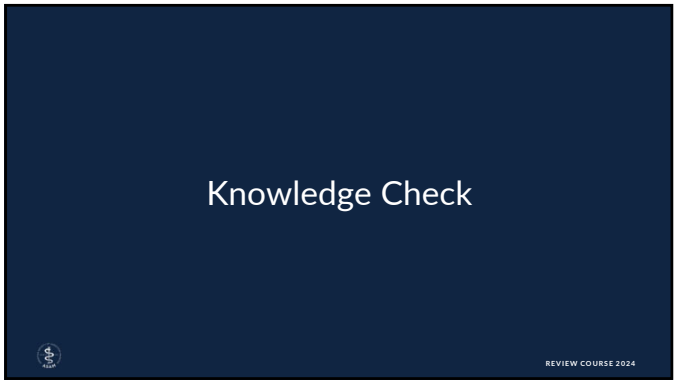
Knowledge Check
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At her 10th college reunion, Anna bumps into Marie, her old roommate from their junior year abroad. “Anna!” Marie exclaims. “Do you remember sipping wine and snacking on brie and crackers at the café by the Seine? And that waiter? Jacques… Mon Dieu!” Anna has not had any alcohol for several years but suddenly feels an intense craving for alcohol. What part of Anna’s brain got activated by Jacques, the hot waiter, just now?

A. Medial Orbito-Frontal Cortex (OFC)

B. Lateral Orbito-Frontal Cortex (OFC)

C. Hippocampus and Extended Amygdala

D. Insula

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Robert has been addicted to Candy Crush Saga since high school. He must also study for the ABPM boards on Friday. It’s now 10 pm on Thursday evening, and he hasn’t started looking at the lectures. “Hmmm…,” he thinks to himself. “If I get some Swedish fish to grab some candies, I can reach Lollipop Meadow by midnight, which will give me such a sense of accomplishment that I will have a clear head tomorrow to tackle any question. Perfect plan, to Lollipop Meadow it is!” What part of Robert’s brain was activated by Lollipop Meadow?

A. Medial Orbito-Frontal Cortex (OFC)

B. Lateral Orbito-Frontal Cortex (OFC)

C. Hippocampus and Extended Amygdala

D. Insula

41

Which part of the brain is responsible for integrating, giving meaning, and helping people understand sensations such as hot, cold, hungry, full, and thirsty—along with cravings for a drug such as tobacco?

A. Medial Orbito-Frontal Cortex (OFC)

B. Lateral Orbito-Frontal Cortex (OFC)

C. Hippocampus and Extended Amygdala

D. Insula

42

Thank You

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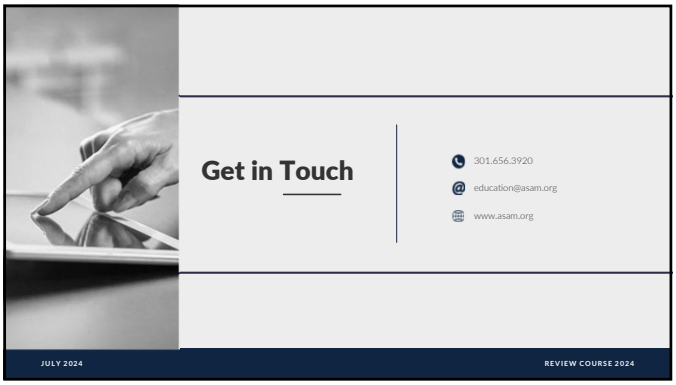

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ASAM REVIEW COURSE 2024

Alcohol Use Disorder: Neurobiology, Diagnosis and Treatment

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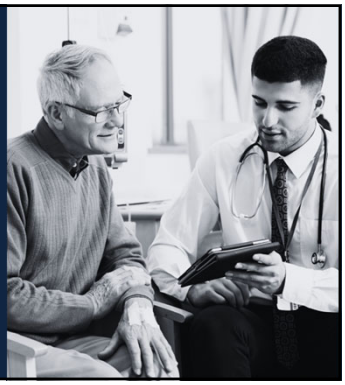
VA Long Beach Healthcare System



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Financial Disclosure

Ricardo Restrepo, MD, MPH

- No Disclosures

REVIEW COURSE 2024

2

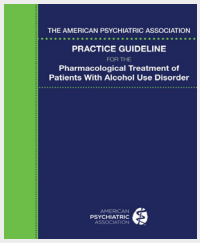
Outline

1. Historical View
2. Neurobiology
3. Epidemiology
4. SBIRT and Clinical Screening Test
5. Diagnosis
6. Biomarkers
7. Phases of Alcohol Treatment and Related Syndromes
8. CIWA-Ar and Management
9. Relapse Prevention Pharmacotherpy and Psychotherapy
10. New Directions
11. Conclusion

3

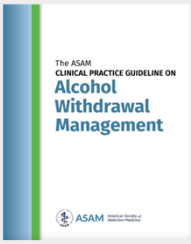
APA Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder

December 2017



ASAM Clinical Practice Guideline on Alcohol Withdrawal Management

January 2020



4

Historical View: Alcohol Use Disorder an Ancient Problem or a Disease?

After the flood, Noah plants a vineyard, makes wine and gets drunk. (Genesis 9:21)

"Who hath woe? Who hath sorrow? Who is always fighting? Who is always complaining? Who hath wounds without cause? Who has bloodshot eyes?

They who tarry long at the wine; when it sparkles in the cup. Don't let the smooth taste deceive you. For in the end it bites like a poisonous serpent. And you will say, 'They hit me, but I didn't feel it.'

Your eyes will see strange visions and you will say strange thoughts. Yet when you awaken, you seek it yet again."
(Proverbs 23:29 (~1,000 BC)

Pliny the Elder: Gaius Plinius Secundus Naturalis Historia: "drunkeness brings pallor and sagging cheeks, sore eyes, and trembling hands that spill a full cup, of which the immediate punishment is a haunted sleep and unrestful nights..."

5

Case: RR

Mr. RR is a 58 –year-old, Latino, married, male owner of a music theater in Los Angeles. He is being referred for evaluation to assess his drinking and depression after his older brother, who in the past had problems with alcohol, recommended him.

6

Case: RR

He presents for his evaluation thinking alcohol helps him to manage:

- Depression
- Insomnia
- Irritability and anxiety

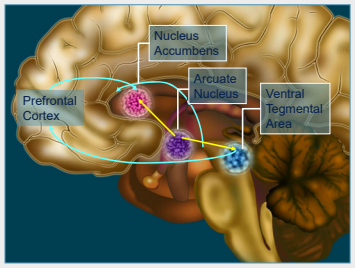
7

Case: RR

SA history: He reports that he grew up drinking. His first drink was at age four when he tasted the left-over alcohol from a party in his family home. He describes falling in love with the taste of wine and waited every weekend for his family to throw another party.

8

Alcohol Use Disorder a Disease?



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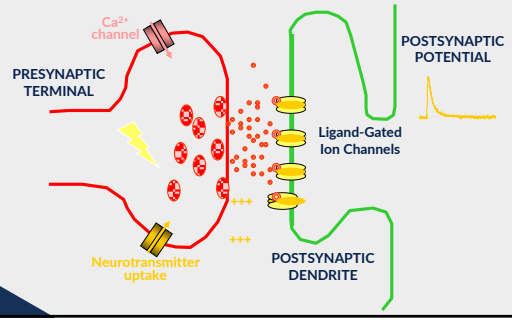
Neurotransmitter Systems

GABA	→	CNS Inhibition
Glutamate	→	CNS Excitation
Opioid	→	Euphoria
Dopamine	→	Addiction
Serotonin	→	Impulsivity
Cannabinoid	→	Pleasant Feeling

10

Steps in Synaptic Transmission



11

Case: RR

Substance abuse h/x and symptoms

He then started to drink at age 12 years old on weekends and continued daily for the past 30 years. While he had difficulties quantifying the amount he consumes, he states that he rarely has "too much," although he admits occasionally missing work due to hangovers and driving while intoxicated (luckily, no accidents, no DUI).

12

Case: RR

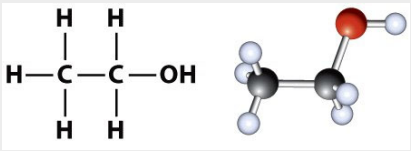
Substance abuse h/x and symptoms

His last drink was the previous night. He explained he often has diarrhea and shakes in the morning, which he attributes to "anxiety" because these symptoms are alleviated with 1 or 2 alprazolam that has been prescribed by his PCP for the past decade.

No other drugs or substance use history.

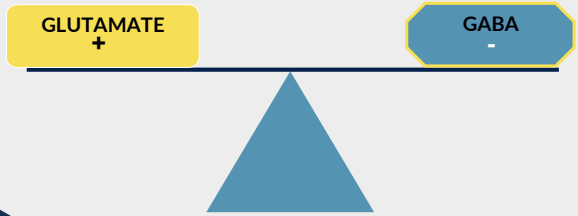
13

Alcohol (Ethanol C2 O1 H6)



14

Acute Alcohol Intake



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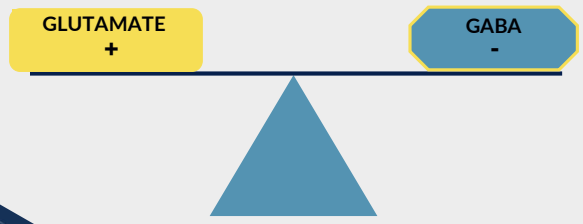
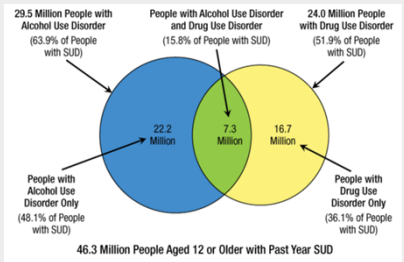
Chronic Alcohol Intake



16

Alcohol Use Disorder and Drug Use Disorder in the Past Year: Among People Aged 12 or Older with a Past Year Substance Use Disorder (SUD); 2021



Note: Drug Use Disorder includes data from all past year users of marijuana, cocaine, heroin, hallucinogens, inhalants, methamphetamine, and prescription psychotherapeutic drugs (i.e., pain relievers, tranquilizers, stimulants, or sedatives)

FFR1.8

17

Epidemiology
Scope of Alcohol-Related Problems

- ~140,000 people die (380 per day) annually from alcohol-related causes in the U.S from 2015-2019
- Nearly 29.5 million people ages 12 and older had AUD in 2021
- 894,000 adolescents ages 12 to 17 with AUD in 2021
- 4th leading preventable cause of death in U.S. is AUD

Sources: CDC 2022 ; SAMHSA Prevalence – NSDUH (2021 and 2015)

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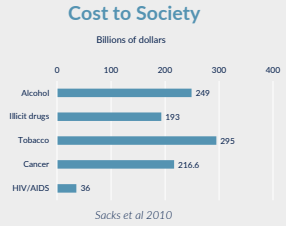
Cost and Scope of Alcohol-Related Problems



Sacks et al 2010

- ~ 50% of U.S. liver disease deaths attributable to alcohol misuse (2021)
- Increase 50% in emergency department visits and hospitalizations related to alcohol between 2006-2014
- Among people who die by suicide, AUD is the second most common mental disorder and involved in roughly 1 in 4 deaths by suicide

Sources: Prevalence – NSDUH (2021, 2019), NIH 2023

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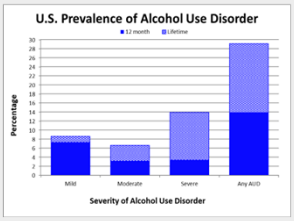
Epidemiology/Prevalence

Prevalence:

- Worldwide (Slade et al., 2016)
  - Lifetime 20%
  - 12 month 8.5%
  - In 2012 about 3.3 millions deaths, or 5.9 % of a global deaths, were attributable to alcohol consumption
- U.S. (Grant et al. 2015, 2017)
  - Lifetime 29%, with severe alcohol use disorder (AUD) in about half
  - 12-month 13.9 %
  - 12-month rates of AUD increased by ~50% between 2001-2002 and 2012-2013



Based on data from Grant et al. Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiatry. 2015 Aug;72(8):757-66. (Information shared by APA)

20

Epidemiology/Demographics

AUD affects individuals of all demographic groups

- Onset: 18-29 years
- Ethnicity (12-month prevalence):
  - American Indian/Alaska Native 19.2%
  - African American 14.4%
  - White 14%
  - Hispanic 13.6%
  - Asian-American/Pacific Islander 10.6%
- Gender (12-month prevalence):
  - Men 17.6%
  - Women 10.4%

Grant et al. 2015

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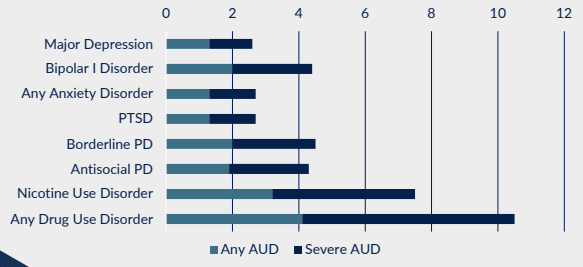
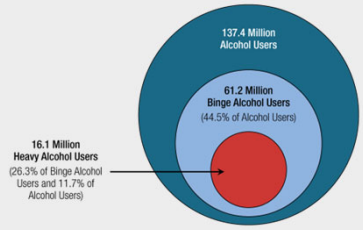
Adjusted Odds Ratios of Lifetime AUD and Other Conditions



Based on data from Grant et al. JAMA Psychiatry. Aug;72(8): 757-66, 2015 (information shared by APA)

22

Past Month Alcohol Use, Binge Alcohol Use, and Heavy Alcohol Use: Among People Aged 12 or Older; 2022



Note: Binge Alcohol Use is defined as drinking five or more drinks (for males) or four or more drinks (for females) on the same occasion on at least 1 day in the past 30 days. Heavy Alcohol Use is defined as binge drinking on the same occasion on 5 or more days in the past 30 days; all heavy alcohol users are also binge alcohol users.

National Survey on Drug Use and Health 2022

FFR1.8

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How Much is "too much"?

Heavy Drinking

- WOMEN:
  4 or more standard drinks in a sitting.
  (8 or more per week.)
- MEN:
  5 or more standard drinks in a sitting.
  (15 or more per week.)

Binge Drinking

- A pattern of drinking that brings blood alcohol concentration (BAC) levels to 0.08g/dl
- WOMEN:
  4 or more drinks on same occasion in about 2 hours
- MEN:
  5 or more drinks in same occasion in about 2 hours

Emerging Trend- High Intensity Drinking

Consuming ETOH at levels that are two or more times the gender-specific binge drinking thresholds

10 or more standard drinks (or alcoholic drink equivalents) for males and 8 or more for females

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COVID and Alcohol Use Disorder

- Data from a national survey of U.S. adults on their drinking habits found that excessive drinking (such as binge drinking) increased by 21% during the COVID-19 pandemic.
- More than a dozen studies have found that 20% to 40% of individuals surveyed reported consuming more alcohol than usual during the pandemic, based on National Institute on Alcohol Abuse and Alcoholism (NIAAA) information

NIAAA National Institute on Alcohol Abuse and Alcoholism 2021

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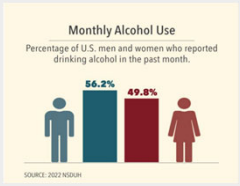
Alcohol use is increasing more in women than men in USA

Monthly Alcohol Use

Percentage of U.S men and women who reported drinking alcohol in the past month



Over the last century, gaps between males and females have narrowed for prevalence of drinking, total amount consumed, frequency, binge drinking, early onset drinking, having alcohol use disorder, drunk driving and self reported consequences

In the last decade differences narrowed further. Rates of alcohol use disorder (AUD) have increased in women by 84% over the past ten years relative to a 35% increase in men (Grant et al., 2017),

Women are more likely to experience blackouts, liver inflammation, brain atrophy cognitive deficits and some cancers. (Slade T et al. BMJ 2016)

2021 National Survey on Drug Use and Health

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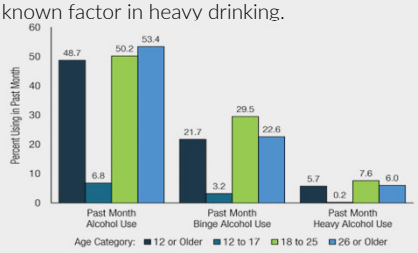
Population-based epidemiological surveys show harmful drinking levels

Age is a known factor in heavy drinking.



SAMHSA 2022

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DSM-5 : Criteria for Alcohol Use Disorders

1. Use In Larger Amounts / Longer Periods Than Intended
2. Unsuccessful Efforts To Cut Down
3. Excessive Time Spent Taking Drug
4. Failure To Fulfill Major Obligations
5. Continued Use Despite Knowledge Of Problems
6. Important Activities Given Up
7. Recurrent Use In Physically Hazardous Situations
8. Continued Use Despite Social Or Interpersonal Problems
9. Tolerance
10. Withdrawal
11. Craving

Severity:
0 To 1 Criteria: No Diagnosis
2 To 3 Criteria: Mild
4 To 5 Criteria: Moderate
6 Or More Criteria: Severe

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Underdiagnoses and Unmet Treatment Needs

- Only 1 in 6 US adults report ever having asked by a clinician about their drinking behavior
- Despite high prevalence, societal cost, and available treatments, AUD remains undertreated
- <1 in 10 with a 12-month AUD diagnosis receive any treatment:
  - Self-help groups
  - Psychotherapy
  - Pharmacological treatments
- Treatment received by patients varies based on geography, insurance coverage, and formulary restrictions

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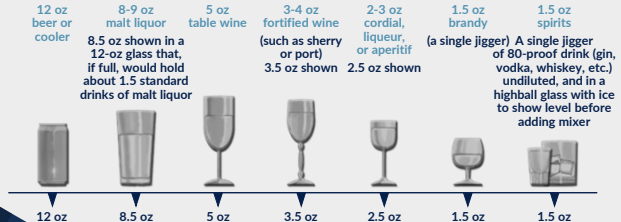
What is a standard drink?

- 1 Standard Drink = 14 gr. (0.6 oz.) of pure alcohol.
- The average person metabolizes about 1 Standard Drink per hour.



Adapted from www.niaaa.nih.gov

30

Intoxication Features

1 drink → BAC = ~15 mg% (0.015 g/dl)

BAC mg %	Clinical Manifestation
0-100 mg/dl	Well-Being
100-200 mg/dl	Incoordination
200-300 mg/dl	Ataxia
300-400 mg/dl	Stage 1 Anesthesia, amnesia, hypothermia
400-600 mg/dl	Coma
600-800 mg/dl	Death

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The Rules of Twenties

Going Up

- MEN: Each drink adds 20 mg/dL to one's BAL.
- WOMEN: Each drink adds 40 mg/dL to one's BAL.

Coming Down

- We metabolize 20 mg/dL every 60-90 minutes (zero order kinetics).

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Women and Pregnancy

- There are three general reasons that females show higher BACs (and greater intoxication) than males if they drink the same amount of alcohol.
- Body composition: In females a greater percentage of body mass is fat compared to males
  - Result – The concentration of alcohol is increased in the female bloodstream compared to the male body
- Stomach alcohol dehydrogenase (ADH): Females have very little of this enzyme compared to males
  - Result – Females do not metabolize alcohol before it gets out of the stomach. Therefore, the blood alcohol concentration (BAC) is higher for females versus males
- Liver ADH: Females have a less active form of this enzyme than males.
  - Result – Females do not metabolize alcohol as efficiently as males, thereby increasing the BA

33

Women and Pregnancy

Fetal Alcohol Spectrum disorders (FASD): Growth retardation, Facial malformations, Small head, Greatly reduce intelligence.

- FASD is the most common known preventable cause of mental impairment.
- The prevalence of FASD : 50 per 1,000 (May et al., 2009 and CDC 2016)
- 40,000 infants per year in US

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Case: RR

Past Medical h/x: HTN for 10 years, GERD and H/x of pancreatitis.

Medications:

- Lisinopril 40 mg qam,
- Omeprazole 20 mg daily
- Zolpidem XR 6.25 mg qhs prn for insomnia
- Alprazolam 1-2 mg tid a day for anxiety.

35

Case: RR

Vital Signs: BP:150/95
Pulse: 90x'

CBC normal with the exception of Increased MCV equal 102 (80-96)
Electrolytes and renal function: normal
Hepatic function:

- GGT 141 (10-42),
- AST 60 (15-40)
- ALT 40 (10-40)
- AST/ALT ratio 1.5
- CDT score exceeded the cutoff and so you performed a diagnostic evaluation

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Preventing and Treating AUD

There are evidence-based interventions for preventing and treating AUD:

- Screening, Brief Intervention, and Referral to Treatment (SBIRT)
- Professionally-led behavioral interventions
- FDA-approved medications
- Mutual support groups, such as Alcoholics Anonymous

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SBIRT

- Screening quickly assesses the severity of substance use and identifies the appropriate level of treatment.
- Brief intervention focuses on increasing insight and awareness regarding substance use and motivation toward behavioral change.
- Referral to Treatment provides those identified as needing more extensive treatment with access to specialty care.

www.niaaa.nih.gov/guide
http://www.sbirtcolorado.org/healthcare_videosandwebcasts.php

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Screening Tools

Alcohol Screening is an Effective Prevention Strategy

The CAGE Questionnaire

- Cut Down
- Annoyed
- Guilty
- Eye-Opener

2 or more positive responses are strongly associated with alcohol dependence.

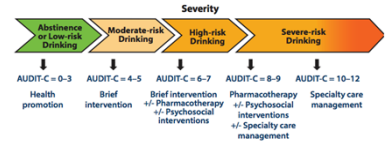
National Institute on Alcohol Abuse and Alcoholism (NIAAA): "Helping Patients Who Drink Too Much"

39

AUDIT-C Questionnaire

Alcohol Use Disorder Identification Test

Question	0 Points	1 Point	2 Points	3 Points	4 Points
How often did you have a drink containing alcohol in the past year?	Never	Monthly or less	2–4 times per month	2–3 times per week	4 or more times per week
On days in the past year when you drank alcohol how many drinks did you typically drink?	1–2	3–4	5–6	7–9	10 or more
How often do you have 6 or more drinks on an occasion in the past year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily



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The Role of Biomarkers in The Treatment of ETOH

- Provide objective outcome measures in alcohol research or evaluating an alcohol treatment program.
- Screen for individuals unable/unwilling to accurately report drinking behavior (e.g., fear, embarrassment, or adverse consequences).
- Evidence of abstinence in individuals prohibited from drinking.
- Enhance patient motivation to stop/reduce drinking.
- Diagnosis tool by assessing contribution of alcohol to the disease.
- Identify relapse early.
- Fear of detection by biomarkers may dissuade drinking.

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Types of ETOH Biomarkers

Indirect Tests

- Manifestations of organ damage often due to drinking
  - gamma glutamyltransferase (GGT)
  - aspartate amino transferase (AST, SGOT)
  - alanine amino transferase (ALT, SGPT)
  - macrocytic volume (MCV)
- Reflections of alcohol's effects on other metabolic processes -
  - carbohydrate-deficient transferrin (CDT) - Only FDA Approved alcohol biomarker

Direct Tests

- Reflections of alcohol use
  - ethyl glucuronide (EtG) and ethyl Sulfate (EtS)
  - Phosphatidylethanol (PEth)

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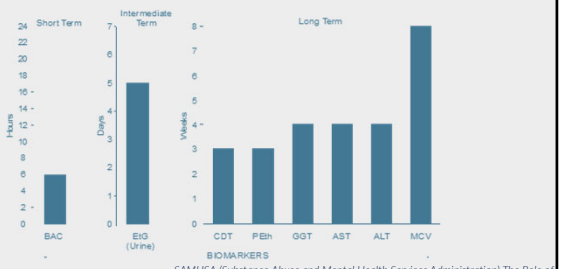
Window of Assessment for Various Alcohol Biomarkers



SAMHSA (Substance Abuse and Mental Health Services Administration) The Role of Biomarkers in the treatment of alcohol use disorders, 2012 Revision

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Characteristics of Assessment for Various Alcohol Biomarkers

Marker	Time to Return to Normal with Abstinence	Level of Drinking	Comments	Blood test normal range
GGT	2-4 weeks of abstinence	~ 5 drinks (>60g/day) for several weeks	Many sources of false positives--liver disease, diabetes, smoking, obesity, age, anticonvulsants, etc.	W: 0-45 U/L M: 0-53 U/L
SGOT/AST	2-4 weeks of abstinence	Unknown but heavy	Many sources of false positives (see GGT) in addition to excessive coffee consumption	10 - 34 U/L
SGPT/ALT	2-4 weeks of abstinence	Unknown but heavy	Many sources of false positives (see GGT) Less sensitive than AST	8-37 U/L
MCV	Up to several months	Unknown but heavy	Slow return to normal limits even with abstinence renders it a poor independent indicator of relapse. More specific than GGT. Unlike other markers, no strong gender effect	80-100fL
CDT	2-4 weeks	~ 5 drinks(>60g/day) for 2 weeks	Few sources of false positives. Good marker of relapse	<60 mg/L

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Diagnostic Sensitivity and Specificity of Biomarkers

	Sensitivity (%)	Specificity (%)
CDT	69	92
CDT/transferrin	65	93
GGT	73	75
AST	50	82
ALT	35	86
MCV	52	85

Bell, et al. Alcoholism: Clinical and Experimental Research 1994

45

Case: RR

His last drink was the previous night. He explained he often has insomnia, diarrhea, palpitations, and shakes in the morning, which he attributes to "anxiety" because these symptoms are alleviated with 1 or 2 alprazolam that has been prescribed by his PCP for the past decade.

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Phases of Alcoholism Treatment

Detoxification
- Primary goal is to achieve an alcohol-free state
- Wide spectrum of severity
- Drug-specific syndromes: opiates, cocaine, alcohol, benzodiazepines

Relapse Prevention
- Primary goal is to maintain an alcohol-free state
- Chronic Treatment

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Introduction Alcohol Withdrawal

Epidemiology

Neurobiology
- Neurotoxicity
- Kindling

Management of Alcohol Withdrawal
- Benzodiazepines
- Anticonvulsants

Real World Implications
- Outpatient vs. Inpatient
- Evaluation and Management

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Epidemiology of Alcohol Withdrawal

- Not well studied
- Significant symptoms occur in 13% to 71% of individuals presenting for detoxification
- Up to 10% of individuals undergoing alcohol withdrawal require inpatient medical treatment
- Estimated mortality up to 2%

Saitz R, Mayo-Smith MF, Roberts MS, Redmond HA, Bernard, DR, Calkins DR. JAMA. 1994;272:519-523.

49

Alcohol Withdrawal and Kindling

- Repeated episodes of alcohol withdrawal likely to worsen
- Exacerbation of symptoms may be due to a kindling process
- Positive relationship of alcohol withdrawal seizures to repeated detoxification

50

Managing Alcohol Withdrawal

Principles of treatment

- Alleviate symptoms
- Prevent progression of symptoms
- Treat underlying comorbidities

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Alcohol Withdrawal Treatment

- Substitute cross-dependent drug (benzodiazepine)
- Gradually withdraw substitute drug
- Supplement vitamins and minerals
  - Thiamine
  - Folic acid
  - Multivitamin
- An array of acid–base disorders and electrolyte disorders can occur in patients with chronic alcohol-use disorder, irrespective of their social circumstances.
- Supportive treatment
  - Decrease stimulation, increase fluid and caloric intake

52

Alcohol Withdrawal Treatment

Thiamine Deficiency

Thiamine
- Important cofactor for several enzymatic reactions
- Cerebral glucose utilization
- Glutamate elimination

Wernicke's Encephalopathy
- Partial to complete paralysis of extra ocular muscles
- Nystagmus
- Ataxia
- Mental disturbances
- Mortality: 10-20% if untreated
- Treatment: Thiamine replacement PRIOR dextrose administration

Korsakoff's Psychosis
- Antegrade amnesia
- Confabulations

53

States of AWS

1. Autonomic Hyperactivity
2. Hallucinations
3. Neuronal excitation
4. Delirium Tremens

There is not necessarily a linear progression.

54

States of AWS

Autonomic Hyperactivity
- Clear Sensorium
- Tremulous
- Diaphoresis
- Anxiety
- Nausea/Vomiting
- Increase cathecolamines in urine, serum and CSF
- Start 6 hrs after last drink Peak 24-48 hrs

Hallucinations
- Most common= VISUAL

Neuronal excitation
- Seizures (Generalized Tonic – Clonic)
- Up to 10%
- Most common in first 24 - 48 hours after last drink

55

States of AWS

Delirium Tremens (DTs)
- Most often occur within 72 hours after the last drink
- Delirium with Tremor
- Autonomic hyperactivity
- Hallucinations
- Electrolyte abnormalities
- Dehydration
- Hemodynamic instability
- Mortality up to 15%
- Cardiovascular/respiratory collapse

56

CIWA-Ar

Clinical Institute Withdrawal Assessment of Alcohol, Revised

- It requires under two minutes to administer
- It requires no medical knowledge
- It provides you with a quantitative score that predicts the severity of withdrawal from alcohol

57

Assessment of Alcohol Withdrawal CIWA-Ar

Symptoms	Range of Scores
Nausea and Vomiting	0 (no nausea, no vomiting) -7 (constant nausea and/or vomiting)
Tremor	0 (no tremor) - 7 (severe tremors, even with arms not extended)
Paroxysmal sweats	0 (no sweat visible) - 7 (drenching sweats)
Anxiety	0 (no anxiety, at ease) - 7 (acute panic states)
Agitation	0 (normal activity) - 7 (constantly trashes about and pacing)
Tactile disturbances	0 (none) - 7 (continuous hallucinations)
Auditory disturbances	0 (not present) - 7 (continuous hallucinations)
Visual disturbances	0 (not present) - 7 (continuous hallucinations)
Headache	0 (not present) - 7 (extremely severe)
Orientation/clouding of sensorium	0 (orientated, can do serial additions) - 4 (Disorientated for place and/or person)

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CIWA-Ar Determining Need of Pharmacotherapy

- <8: Minimal – Mild AW, Drug therapy not necessarily indicated
- 8-15: Moderate AW, Drug therapy indicated.
- >15: Severe, Drug therapy absolutely indicated, consider inpatient treatment

http://www.chce.research.va.gov/apps/PAWS/quiz/q1.html

59

Mechanisms Underlying Alcohol Withdrawal

- Multiple neuroadaptive changes in CNS
  - Decreased GABA activity
  - Increased glutamate activity
  - Upregulated calcium channel activity
  - Increased noradrenergic activity
- Alcohol withdrawal is associated with increased CNS activity

CNS=central nervous system; GABA=gamma-aminobutyric acid.

Anton RF, Becker HC, eds. Pharmacotherapy and pathophysiology of alcohol withdrawal. (Handbook of Experimental Pharmacology.) 1995.

60

Case: RR

You apply your knowledge and training through Motivational Interviewing. Your open–ended questions and affirmations reviewed with patient's possibilities set the bases for a good rapport with Mr. RR. As part of the treatment dialogue, you showed Mr. RR. his BP elevation 150/90, CIWA:8, and his scores on the CDT, GGT and AST/ALT. You noted that the values were outside the reference ranges for the tests.

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Case: RR

You then explained, in a direct, yet empathetic manner, the significance of the scores and noted that GGT and AST/ALT levels this high can reflect liver damage and that CDT levels this high usually reflect heavy drinking. Mr. RR then agrees to start an outpatient alcohol treatment program.

62

Treatment Plan

There are several evidence-based options for non-pharmacological treatment that have minimal harms:

- Motivational Enhancement Therapy (MET): manualized psychotherapy based on the principles of motivational interviewing; shown to have a small to medium effect size on achieving abstinence
- Cognitive Behavioral Therapy (CBT): focusing on the relationships between thoughts, feelings, and behaviors; help manage urges and triggers

63

Treatment Plan

There are several evidence-based options for non-pharmacological treatment that have minimal harms:

- Medical Management (MM): manualized treatment that provides education and strategies to support abstinence and promote medication adherence
- Community based peer support groups such as Alcoholics Anonymous (AA) and other 12-step programs: helpful in achieving long-term remission but not for replacing formal medical treatment

64

Alcohol Detoxification Use of Benzodiazepines

- First line agent (gold standard)
- Loss of inhibition/sedation due to lack of ETOH
- Treatment: Replace the GABA activation (inhibition)
- Benzodiazepines:
  - If hepatic impairment: oxazepam or lorazepam
  - Provide dosing for 24 hour intervals – patient must be re-evaluated before more is provided
    - Vital Signs
    - CIWA-Ar

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Benzodiazepines options

Chlordiazepoxide
- Only available in oral form (PO)
- Longer half life than most benzos (5-30 hrs)

Diazepam
- Lipophilic ⇨ rapid onset of action

Lorazapem
- Available in oral form (PO) and IV
- Half life (12-18 hrs)
- Simple metabolism of hepatic glucuronidation (no active metabolite)
- Ideal for patients with cirrhosis/liver damage and elderly population

66

Indications for Outpatient withdrawal treatment

- CIWA <8 or some with CIWA 8 –15
- No hx. of AW seizures/delirium
- No serious medical/surgical problems
- No serious psychiatric/drug hx
- Social support
- Supervision/housing available

67

Indications for inpatient withdrawal treatment

- History of DTs or withdrawal seizures
- Alcohol withdrawal severity (CIWA>10) + other criteria (e.g Abnormal lab results, Utox + for other substances)
- Pregnancy
- Major medical/surgical problems
- Inability to tolerate oral medication
- Imminent risk to harm himself and/or others
- Active psychosis or cognitive impairment
- Recurrent unsuccessful attempts at ambulatory detoxification

Muncie HL Jr, Yasinian Y, Oge' L. Am Fam Physician. 2013 Nov 1;88(9):589-95.
Lindsay et al. Journal of Addiction Medicine September 2020

68

Treatment of Mild-Moderate Alcohol Withdrawal CIWA-Ar- 8 to 14

Long-acting Benzodiazepines:

- Chlordiazepoxide (Librium) 50-100 Mg Po Q 6-8 Hrs.
- Diazepam (Valium) 10-20 Mg Po Q 6-8 Hrs.

Short-acting Benzodiazepines:

- Lorazepam (Ativan) 2-4 Mg Po Q 1-4 Hrs.

69

Treatment of Severe Alcohol Withdrawal CIWA-Ar > 15

Diazepam 10 mg IV
- Repeat 5 mg IV q 5 Min Until Calm

Lorazepam 4 mg po q 1 hr, PRN
- Moderate To Severe Liver Disease
- Elderly Or Confused Patients
- Very Ill Or Debilitated Patients
- Can Be Given PO, IV Or M

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Alcohol Detoxification

Use of Anticonvulsants

Anticonvulsants Reduce Gaba Activity

- CBZ: Reduced rebound withdrawal & post-detox drinking (Malcolm, 2002)
- Gabapentin normalizes alcohol-induced effects on GABA and glutamate; has no hepatic metabolism
- Gabapentin more effective than lorazepam in reducing post-detox drinking (Myrick, 2009)
- Gabapentin, divalproex & vigabatrin may prove useful
- Caution: CBZ & divalproex have limited use in patients with severe hepatic or hematologic disease

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Alcohol Detoxification

Anticonvulsants Effectiveness and Limitations

Advantages	Disadvantages
• No abuse liability • Cognition • Neuroprotective • Protracted Withdrawal	• Limited clinical experience • Hematological side effects • Liver toxicity

72

When to Consider Pharmacotherapy

- Anti-craving Medication as the new standard of care
  - Consider immediately post-detoxification for ALL patients with alcohol use disorder
  - Efficacy requires counseling and/or frequent physician monitoring
- Most FDA approved medications for SUDs can be used in outpatient settings
- Exception: Methadone maintenance therapy: can only be used for treatment of opioid addiction in licensed opioid treatment programs

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Pharmacogenetics in AUD treatment

Medication	Genetic Variant	Outcome Moderated	Notable Studies
Topiramate	*GRIK1* (rs2832407)	Heavy drinking days (%); side effects	Kranzler et al., 2014 (2); Ray et al., 2009 (4)
Naltrexone	*OPRM1* (Asn40Asp), (rs1799971), DRD4 VNTR	Heavy drinking days (%); abstinence rates; relapse to heavy drinking	Anton et al., 2008 (12); Kim et al., 2009 (13); Oslin et al., 2003 (14); Tidey et al., 2008 (15)
Ondansetron	LL/LS/SS (5-HTTLPR) (rs1042173), *SLC6A4* (5-HTTLPR)	Drinks per drinking day; days abstinent (%)	Johnson et al., 2011 (9)
Sertraline	5-HTTLPR triallelic *SLC6A4*	Heavy drinking days (%); drinking days (%)	Kranzler et al., 2011 (8)
Acamprosate	*GATA4* (rs1327367)	Relapse	Kiefer et al., 2011 (10)
Disulfiram	*DBH* (rs1611115)	Adverse events	Mutschler et al., 2012 (11)

Note: OPRM 1 predictive value for NTX response has not been supported (Schacht, J., Randall, P., Latham, P. et al 2017)

Batki & Pennington (2014) Am J Psychiatry
Hartwell and Kranzler (2019)Expert Opinion on Drug Metabolism & Toxicology

74

Alcohol Use Disorder (Relapse Prevention) FDA Approved

- Naltrexone (Revia): 1994
- Long Acting Naltrexone IM (Vivitrol): 2006

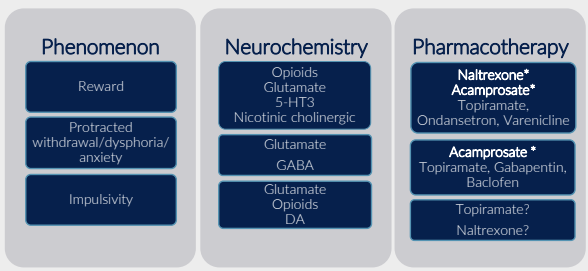
↓ Binge drinking

- Acamprosate (Campral): 2004 → Maintain abstinence
- Disulfiram (Antabuse): 1949 → With supervision improve treatment adherence
- Nalmefene (2016) *European Medicines Agency (EMA)*

↓ Heavy drinking days

75

Neurochemical Targets for AUD



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Pharmacotherapy of Alcohol Use Disorder:
Naltrexone-oral/Mechanism of Action

- Reduces positive reinforcement (reward craving)
  - Potent inhibitor at mu opioid receptors
- Modulates the mesolimbic dopamine system in the VTA & projections to the nucleus accumbens
- There is mixed evidence around markers that predict a favorable response to naltrexone treatment, such as:
  - Male sex
  - A positive family history of alcoholism
  - High levels of craving,
  - Polymorphism (asp variant) of the opioid receptor gene OPRM1?

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Pharmacotherapy of Alcohol Use Disorder:
Naltrexone-oral/Mechanism of Action

- The patient does not experience the full euphorogenic/reinforcing effect of alcohol.
  - suppresses/reduces endogenous opioids (beta-endorphin) involved in the reinforcing (pleasurable) and subsequent reduces DA in NAc effects of alcohol and possibly craving
- Prevents a slip from becoming a full-blown relapse

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Pharmacotherapy of Alcohol Use Disorder:
Naltrexone-oral / Effectiveness

- Effective in reducing relapse to heavy drinking.
- A meta-analysis of (N:16 studies and 2347 patients) found a:
  - risk decrease (RD) for a return to any drinking
  - (risk decrease = −0.05; 95% CI, −0.10 to −0.002; number needed to treat = 20)
- (19 studies N: 2875) found also a:
  - risk decrease (RD) of binge drinking
  - (risk decrease = −0.09; 95% CI, −0.13 to −0.04; number needed to treat = 12)
- Medication compliance may be a limiting factor in oral treatment.

Kranzler Hr et al JAMA 2018 ; Srisurapanont M, Jarusuraisin N. Cochrane Database Syst Rev 2005;(1):CD001867.

79

Pharmacotherapy of Alcohol Use Disorder:
Naltrexone-oral / Dosing and Safety

Oral Naltrexone Hydrochloride
- FDA approved dose: 50 mg per day
- Antagonist of mu , delta and kappa opioid receptors.
- Antagonizes opioid-containing agents, but no other significant drug-drug interactions.

- Some have used 100 mg daily with rationale that naltrexone has been effective for heroin addiction at doses of 100mg-100mg-150 mg q Monday, Wednesday, and Friday; an effective plasma concentration can be obtained even if some doses are missed

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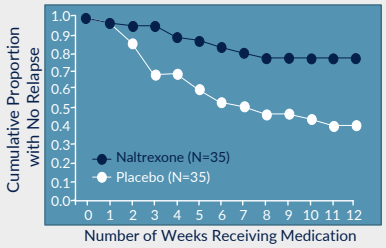
Pharmacotherapy of Alcohol Use Disorder:
Naltrexone-oral /Dosing and Safety

- Side effects
  - GI: abdominal pain, diarrhea, decreased appetite, nausea
  - Sedation: daytime sleepiness, fatigue, insomnia, headache
- Reversible hepatoxicity
  - LFT's should be monitored closely (check LFT's prio starting medication)
- Works best with complaint patients
  - Requires counseling (CBT) or frequent MD monitoring visits (Project Combine, 2006)
  - Efficacy questioned in women (O'Malley, 2007)

Physician's Desk Reference (www.PDR.net) and Epocrates. Accessed on September 1, 2011.

81

Naltrexone-Oral in the Treatment of Alcohol Use Disorder



Volpicelli et al., Arch Gen Psychiatry, 1992

82

Pharmacotherapy of Alcohol Use Disorder:

Long-Acting Naltrexone (IM)

Extended-Release - Injectable Naltrexone

- 1 injection per month/ 380 mg
- 100 µm diameter microspheres of naltrexone and polymeric matrix.

- Advantages: once a month injection can be done in clinician's office
- Better adherence with once monthly dosing
- More stable plasma concentrations compared to the oral formulation

Garbutt et al. JAMA. 2005;293:1617-1625. Physician's Desk Reference (www.PDR.net) and Epocrates. Accessed on September 1, 2012.

83

Pharmacotherapy of Alcohol Use Disorder:

Long-Acting Naltrexone (IM) Dosing and Safety

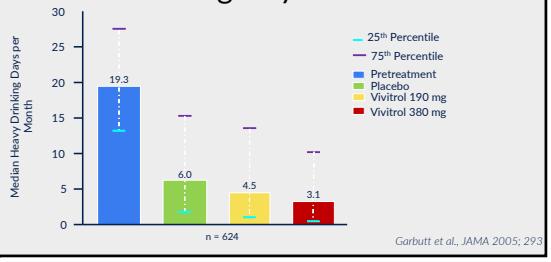
Extended-Release Injectable Naltrexone

- Side effects: nausea & headaches; more sedation than with the oral formulation
- LFT's should be monitored closely
- Injection site reactions possible
- Best results in patients sober 1 week prior to starting the medication
- Efficacy shown in more severe alcoholics
- Reduction in heavy-drinking days (48.9% vs 30.9% on placebo)
- Pregnancy Category C , acceptable for use when breastfeeding

Pettinati HM, Alcohol Clin Exp Res, May 2011

84

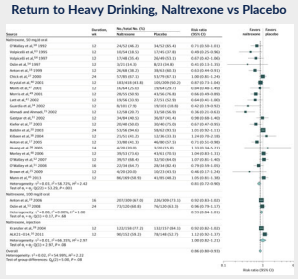
Naltrexone-injectable in the Treatment of Alcohol Use Disorder Results: Heavy Drinking Days



Garbutt et al., JAMA 2005; 293

85

Evidence of Naltrexone in both forms PO and IM



McPheeters M et al., Pharmacotherapy for Alcohol Use Disorder: A Systematic Review and Meta-Analysis. JAMA. 2023 Nov 7;330(17):1653-1665. doi: 10.1001/jama.2023.19761. PMID: 37934220; PMCID: PMC10630900

86

Protracted Withdrawal Symptom

- Sleep dysregulation
- Irritability
- Mood instability
- Anxiety

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Pharmacotherapy of Alcohol Use Disorder:
Acamprosate/ Mechanism of Action

- Stabilizes glutamatergic neurotransmission altered during withdrawal (Littleton 1995).
- Chronic ETOH exposure alters GABA & NMDA systems
  - Restores balance between inhibitory & excitatory neurotransmission
- Anticraving, reduced protracted withdrawal
- Reduce negative reinforcement (abstinence craving)
- No abuse liability, hypnotic, muscle relaxant, or anxiolytic properties

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Pharmacotherapy of Alcohol Use Disorder:
Acamprosate/ Effectiveness

- Effective in improving abstinence.
- A meta-analysis (16 studies; N = 4847) concluded that acamprosate treatment was associated with a greater reduction than placebo in the risk of drinking among abstinent patients but no reduction in the likelihood of binge drinking.
  - (risk decrease = −0.09; 95% CI, −0.14 to −0.04; number needed to treat = 12)
- The US trial showed efficacy only in patients motivated for abstinence.

Jonas et al Jama 2014; Kranzler HR, Gage A. Am J Addict. 2008;17:70-76. Mason BJ et al. J Psychiatr Res. 2006;40:383-93.

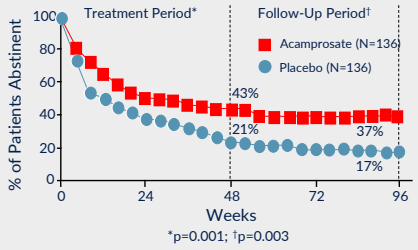
89

Pharmacotherapy of Alcohol Use Disorder:
Acamprosate/Dosing and Safety

- 666 mg three times a day (2000 mg daily)
- Excreted by the kidneys; no liver metabolism
- Contraindicated: significant renal disease with creat cl <30ml/min or those who are pregnant
- Mild diarrhea (16% acamprosate vs. 10% placebo)
- Recommendation: patients with hepatic disease or those treated with opioids. Advantage when a patient is taking multiple medications
- No drug-drug interactions.
- Pregnancy category C

90

Acamprosate in the Treatment of Alcohol Use Disorder

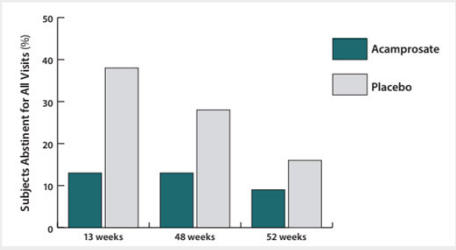


*p=0.001; †p=0.003

Sass et al., Arch Gen Psychiatry, 1996

91

Acamprosate in the Treatment of Alcohol Use Disorder

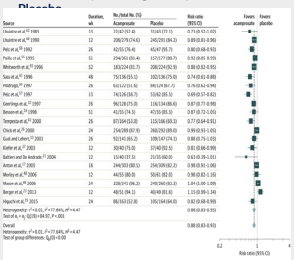


Kranzler HR, Gage A. Acampro sate efficacy in alcohol-dependent patients: summary of results from three pivotal trials. Am J Addict. 2008;17(1):70–6.

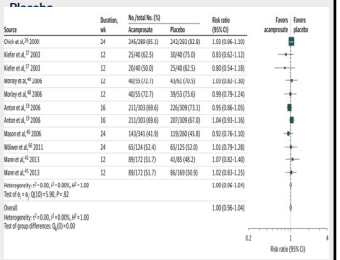
92

Evidence of Acamprosate

Return to Any Drinking, Acamprosate vs



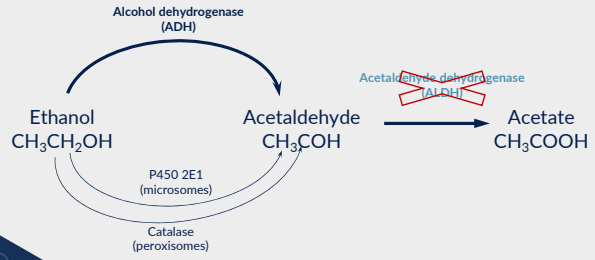
Return to Heavy Drinking, Acamprosate vs



McPheeters M et al., Pharmacotherapy for Alcohol Use Disorder: A Systematic Review and Meta-Analysis. JAMA. 2023 Nov 7;330(17):1653-1665. doi: 10.1001/jama.2023.19761. PMID: 37934220; PMCID: PMC10630900

93

Pharmacotherapy of Alcohol Use Disorder:
Disulfiram Mechanism of Action



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Pharmacotherapy of Alcohol Use Disorder:
Disulfiram/ Mechanism of Action

- Alcohol → Acetaldehyde → Acetate
- Disulfiram irreversibly binds to acetaldehyde dehydrogenase inhibiting the metabolism of acetaldehyde to acetate.
- Acetaldehyde accumulates resulting in a very unpleasant reaction Disulfiram –Ethanol Reaction (tachycardia, headache, nausea/vomiting, hypotension, sweating, warmness and flushing of the skin, dizziness, blurred vision and confusion).

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Pharmacotherapy of Alcohol Use Disorder:
Disulfiram Effectiveness

- Second Line Treatment
- In a meta-analysis of 22 studies was associated with:
  - Sustained abstinent compared to control conditions only in open-label studies
- Double-blind, placebo-control study design is not helpful as both the medication and the placebo pills may (or may not) result in fear of drinking.
- Most studies are negative, but disulfiram may be helpful for a better response than control conditions when medication adherence was supervised

Diehl et al. Alcohol Alcohol. 2010;45:271-277. Fuller RK et al. JAMA. 1986;256:1449-55. Kranzler HR, Soyka M. Diagnosis and Pharmacotherapy of Alcohol Use Disorder: A Review. JAMA. 2018;320(8):815–824.

96

Pharmacotherapy of Alcohol Use Disorder:

Disulfiram Dosing and Safety

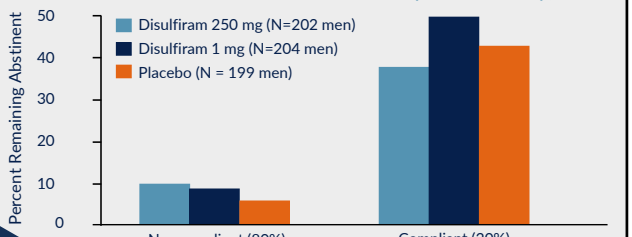
- 250-500 mg daily.
  - First dose 12 hours after the last drink;
  - 500mg PO each morning for 1-2 weeks, then 250mg PO each morning
- Some liver toxicity; monitor LFTs at the beginning, 2 weeks, 3 months and then every 6 months. Caution with CAD. Contraindicated: psychosis, significant liver disease, esophageal varices, pregnancy, impulsivity, severe pulmonary disease, seizures, CRF (Barth et al., 2010)
- Inhibits hepatic microsomal enzymes and increases drug levels (phenytoin, warfarin, isoniazid, metronidazole, TCA and benzodiazepines among others)
- Pregnancy category C
- SIDE EFFECTS: skin/acneiform eruptions, drowsiness, headache, metallic taste, decreased libido/potency

Physician's Desk Reference (www.PDR.net) and Epocrates. Accessed on March 1, 2018.

97

Disulfiram in the Treatment of Alcohol Dependence

Disulfiram and Abstinence Rates (VA Cooperative Study)



Fuller RK et al. JAMA. 1986; 256:1449-1455

98

MAT + FDA Approved

Medication (typical dose)	Mechanism of action	Adverse effects	Cautions	Lab monitoring	Other
*Naltrexone (50-100mg PO daily or 380mg IM monthly)	Blocks opioid receptors May reduce rewarding effects of alcohol	Nausea Headache, dizziness, insomnia Anxiety *Injection site reaction	Need 7-10 days "opioid free" if patient previously receiving chronic opioids Do not use if: Current opioid use LFTs ≥ 5x upper limit of normal	LFTs prior and during treatment	Number needed to treat to reduce heavy drinking days is 12
*Acamprosate (666mg PO three times daily)	Levels out GABA + glutamate activity	Diarrhea	CrCl 30-50 mL/min: 333mg PO three times daily Do not use if: CrCl ≤ 30 mL/min	Renal function (basic metabolic panel) prior and during treatment	Prolongs periods of abstinence
*Disulfiram (250-500mg PO daily)	Blocks acetaldehyde dehydrogenase Blocks enzyme involved in dopamine metabolism	Disulfiram-alcohol reaction if combined Rare but notable: acute liver failure	Need ≥ 12h alcohol abstinence Many medication interactions Do not use if: Severe cardiac disease or coronary occlusion Primary psychotic disorder	LFTs prior and during treatment	Daily observed disulfiram Targeted disulfiram (e.g. weddings, reunions, holidays)

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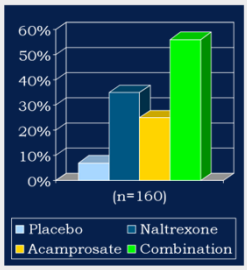
Combinations

- Naltrexone and acamprosate have different mechanisms of action and may work synergistically on cravings:
  - Naltrexone on positive reinforcement
  - Acamprosate on negative reinforcement
- Medications and psychotherapy.

Rosner S et al. J Psychopharmacol. 2008;22:11-23.

100

Naltrexone/Acamprosate



- Abstinence rates during a 12-week trial with:
  - Naltrexone 50 mg QD,
  - Acamprosate 666 mg TID.
- The combination of the two medications helped alcoholics stay abstinent (P=0.002) better than each drug alone.

Adapted from Kiefer F et al. Arch Gen Psychiatry. 2003;60:96.

101

Project MATCH

- Compared outcome efficacy for patients matched to treatments based on a prior hypotheses about 11 client attributes
- Treatment was for 12 weeks; follow-ups continued for years
- 12-Step programs, CBT and MET were compared
- Each of the three methods helped in the treatment of alcoholism
  - However outpatients who received TSF were more likely to remain abstinent after 1 year following treatment
- There were a few matching effects, and they were weak

102

The COMBINE Study

- 1383 patients with alcohol dependence randomized to varying combinations of oral Naltrexone, Acamprosate, combined behavioral intervention (CBI) and medical management (MM)
- Patients received naltrexone, acamprosate, both, or neither
- Half of patients received psychotherapy in addition to medical management
- One patient cohort received psychotherapy alone, no pills

JAMA. 2006;295:2003-2017

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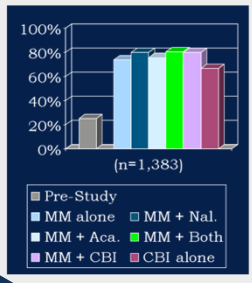
The COMBINE Study



- Percentage of abstinent days per month during a 16-week treatment trial with:
  - Naltrexone 100 mg QD,
  - Acamprosate 1 g TID.
- All treatment groups had an increase in % days abstinent. Overall effect was from 25% to 73%.

Adapted from Anton et al. JAMA. 2006;295:2003-2017

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The NIAAA COMBINE Study Results

- For patients receiving MM, naltrexone, or CBI therapy, improved outcomes over placebo plus MM
  - Naltrexone + MM had the best outcome
- Acamprosate did not add benefit to naltrexone or CBI, and was no more effective than placebo plus MM
- Taking tablets and seeing a health care professional was more effective than receiving CBI alone (possible placebo effect)
- One-year outcome: no significant differences among the groups

N=1383 (16 weeks trial)	Good Clinical outcome
MM and Placebo	58 %
MM and Placebo and CBI	71%
MM and Naltrexone	74%

CBI: Combined Behavioral Intervention
Good Clinical Outcome: Abstinence or drinking moderate amounts without problems P<0.025 (interaction p-value 0.02)

Adapted from Anton et al. JAMA. 2006;295:2003-2017

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Other Pharmacological Agents

Anticonvulsants
- Topiramate
- Gabapentin
- Carbamazepine
- Valproic Acid

GABA agonist
- Baclofen

Alpha1 adrenergic blocker
- Doxazosin
- Prazosin

Alpha 2 agonists
- Clonidine

Serotonin (5-HT3) antagonists
- Ondansetron
- Mirtazapine

Selective Serotonin Reuptake Inhibitors

Partial agonist for the α4β2 nicotinic acetylcholine receptor subtype (nACH)
- Varenicline

Mu and delta opioid antagonist and partial kappa agonist
- Nalmefene

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Conclusions

- Identify the need of your patients to get treatment
- Substance use disorders are chronic, be ready for relapses
- Prevention is based on screening and early Intervention
- CIWA-Ar is your best ally for AWS
- AWS=BZD most effective, safest and cheapest treatment
- Medications for Alcohol Use Disorder are relatively safe but modestly effective
- Naltrexone is best for "cutting down."
- Acamprosate is best for preventing "the first drink."
- Pharmacotherapy and psychotherapy modalities can be offered by you
- Pharmacotherapy and psychotherapy modalities are effective and scientifically based approaches

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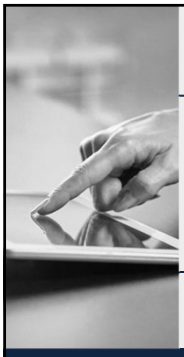

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JULY 2024 REVIEW COURSE 2024

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ASAM REVIEW COURSE 2024

Opioid Use Disorder: Science, History, and Clinical Implications

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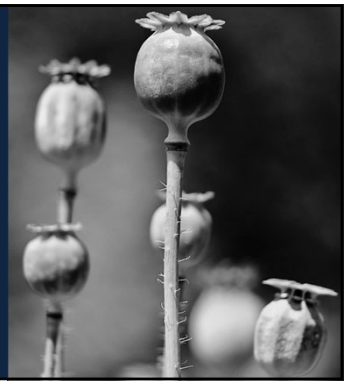

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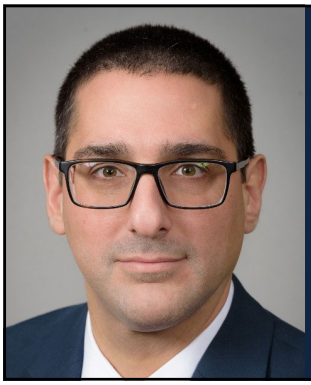

Financial Disclosure

Soteri Polydorou, MD

- No relevant disclosures

REVIEW COURSE 2024

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Outline

1. Opioid Use Trends
2. History
3. Regulations
4. Neurobiology
5. Intoxication and Withdrawal
6. Medications for Opioid Use Disorder

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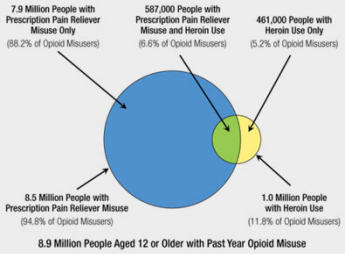
The Need for Treatment

- Opioid Use Disorder 2.7 million
  - Prescription opioid misuse 8.5 million in past year
  - Fentanyl 686,000 people in past year
  - Heroin use 1 million
    - >100% increase from 2004 to 2016
    - Lifetime use 5.7 million, doubled from 2002 to 2018
    - 4 of 5 new heroin users previously used prescription opioids
- 15-yr reduction in life expectancy



Lewer 2020; NSDUH 2022, SAMHSA

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The Need for Treatment is Growing

Nationally

- Over 100,000 lethal ODs in 2022
- Almost 80% of all overdose deaths involve an opioid
- 90% of fatal opioid overdoses involve synthetic opioids, fentanyl
- Heroin users, >100% increase from 2004 to 2016
- 4 out of 5 new recent heroin users previously abused prescription opioids
- >140 OD deaths from opioids daily in US
- 2010 to 2016 heroin related deaths increased by 500%
- 2015 to 2019 fentanyl related deaths increased by over 400%

Leading Causes of Death in US 2022	Annual Deaths
Heart Disease	702,880
Cancer	608,371
Unintentional Injuries	227,039
COVID-19	186,552
Stroke	165,393
Chronic Lower Respiratory Diseases	147,382
Alzheimer Disease	120,122
Diabetes Mellitus	101,209
Renal Disease	57,937
Chronic Liver Disease and Cirrhosis	54,803

CDC, Health Alert Network, NSDUH, SAMHSA, CSAT, and DOHMH Bureau of Vital Statistics, National Center for health Statistics Data Brief 492 US Mortality 2022

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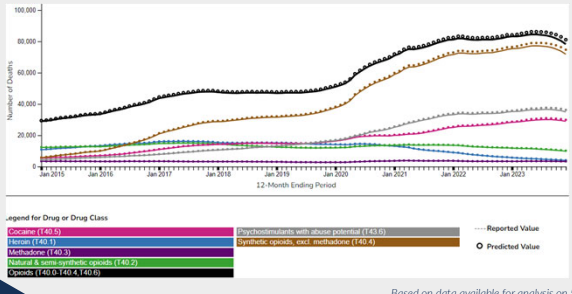
The Need for Treatment is Growing



Based on data available for analysis on 5/5/24.
https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm#dashboard

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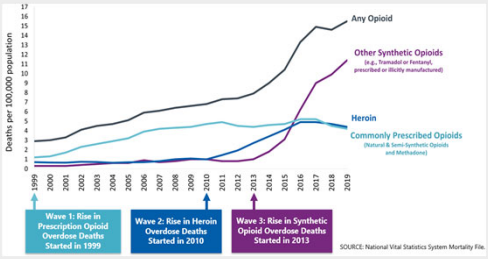
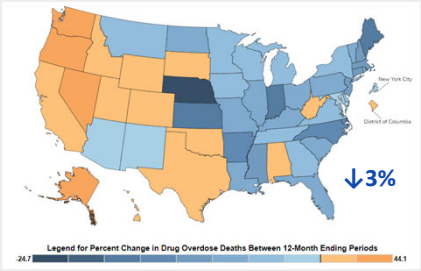
Three Waves of Opioid Overdose Deaths



cdc.gov/drugoverdose

7

Drug Overdose Deaths 12/2022 to 12/2023



https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

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Unintentional Opioid Overdose

Experienced (non-fatal)

- Lifetime 24% - 94% (mean 45%, median 47%, SD 14%)
- Past Year 9% - 36% (mean 18%, median 17%. SD 10%)

Witnessed (non-fatal and fatal)

- Lifetime 48% - 96% (mean 73.3%, median 70%, SD 14%)

1 Year All Cause Mortality

- 5% of Non-Fatal Opioid Overdose Presentations to ED or Hospital Admission

Martins S et al 2015, Leece P, et al. 2020, Weiner S et al. 2020

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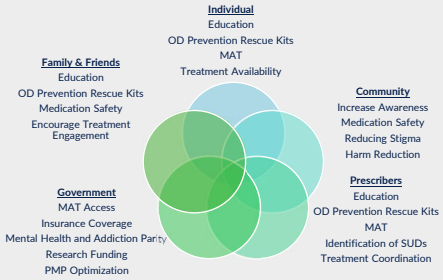
Opportunities to Reduce Risk



Hawk K et al 2015

10

3400 BC

1898

1839

1935

11

U.S. Government Involvement

Congress passes multiple laws aimed at reducing the increase in heroin/morphine/opium addiction.

- 1905-Opium banned
- 1906-Pure Food and Drug Act- labeling of all medications by pharmaceutical companies
- 1914-Harrison Narcotics Act (HNA)
  - 1919- Supreme Court sides with Treasury interpretation that physician prescribing of opioids for treatment of opioid addiction was violation of HNA
  - Later Supreme Court rulings from 1921 and 1926 reverses interpretation of HNA saying the federal government had overstepped its authority to regulate the practice of medicine

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U.S. Government Involvement

- 1970-Comprehensive Drug Abuse Prevention & Control Act (Controlled Substances Act)
- 1974 – Narcotic Addict Treatment Act of 1974
- 2000- Drug Addiction Treatment Act (DATA) of 2000– An Amendment to the Controlled Substances Act
  - Allows treatment of opioid dependence with narcotic schedule III, IV, V, or combinations of such drugs
  - Buprenorphine designated Schedule III and FDA approved for treatment of opioid dependence
  - Capacity to refer patients for counseling

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U.S. Government Involvement

- 2016 Comprehensive Addiction and Recovery Act (CARA)
- 2018 Support for Patients and Communities Act
- 2020 HHS Public Health Emergency Declaration, DEA partners with SAMHSA (temporary)
- 2021 HHS Updates Practice Guidelines for the Administration of Buprenorphine for Treating OUD

Over 100,000 practitioners hold waivers, 71,000 with 30-limit, 22,000 with 100-limit, <10,000 with 275-limit

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2023 Consolidated Appropriations Act

Section 1262, Mainstreaming Addiction Treatment Act (MAT Act)

Buprenorphine DATA-Waiver is *ELIMINATED!*

Effective January 12, 2023

- A DATA-Waiver registration is no longer required to treat patients with buprenorphine for opioid use disorder
- Prescriptions for buprenorphine only require a standard DEA registration number
- No caps on the number of patients a prescriber may treat for opioid use disorder with buprenorphine
- The Act does not impact existing state laws or regulations that may be applicable

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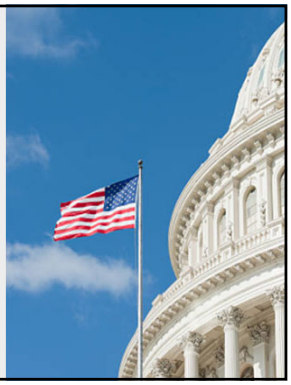
2024 HHS/SAMHSA Final Rule on Opioid Use Disorder Treatment

- Reduces barriers to receiving care
- Supports a patient-centered approach
- Promotes practitioner autonomy
- Removes stigmatizing and outdated language



https://www.federalregister.gov/documents/2024/02/02/2024-01693/medications-for-the-treatment-of-opioid-use-disorder

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Highlights of the Final Rule

- Modifies medical exam requirement to facilitate treatment initiation
- Methadone: telehealth screening and full exam must be audio-visual, NOT audio only
- 1st day dose should not exceed 50mg, limited exceptions
- Buprenorphine: telehealth screening and full exam can be audio-visual or audio only
- Allows medication units to be community pharmacies and allows them to offer take-home methadone
- Allows split dose as clinically indicated
- Allows Medical Directors to delegate responsibilities to other practitioners (NP/PA)
- Patient refusal of counseling does not preclude care at OTP
- Accreditation, CAP extended to 180d following survey report
- Interim treatment (to comprehensive maintenance treatment) expanded from 120d to 180d, state dependent, only if needed (>14d)

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Methadone Take-Home Doses/Schedule

- Take-home methadone schedules are significantly increased in regulation
- In treatment 0-14 days, up to 7 unsupervised take-home doses of methadone may be provided to the patient
- Treatment days 15-30, up to 14 unsupervised take-home doses of methadone may be provided to the patient
- From 31 days in treatment, up to 28 unsupervised take-home doses of methadone may be provided to the patient

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Methadone Take-Home Doses/Schedule

- In determining which patients may receive unsupervised doses, the medical director or program medical practitioner shall consider, among other pertinent factors that indicate whether the therapeutic benefits of unsupervised doses outweigh the risks, the following criteria:
- Absence of active substance use disorders, other physical or behavioral health conditions that increase the risk of patient harm as it relates to the potential for overdose, or the ability to function safely;
- Regularity of attendance for supervised medication administration;
- Absence of serious behavioral problems that endanger the patient, the public or others;
- Absence of known recent diversion activity; and
- Whether take home medication can be safely transported and stored; and
- Any other criteria that the medical director or medical practitioner considers relevant to the patient's safety and the public's health.

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Overview

- Addictive drugs produce an enhancement in extracellular dopamine levels in the nucleus accumbens and other limbic structures as well as cortical areas.
- Endorphin-Opioid Receptor binding results in an increase in dopamine release in the mesolimbic and mesocortical pathways but unlike exogenous Opioid-OR binding the effect is less robust and does not result in habituation.

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Terminology

Endorphins - describes the whole class of endogenous opioid ligands
- Beta-endorphin, enkephalin, dynorphin

Opioid - describes entire class of non-endogenous (natural or synthetic) and endogenous compounds that bind to one or more types of opioid receptors
- Methadone, fentanyl, oxycodone

Opiate - describes compounds naturally derived from the poppy plant
- Morphine, codeine

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Opium Poppy: Papaver Somniferum

Alkaloid Content

- **Morphine,** 7-25%, opiate analgesic, named after Morpheus, the Greek God of dreams
- **Noscapine**. 4-15%, central acting antitussive, no morphine-like effect of dependence or tolerance
- **Codeine**. 1-6%, opiate analgesic
- **Thebaine**. 1-6%, important intermediate for the synthesis of semisynthetic opioids e.g., buprenorphine
- **Papaverine**. 1-5%. smooth muscle relaxant

Poppy Seeds: *UDS → + Opiates, Morphine, Codeine (cut-off dependent)*

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Endogenous Opioids & Opioid Receptors

Endorphin Class	Opioid Receptor Type
Beta-endorphin Endomorphin	Mu Opioid Peptide Receptor
Dynorphin	Kappa Opioid Peptide Receptor
Enkephalin	Delta Opioid Peptide Receptor
Orphanin/Nociceptin (opiate-like)	*Nociceptin/Orphanin FQ Peptide Receptor, Opioid Receptor Like-1*

Multiple opioid receptor polymorphisms identified

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Opioid Receptors

All Opioid Receptors
Seven transmembrane domain
G protein-coupled
Primarily inhibitory pathways

Mu Opioid Receptor (OPRM) Activation (predominantly beta-endorphin)
Reduces cAMP
Inhibits transporter release of GABA, glycine, and glutamate
- Inhibition of GABA in ventral tegmental area (VTA)→increases dopamine release throughout mesolimbic (amygdala, ventral pallidum, hippocampus, NAcc)-mesocortical (prefontal cortex, orbitofrontal cortex, anterior cingulate) dopaminergic fields.

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Opioid Receptors

Mu Opioid Receptor (OPRM) Activation (predominantly beta-endorphin)

- Widely dispersed across a wide variety of brain regions, including cortex, striatum, thalamus, hippocampus, locus coeruleus, ventral tegmental area, nucleus accumbens, amygdala
- Mu receptors also mediate rewarding properties of non-opioid drugs of abuse including cannabinoids, alcohol and nicotine, or even natural reinforcers such as social interactions
- Physiologic effects of intoxication and withdrawal

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Opioid Receptors

Kappa Opioid Receptor (OPRK) Activation (predominately dynorphin A)

- Identified in various CNS regions such as the nucleus accumbens, caudate–putamen, olfactory tubercle, bed nucleus of the stria terminalis, medial preoptic area, paraventricular nucleus, supraoptic nucleus, dorsomedial, and ventromedial hypothalamus, amygdala, midline thalamic nuclei, periaqueductal gray, raphe nuclei, parabrachial nucleus, locus coeruleus, spinal trigeminal nucleus, and the nucleus of the solitary tract.
- Mediates dysphoric activities of both opioids and cannabinoids and therefore opposes mu receptors in regulating the hedonic tone and modulating stress-induced relapse.

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Opioid Receptors

Delta Opioid Receptor (OPRD) Activation (predominately enkephalin)

- Identified in various CNS regions including thalamus, amygdala, NAcc, locus coeruleus, VTA, and others
- Lack of familiar opioid characteristics like respiratory depression, reinforcing effects as measured in self-administration studies, and opioid (mu or kappa) withdrawal symptoms.
- Delta receptors are less directly involved in hedonic control.
- Distinct from mu and kappa receptors, delta receptors may play a role in emotional responses and show anxiolytic activity along with benefits in analgesia resulting from inflammatory states.

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Role of Endorphin Systems in Normal Physiologic Functions

- Endogenous response to pain
- Neuroendocrine functions
  - Stress-response systems including HPA axis
  - Reproductive function including HPG axis
- Immunologic function
- Gastrointestinal function
- Cardiovascular function
- Pulmonary function
- Mood, affect, cognition

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Additional Opioid Effects

- CNS → Sedation, Analgesia, Euphoria
- GI → Constipation, Nausea
- Endo → ↓Testosterone, ↑Prolactin , ↓ FSH, LH
- Urinary → Retention
- Cardiovascular → Vasodilatation, ↑ QTc
- Miosis
- Tolerance Varies

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Opioids of Note

- Fentanyl ↑ Temp → ↑ Skin Absorption
- Meperidine → Normeperidine → Neuroexcitation, MAO interactions Serotonin Syndrome
- Tramadol weak mu, ↑ 5HT, ↑ NE, Seizures, (Sched. IV), serotonin syndrome
- Tapentadol mu agonist, ↑ NE (5HT), serotonin syndrome
- Kratom, low dose (1-5g) stimulant resembling caffeine/cocaine, high dose (5-15g) opioid like effects, analgesic/sedation reversed by naloxone, possible assoc with hepatic cholestasis—dose dependent
- Tianeptine, antidepressant similar to TCAs, mu and delta agonist, anticholinergic

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Opioid Potency

Opioid	*Relative Potency*	*Lethal Dose*
Morphine	1x	1 Pea
Diacetylmorphine (heroin)	2x	1 Sunflower Seed
Fentanyl	100x	1 Sesame Seed
Sufentanil	500x	1 Grain of Sand
Carfentanil	10,000x	0.5 Grain of Salt

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Role of Medications in the Treatment of Opioid Use Disorder

Overdose
- Acute intervention, possible reversal, and close monitoring

Withdrawal/Early Stabilization
- Reduction and stabilization of withdrawal symptoms
- Opportunity to initiate and engage in ongoing addiction treatment

Maintenance Therapy
- Prevents or eliminates withdrawal
- Diminishes or eliminates drug craving and use of illicit opioids
- Blocks or attenuates the effects of heroin and other abused opiates
- Risk/harm reduction, reduces overdose risk
- Increased treatment retention and engagement in comprehensive rehabilitation
- Decreased medical and psychiatric symptoms, improves health, reduced risk of HIV and Hep C infection
- Improved social determinants such as employment, family relations
- Decreased criminal behavior

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Opioid Overdose

Classic Triad Seen In Overdose

- *Miosis (Dilated With Prolonged ↓ PO2)*
- *Decreased level of Consciousness/Coma*
- *Respiratory Depression*
- Pulmonary Edema (Non-cardiogenic)
- Seizures
  - Meperidine, Tramadol

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Management of Opioid Overdose

- Ventilatory support if needed
- Parenteral Naloxone
- If IV access, bolus 0.1mg/min titrated to
  - RR>10/min
  - Improved level of consciousness
  - No withdrawal
  - If needed ongoing IV infusion 2/3 of initial bolus dose/hr.
- If no IV access, 0.4-0.8mg SQ or IM and observe
- Naloxone OD Prevention Kits

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Opioid Overdose Education and Naloxone Distribution (OEND) Programs

- Improved trainee Strang 2006 knowledge of OD safely and effectively administer naloxone
- Some evidence suggests trainees reduced IV use and were more likely to enter treatment 6 months after training. Seal 2005.
- Chicago, OD deaths reduced after introduction of OOPPs. Maxwell S 2006
- Mass, ↓27% in OD deaths low implementation (1-100/100k) vs ↓46% in high implementation (>100/100k). *Walley AY 2013.*
- But still…
  - Study of >500 MDs reported 54% would NEVER consider prescribing naloxone to an IVDU. *Beletsky L 2007.*

36

Pitfalls Opioid Analgesic ODs

- Need for repeated naloxone treatment with longer acting opioids (methadone), and more potent opioids (fentanyl, carfentanil)
- Check for Fentanyl Patch under clothing
- Fentanyl chest wall/skeletal muscle rigidity
  - Most common with rapid IV administration, not dose related
  - Ventilation, naloxone, neuromuscular blocking agent
- Xylazine (non-opioid sedative, alpha2 adrenergic agonist) increasingly identified with illicit fentanyl, complex/severe wounds
- Alert to possible acetaminophen or other OD

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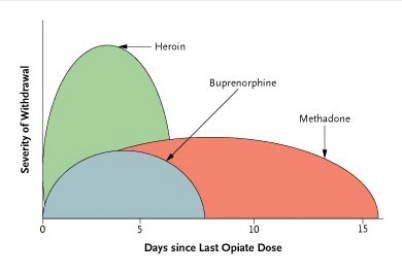
Severity of Opioid-Withdrawal Symptoms after Abrupt Discontinuation of Equivalent Doses of Heroin, Buprenorphine, and Methadone



Kosten and O'Connor, 2003

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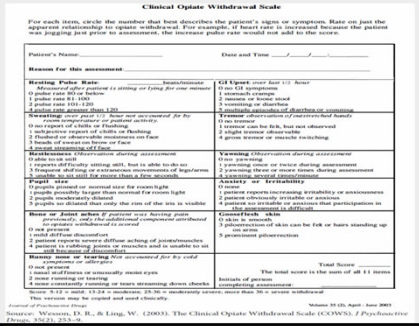
Clinical Opiate Withdrawal Scale (COWS)



Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____ :____

Reason for this assessment:_____

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
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 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection
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

This version may be copied and used clinically.

Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253-9.

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Clinical Opiate Withdrawal Scale (COWS)

- Methadone—Hospitalized, OTP, very limited other licensed OP
- Buprenorphine—DEA licensed prescribers, no longer limited to those with DATA waivers, MD/DO/PA/NP, OTP
- Symptomatic Meds, e.g., Clonidine, Lofexadine, NSAIDS, Imodium, B/Zs
- 72 Hour Rule: Methadone Dispense Only

Table 2. Medication Treatment for Opioid Withdrawal.*

Protocol	Examples	Effects and Comments
Medication		
Opioid agonists	Methadone (20 to 35 mg daily) or buprenorphine (4 to 16 mg daily), tapered over several days or weeks	Withdrawal symptoms are decreased in severity. Methadone and other opioid agonists are currently restricted to inpatient settings or licensed programs; buprenorphine is now approved by the FDA for this purpose.
Nonopioid drugs	Clonidine (0.2 mg 3 times daily) or lofexidine (0.2 mg twice daily), administered for approximately 10 days for heroin and 14 days for methadone	Withdrawal symptoms are decreased in severity. Lofexidine is less likely to produce hypotension but is not currently approved by the FDA for this purpose.
Rapid and ultra-rapid detoxification	Protocols include a variety of medications: opioid antagonists (naloxone or naltrexone), clonidine, sedatives, antiemetic agents, analgesics, anesthetics	Withdrawal is precipitated with an opioid antagonist, and symptoms are managed with a variety of adjuvant medications. Patients are awake or lightly sedated for rapid detoxification; they are under heavy sedation or general anesthesia for ultra-rapid detoxification. Both methods require special training, equipment, or both. Research on efficacy is limited.

* FDA denotes Food and Drug Administration.

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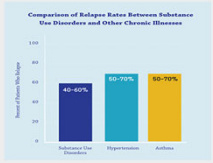
Opioid Use Disorder Treatment Outcome*

Methadone Maintenance	50 – 80%
Buprenorphine-Naloxone Maintenance	40 – 70%**
Naltrexone Maintenance (oral, depot)	10 – 20%, 20-60%***
"Drug Free" (no pharmacotherapy)	5 – 20%
Short-term Detoxification (any mode)	5 – 20% (limited data)

* One year retention in treatment and/or follow-up with significant reduction or elimination of illicit use of opiates
** Effective dose 16-24mgs equal to 60 to 80 mg/d or possibly greater of methadone.
*** 6 month treatment with extended release naltrexone



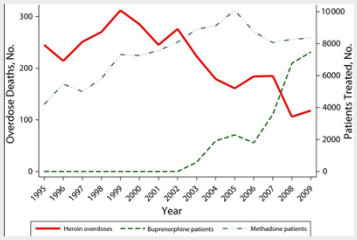
Methadone and Buprenorphine maintenance treatment reduces overdose risk by 37-86%

>350,000 in OTPs on methadone and est. >800,000 on buprenorphine

Kreek 1996, 2001, 2003, 2006, Krupitsky 2011, Fudala 2003, Weiss 2011, Woody 2008, Mattick 2009, Lee 2016+2017, CSAT

41

Access to Treatment

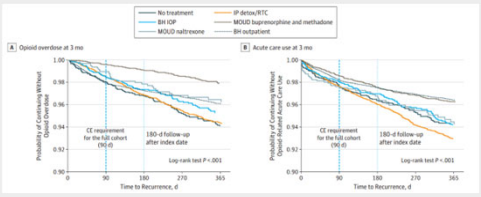


Buprenorphine treatment was associated with a 37% annual decline in heroin overdose deaths.

Schwartz RP, Am J Public Health 2013

42

Access to Treatment

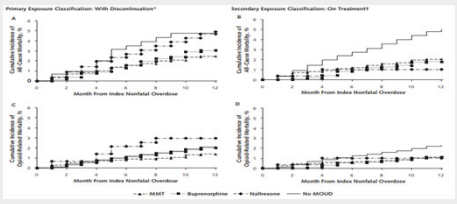


Treatment with buprenorphine or methadone was associated with reduced risk of overdose and serious opioid-related acute care use at 3 month and 12 month follow up.

Wakeman et al. JAMA 2020

43

Access to Treatment

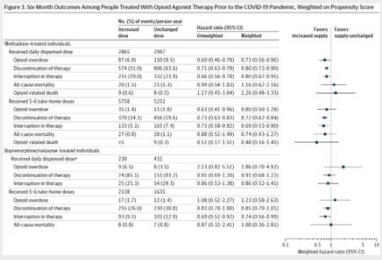


12 months after a nonfatal overdose, compared with no MOUD, both methadone and buprenorphine were associated with decreased all-cause mortality and opioid-related mortality

Larochelle et al. Annals of Internal Medicine 2018

44

COVID and OUD Treatment Outcomes



No statistically significant increases in opioid-related overdoses over 6 months

Gomes et al. JAMA 2022

45

Buprenorphine

Onset of action 30-60min
Peak effect 90-100min, half-life 24-42 hr
Metabolism via CYP 3A4 isoenzyme

- Those on CYP 3A4 inhibitors (azole, antifungals, macrolide antibiotics, and HIV protease inhibitors) should be closely monitored, and dose adjustments may need to be made
- Those on CYP 3A4 inducers (phenobarbital, carbamazepine, phenytoin, and rifampin) should also be monitored, and dose adjustments may need to be made

Can alter liver enzymes

- Liver function should be monitored periodically depending upon any recent symptoms or history of hepatitis
- Consider dose reduction or transition to mono formulation if ≥3x upper limit of normal

Pregnancy

- MOTHER study, mono (without naloxone) formulation, reduced morphine/NAS/hospitalization

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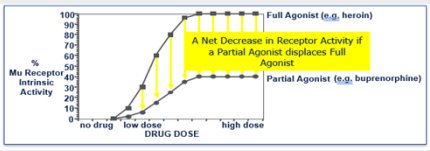
Buprenorphine

Multiple FDA Approved Formulations for OUD: SL film or tablet, monthly SQ

- Partial agonist of the μ-opioid receptor and antagonist of the κ-opioid receptor.
  - *High affinity* for μ-opioid receptor
    - Competes with other opioids and inhibits their effects
  - *Slow dissociation* from μ-opiate receptor
    - Prolonged therapeutic effect
- At low doses, acts as an agonist; in patients dependent on high doses of chronic opioids sudden initiation at high doses results in antagonist clinical effects.



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Induction

Opiate Withdrawal Symptoms

- 6-18 hrs after last use of short-acting opioids (heroin, oxycodone), or 24-48 hrs after longer-acting opioids (methadone)
- Clinical Opiate Withdrawal Scale (COWS) score of ≥8-10

Day 1: Start with buprenorphine (+/-naloxone) 2-4 mg SL

- Consider additional 2-4mg after 1-2 hrs if continued elevation of COWS and no precipitated withdrawal
- May consider additional 2-4 mg 6 hrs later if OWS persist
- FDA Approved Total Day 1 dose 8 mg, but may clinically increase dose further based on persistent OWS

Day 2: Provide total day 1 dose (routinely given as single dose)

- May increase by 4mg twice daily for ongoing symptoms (8 mg total)
- Total Day 2 dose 16 mg

Adjuvant medications:

- Clonazepam 0.5 to 1mg tid prn, Clonidine 0.1 to 0.2mg q4 prn, Trazadone 100mg qhs prn, NSAIDS, Antiemetics/GI (promethazine 25mg IM, loperamide 4mg PO, octreotide 50 mcg SQ), IVF

Low/Micro Dosing Inductions: Typically utilize 0.5mg initial dose while patient continues on full opioid agonist. Slow titration to maintenance doses over 3-7 days with d/c of full opioid agonists.

Initiated at-home with physician instructions, during hospitalizations, or ED assessments

SAMHSA Treatment Improvement Protocol 63; Salapenka et al. 2022; robbins et al. 2021; Penn Medicine https://penncamp.org/clinical/micro-dosing/

48

Buprenorphine

Generic name	Brand Name	Route	Doses
Buprenorphine	Subutex	Sublingual tablets	2 mg; 8 mg
Buprenorphine/naloxone	Suboxone	Sublingual film	2 mg/0.5 mg; 4 mg/1 mg; 8 mg/2 mg; 12 mg/3 mg
Buprenorphine/naloxone	Suboxone	Sublingual tablets	2 mg/0.5 mg; 8 mg/2 mg
Buprenorphine/naloxone	Zubsolv	Sublingual rapid-dissolve tablets	0.7 mg/0.18 mg; 1.4 mg/0.36 mg; 2.9 mg/0.71 mg; 5.7 mg/1.4 mg; 8.6 mg/2.1 mg; 11.4 mg/2.9 mg
Buprenorphine extended-release injection for subcutaneous use	Brixadi	Subcutaneous	Weekly 8 mg/0.16 mL; 16 mg/0.32 mL; 24 mg/0.48 mL; 32 mg/0.64 mL Monthly 64 mg/0.18 mL; 96 mg/0.27 mL; 128 mg/0.36 mL
Buprenorphine extended-release injection	Sublocade	Subcutaneous	Monthly 300 mg/1.5 mL monthly after induction for first 2 months 100 mg/0.5 mL maintenance dose monthly (can increase to 300 mg)

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Naltrexone

- Long-acting, competitive, non-selective opioid-antagonist with high affinity to mu-opioid receptors.
- Metabolism via CYP450
- Excretion predominately urine (53-79%), partial feces. 2% excreted unchanged
- Active metabolite 6-beta-naltrexol
- Half-life 4 hours for naltrexone and 13 hours for 6-beta-naltrexol
- High doses may be associated with hepatic toxicity, contraindicated if elev transaminases

50

Naltrexone

Antagonist of the μ-opioid receptor
- Withdrawal treatment for those with physical dependence
- POC toxicology
- Induction protocol

Oral formulation FDA approved 1984
- Once daily, 3xweek alternative
- Low adherence limits use to highly motivated populations *(Cornish 1997, Roth 1997)*

Long-acting formulation, Naltrexone-XR 380mg IM monthly, FDA approved for OUD in 2010, *Preferred Formulation*
- More effective than placebo *(Comer 2006, Krupitsky 2011, Tiihonen 2012)*
- More effective than treatment as usual in criminal justice population *(Lee 2016)*
- Lower medical/surgical related hospitalizations but not overall healthcare utilization found in those in criminal justice system as compared to TAU. *(Lee 2018)*
- Non-inferior to buprenorphine, when randomization occurred after opioid detoxification or those successfully inducted onto XR-NTX. *(Tanum 2017, Lee 2018)*
- Reported ODs in studies is low, however most did not report how overdose events were measured particularly those lost to follow-up. *(Jarvis 2018)*

➢ *Consider OD risk from interrupted antagonist treatment*

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Naltrexone - XR

Initial Readiness Assessment

- Vital signs, urine toxicology (screen for all opioids including, buprenorphine, oxycodone and methadone), recent opioid use history, pregnancy test, assess for contraindications, e.g., active pain requiring opioids

Last Opioid Use ≥14 days

- IF: Good evidence of opioid abstinence in past 2-3 weeks, no withdrawal symptoms, and opioid-negative toxicology.
- THEN: Proceed with the XR-naltrexone injection. May also consider oral naltrexone 12.5mg dose followed by injection next day.

XR-Naltrexone: A Step-by-Step Guide, Naltrexone FAQs, PCSS

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Naltrexone - XR

Last Opioid Use 7-13 days ago, evaluate for withdrawal using COWS

- If COWS >4 treat withdrawal with adjunctive medication and reevaluate in 1-2 days.
- If COWS ≤4 AND opioid-negative toxicology, perform naloxone challenge. If negative, proceed with the XR-naltrexone injection. If positive, adjunctive medication and reevaluate in 1-2 days.

Last Opioid Use <7 days

- Patient may still be physically dependent even with opioid-negative toxicology.
- Treat withdrawal with adjunctive medication and re-evaluate until at least 7 days of no opioid use (See USE within 7-13 days).
- In case of daily opioid use, recommend cessation and conduct buprenorphine-assisted withdrawal management, adjunctive medications, and reassess after 7 days of opioid abstinence. May also consider incorporation of low dose naltrexone titration to facilitate transition to XR-naltrexone.

XR-Naltrexone: A Step-by-Step Guide PCSS, Sullivan 2017

53

Naltrexone / Naltrexone Challenge Test

Naloxone (IM) Challenge Procedure

- Obtain baseline COWS, if 4 or less proceed with the challenge
- Administer naloxone 0.4 mg (1 cc) IM to deltoid and observe for 20 minutes.
- If no change in COWS administer additional 0.8 mg (2 cc) to the other deltoid and monitor for additional 20 minutes
- Test is considered positive if there is a COWS increase of 2 or more from the pre-injection score

Naltrexone (PO) Challenge Procedure

- Obtain baseline COWS; if 4 or less proceed with the challenge
- Administer naltrexone 25 mg p.o. and observe for 90 minutes
- Test is considered positive if there is a COWS increase of 2 or more

XR-Naltrexone: A Step-by-Step Guide, PCSS 2017

54

Naltrexone - XR

Buprenorphine-assisted Withdrawal Management for Naltrexone-XR Initiation

- Wait until the patient is in withdrawal (COWS > 8) and administer buprenorphine (4 mg bid on Day 1)
- Administer adjunctive medications as needed to alleviate residual withdrawal
- Continue adjunctive medication for at least 7 days after the last day of buprenorphine
- Perform naloxone/naltrexone challenge before administering XR-naltrexone

XR-Naltrexone: A Step-by-Step Guide, PCSS 2017

55

Methadone

- Approved by FDA 1972 for opioid dependence
- Mu opioid receptor agonist and NMDA antagonist (reduces development of tolerance)
- 2 enantiomers in equal amounts
  - *l (R)* active, *d (S)* inactive
  - Rapidly absorbed orally with detectable plasma levels at 30min but has a delayed onset of action with peak levels at 2-4 hours with sustained levels for 24 hours.
- Metabolized by CYP450 – several isoforms:
- CYP2D6 – may explain group who need very high doses
- Excreted in urine and feces
  - Avoids accumulation and reduces risk of toxicity for those with renal or liver dysfunction
- Half-life 24-36 hrs but may range from 4-91 hrs

56

Methadone

- 2006 Black Box Warning – risk of QTc prolongation and possibly torsades de pointes/polymorphic VT, dose dependent
- Common side effects: ***constipation, diaphoresis, to a lesser extent sexual dysfunction***
- Safety profile well established including during pregnancy
- *Beware Opioid Conversion Tables!*
- Serum Level – clinical presentation should direct dosing decisions but SML can serve as aid
  - Peak level drawn 2-4 hours after dosing
  - Trough level drawn prior to daily dosing ~24hrs
  - Peak SML less than twice trough

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Methadone

1. **Initial dose** 10-20mg PO (50% dose IM), 20mg eliminates severe withdrawal, first 24hr dose 20-30mg TDD (not routinely recommended to exceed 40mg in first 24 hours)
2. **Craving** reduced by increasing methadone dose by 5-10mg q three to seven days (80-120mg or greater)
3. **"Blocking dose"** (often 80-120mg or greater): tolerance that inhibits the euphoric high

After stabilization, methadone and buprenorphine do not produce euphoria or sedation.

ASAM 2017, 2015, SAMHSA TIP 63

58

The Basics for all OTPs

- Comprehensive Assessments
- Treatment Plans
- Toxicology Testing
- Diversion Control
- Broadening of MAT options from methadone to incorporation of buprenorphine, etc.
- Attendance schedule for medication dispensing
- Guest Medication
- Confidentiality, 42 CFR Part 2
- Regulatory Oversight

59

OUD - Fentanyl

	Buprenorphine	Naltrexone-XR	Methadone
Initiation after last opioid use	Traditional: 1-3 days LDB: same day HDB: 1-3 days	7-14 days for opioid detoxification	Same day
Induction withdrawal risk	Low-Moderate Precipitated withdrawal and post-acute withdrawal may last longer with subtherapeutic dosing	Moderate Precipitated withdrawal if given before completion of acute withdrawal treatment/detoxification Protracted withdrawal may persist 1-2 wks post-induction	Low Mild withdrawal may persist during early titration
Time to full therapeutic dose	1-3 days or longer	1-day post-administration	≥1 week, or longer
Craving Reduction	Moderate Ceiling partial agonist effect	Variable Mechanism of anti-craving effect poorly understood	High Dose-related full agonist effect

PCSS

60

Medication and Treatment Setting – Selection Considerations

- Abstinence to Harm Reduction Continuum
- Chronic Pain or foreseeable need for opioid analgesia
- Pregnant or planning pregnancy
- Recent Overdose or high risk for overdose behavior
- Medical and Psychiatric Co-occurring Disorders
- Diversion Risk
- Additional substance use disorders
- Alternatives

61

Which endogenous opiate receptor type predominantly influences the development of acute opiate withdrawal symptoms?

A. GABA B receptor
B. Kappa opiate receptor
C. Mu opiate receptor
D. Serotonin 5HT-2A receptor

62

Which of the following is the correct order from most to least relative opioid potency?

A. Carfentanil, fentanyl, diacetylmorphine, morphine
B. Fentanyl, carfentanil, diacetylmorphine, morphine
C. Diacetylmorphine, carfentanil, fentanyl, morphine
D. Morphine, diacetylmorphine, carfentanil, fentanyl

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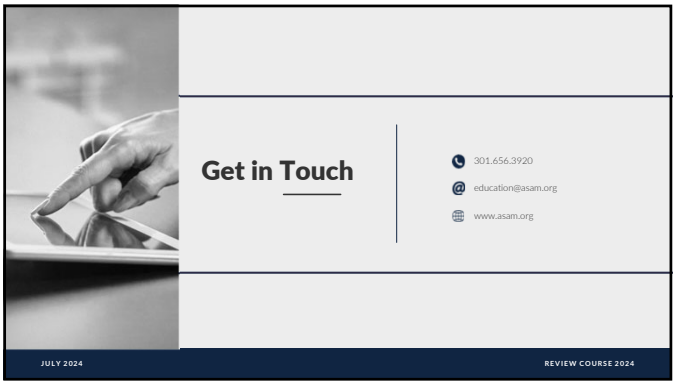
The federal 2024 HHS update to 42 CFR Part 8 authorizes all of the following at accredited Opioid Treatment Programs EXCEPT?

A. Up to 7 unsupervised take-home doses of methadone for patients recently admitted
B. Medical Directors may delegate some responsibilities to other practitioners
C. Medical exam requirement modified to facilitate treatment initiation
D. Counseling services are required for all patients obtaining care at OTPs

64



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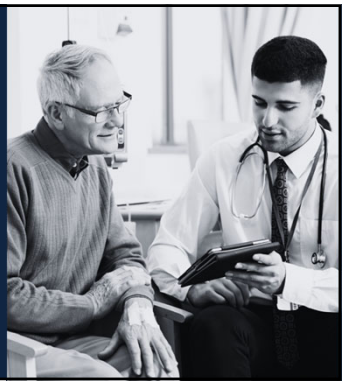
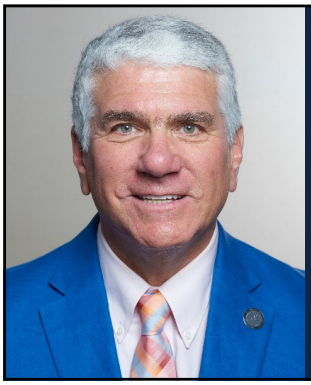
ASAM REVIEW COURSE 2024



Pain and Addiction: Trends and Treatments

Edwin A. Salsitz, MD, DFASAM
Associate Clinical Professor of Psychiatry
Mount Sinai Beth Israel
New York, NY

1



Financial Disclosure

Edwin A. Salsitz, MD, DFASAM

- No relevant disclosures

REVIEW COURSE 2024

2

JAMA. 2016;315(17):1826

3

The Epidemic of Untreated Pain

REVIEW COURSE 2024

4

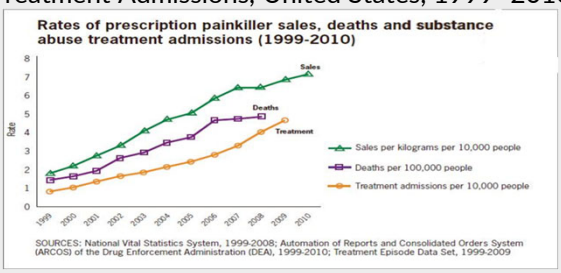
Alleviating Suffering 101
Pain Relief in the USA

- 2011 IOM Report: 116 Million Americans have pain which persists for weeks to years
- $560 - $635 Billion per year
- Some physicians overprescribe opioids, while others refuse to prescribe opioids
- Lack of education: Providers and Patients
- Headache, LBP, Neck Pain, Joint Pain, Fibromyalgia: CNCP

NEJM 366:3 Jan 19,2012

5

Rates of Opioid Overdose Deaths, Sales, and Treatment Admissions, United States, 1999–2010



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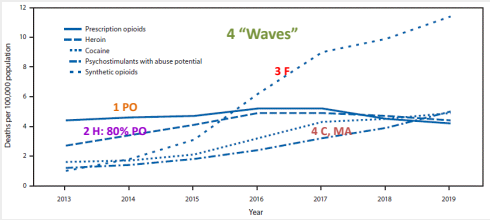
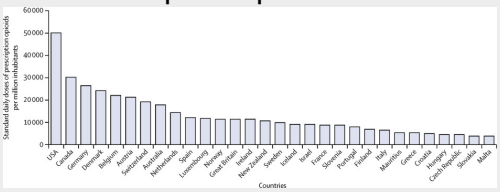
Age-Adjusted Rates of Drug Overdose Deaths Involving Prescription Opioids, Heroin, Cocaine, Psychostimulants with Abuse Potential, and Synthetic Opioids Other than Methadone— United States, 2013–2019



MMWR Morb Mortal Wkly Rep 2021;70:202–207

7

Avoiding Globalization of the Prescription Opioid Epidemic



Top 30 Opioid-Consuming Nations 2012-2014

Lancet, Vol 390, 29 July–4 August 2017, Pages 437-439, Keith Humphreys

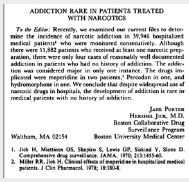
8

How Did We Get Here?

REVIEW COURSE 2024

9

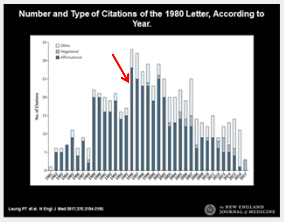
"Perfect Storm"


ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients[1] who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,[2] Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

Jane Porter
Hershel Jick, M.D.
Boston Collaborative Drug Surveillance Program
Boston University Medical Center
Waltham, MA 02154

1. Jick H, Miettinen OS, Shapiro S, Lewis GP, Siskind Y, Slone D. Comprehensive drug surveillance. JAMA. 1970; 213:1455-60.
2. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. J Clin Pharmacol. 1978; 18:180-8.



- **1980→ 2017: 608 citations** : ~75% used as evidence that addiction is rare with COT and made no mention that these were hospitalized patients with few doses of opioids.
- 11 other letters from 1980 were cited on average, 11 times.

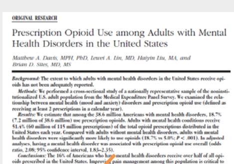
N Engl J Med 1980; 302: 123.
N Engl J Med 376;22 June 2017

10

"Perfect Storm"

- 1995: Introduction of Oxycontin
- 1995: Pain is Fifth Vital Sign
- Publications indicating low risk of addiction
- Thought Leaders with Financial/Pharma Conflicts
- Patient Satisfaction Surveys: "…staff did everything they could to help you with your pain"
- Physicians successfully sued for not treating pain
- No Evidence for long term Effectiveness COT → CNCP
- Physical Dependence vs Addiction

11


ORIGINAL RESEARCH

Prescription Opioid Use among Adults with Mental Health Disorders in the United States

Matthew A. Davis, MPH, PhD, Lewei A. Lin, MD, Haiyin Liu, MA, and Brian D. Sites, MD, MS

Background: The extent to which adults with mental health disorders in the United States receive opioids has not been adequately reported.

Methods: We performed a cross-sectional study of a nationally representative sample of the noninstitutionalized U.S. adult population from the Medical Expenditure Panel Survey. We examined the relationship between mental health (mood and anxiety) disorders and prescription opioid use (defined as receiving at least 2 prescriptions in a calendar year).

Results: We estimate that among the 38.6 million Americans with mental health disorders, 18.7% (7.2 million of 38.6 million) use prescription opioids. Adults with mental health conditions receive 51.4% (60 million of 115 million prescriptions) of the total opioid prescriptions distributed in the United States each year. Compared with adults without mental health disorders, adults with mental health disorders were significantly more likely to use opioids (18.7% vs 5.0%; $P < .001$). In adjusted analyses, having a mental health disorder was associated with prescription opioid use overall (odds ratio, 2.08; 95% confidence interval, 1.83–2.35).

Conclusions: The 16% of Americans who have mental health disorders receive over half of all opioids prescribed in the United States. Improving pain management among this population is critical to reduce national dependency on opioids. (J Am Board Fam Med 2017;30:407–417.)

Conclusions: **The 16% of Americans who have mental health disorders receive over half of all opioids prescribed in the United States.** Improving pain management among this population is critical to reduce national dependency on opioids.

Adverse Selection

J Am Board Fam Med 2017;30:407–417

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New Safety Measures Announced for Opioid Analgesics, Prescription Opioid Cough Products, and Benzodiazepines FDA: August 2016

Table 1. The Danger of Combining Opioids And Benzodiazepines

FDA Warning: Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of (opioid) and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate
- Limit dosages and durations to the minimum required
- Follow patients for signs and symptoms of respiratory depression and sedation

Source: US Food and Drug Administration website. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518697.

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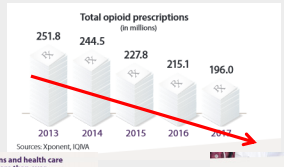
Intended/Unintended Consequences in Reaction to the Prescription Opioid Epidemic

- Prescription Drug Monitoring Programs: PDMP
- Limits on the quantity and dosage prescribed
- UDTs become standard of care
- Education of prescribers: FDA REMS course on Safe and Effective Opioid Mgt.
- CDC Guidelines
- Tamper Resistant/Abuse Deterrent Formulations
- Patients Physically Dependent on Opioids Left in the Lurch
- HEROIN: Cheaper, Readily Accessible
- FENTANYL/Fentanyl Analogues

14

Physicians' Progress to Reverse the Nation's Opioid Epidemic AMA Opioid Task Force 2018 Progress Report



As PDMPs improve, America's physicians and health care professionals are using state PDMPs more than ever.

STATE PDMPs QUERIED THAN 300.4 MILLION TIMES IN 2017

The AMA Opioid Task Force encourages all physicians to enhance their education.

In 2017, more than 549,700 PHYSICIANS

Physicians are helping to improve access to high-quality, evidence-based treatment for opioid use disorder.

15

Journal of Pain Research

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EDITORIAL

Misinterpretation of the "Overdose Crisis" Continues to Fuel Misunderstanding of the Role of Prescription Opioids

Jeffrey J Bettinger[1], William Amarquaye[2], Jeffrey Fudin[3–6], Michael E Schatman[7–9]

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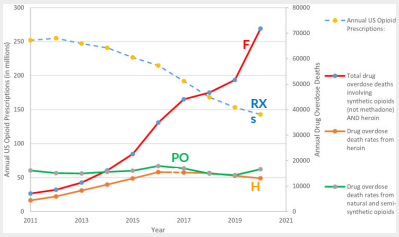
Changes in Annual Opioid Prescriptions Compared to Overdose Death Rates from Different Types of Opioids



CDC Drug Overdose: US Opioid Dispensing Rate Map [Internet]. CDC. Nov 2021

17

CDC Guidelines: 2016 vs 2022

- Similar Recommendations on Opioids as the last option for chronic pain and in many cases of acute pain. Always start with IR opioids for the shortest duration and lowest effective dose.
- Change in Tone: These are guidelines. Use Clinical Individualized Patient-Centered Judgments as to duration, dose, risk/benefit of COT to treat CNCP, and need for tapering.
- These Guidelines are not to used by health systems, pharmacies, insurance companies, medical boards, or governments to determine standard of care.

CDC Guidelines at a Glance

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Start With Non-Pharmacologic Therapy

- Physical Therapy, Exercise
- Cold, Heat
- CBT, MI
- Meditation, Mindfulness
- Acupuncture
- Biofeedback
- Massage
- Aquatic Therapy
- Spinal Cord Stimulation (SCS)

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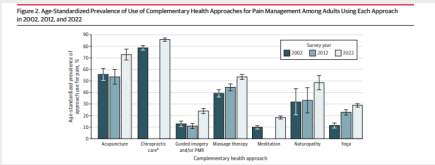
Non-Pharmacologic Therapy



JAMA February 20, 2024 Volume 331, Number 7

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Next Option: Non-Opioid Pharmacotherapy

- Acetaminophen (Efficacy), NSAIDS (Adverse Effects, Cardiac, Elderly)
- Anti-Depressants: TCAs, SSRIs, SNRIs
  - Neuropathic Pain, Nociplastic Pain (e.g., Fibromyalgia), Pain + Depression
- Anti-Convulsants: Gabapentanoids, Topiramate, Carbamazepine
  - Neuropathic Pain, Nociplastic Pain, Migraine Prophylaxis
- Topicals: Lidocaine Patch, NSAIDS, Capsaicin
- "Muscle Relaxants:" Baclofen, Cyclobenzadrine, Methocarbamol, Tizanidine
  - Avoid Benzodiazepines, Carisoprodol (Schedule IV)
- Ketamine: Acute Pain (e.g., ED)
- Interventional Procedures: Epidurals, Nerve Blocks, Neuro-Modulation

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Gabapentanoids: Conclusions

- Significant Misuse Among Patients with SUDs, Primarily OUD Receiving Methadone or Buprenorphine Maintenance.
- Significant Adverse Effects With Therapeutic Doses, and Increased Adverse Effects With Supra-Therapeutic Doses
- Must Adjust for Renal Function
- Full Recovery From Adverse Effects Is The Rule
- **Death Is Uncommon, But Increased In Combination With Opioids**
- Gabapentin Bioavailability ↓ With Increasing Dose
- Weak Evidence For Off Label Pain Treatment
- Should Gabapentin Be Listed On PDMPs (e.g., Ohio, NJ)
- Pregabalin Schedule 5 listed
- Add Gabapentanoids To UDT Screens

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Opioid Pharmacotherapy

- Acute Pain: e.g., Post-Operative, Burn, Severe Trauma
- Limit Duration: NYS- 7days
- **Sickle Cell Disease 2022 Guidelines**
- Cancer Pain
- Palliative Care, Hospice
- End of Life Care
- **Chronic Opioid Therapy (COT) for**
  - **Chronic Non-Cancer Pain (CNCP)**
    - **Effectiveness, Safety, Adverse Effects,**
    - **IR vs. ER**

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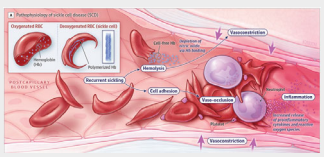
Special Mention: Sickle Cell Disease

- Severe Acute and Chronic Pain
- Reduced Life Expectancy
- Prejudice and Stigma
- Racial Disparities in Opioid Rx
- Placed in the Cancer, Palliative Care and End of Life Category in the 2022 Revised CDC Guidelines
- Increasing Evidence for Buprenorphine Efficacy as COT



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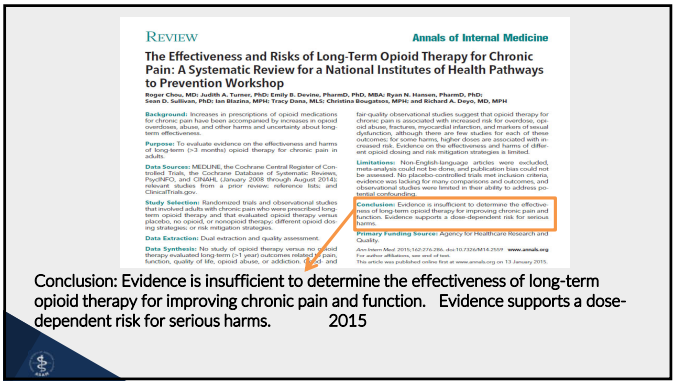

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Initiating Opioid Treatment: CNCP

- Prescribers should regard initial treatment as a therapeutic trial
  - May last from several weeks to several months; **start with IR Opioid**
  - Decision to proceed w/ long-term treatment should be intentional and based on careful consideration of outcomes during the trial
    - Progress toward meeting therapeutic goals
    - Functional Improvement
    - Presence of opioid-related adverse effects
    - Changes in underlying pain condition
    - Changes in psychiatric or medical comorbidities
    - Identification of problematic drug-related behavior, addiction, or diversion

Chou R, et al. J Pain. 2009;10:113-30.

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Can You Land the Opioid Plane?

27

Opioid Tapering/Deprescribing Strategies

- Patient Requests/Agrees vs Patient Resists
- Alternative Treatment if Pain Still Present
- Clonidine/Lofexidine Tablets and Patches
- alpha 2 centrally acting adrenergic agonists→ ↓LC→ ↓NE
- Switch to Methadone
- Switch to Buprenorphine
- Symptomatic Meds: NSAIDS, Loperamide, Benzos(short course), non-benzo sleep meds
- Patients report favorable outcomes after tapering
- Opioid Induced Hyperalgesia

JAMA Internal Medicine May 2018 Volume 178, Number 5
The Journal of Pain, Vol 18, No 11 (November), 2017

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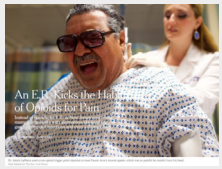
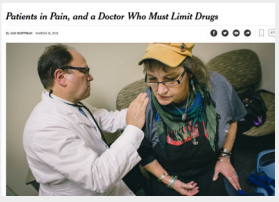




29

FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering

FDA Drug Safety Communication

Safety Announcement

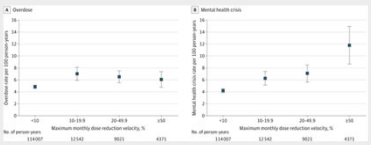
[4-9-2019] The U.S. Food and Drug Administration (FDA) has received reports of serious harm in patients who are physically dependent on opioid pain medicines suddenly having these medicines discontinued or the dose rapidly decreased. These include serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide.

The U.S. Food and Drug Administration (FDA) has received reports of serious harm in patients who are physically dependent on opioid pain medicines suddenly having these medicines discontinued or the dose rapidly decreased. **These include serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide.**

JAMA | Original Investigation

Association of Dose Tapering With Overdose or Mental Health Crisis Among Patients Prescribed Long-term Opioids

Alicia Agnoli, MD, MPH, MHS; Guibo Xing, PhD; Daniel J. Tancredi, PhD; Elizabeth Magnan, MD, PhD; Anthony Jerant, MD; Joshua J. Fenton, MD, MPH



CONCLUSIONS: Among patients prescribed stable, long-term, higher-dose opioid therapy, **tapering events were significantly associated with increased risk of overdose and mental health crisis**

JAMA. 2021;326(5):411-419

30

HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics

Oct. 2019

- The CDC Guideline for Prescribing Opioids for Chronic Pain **does not recommend opioid discontinuation when benefits of opioids outweigh risks.**
- Avoid misinterpreting cautionary dosage thresholds. Guideline recommends avoiding or carefully justifying increasing dosages **above 90 MME/day, it does not recommend abruptly reducing opioids from higher dosages.**
- **Avoid dismissing patients from care.**
- **Reinforced and Incorporated into the 2022 Guidelines**

31

Opioid Rx Disposal

- DEA Take Back Programs
- Some Pharmacies, Some Police Stations
- Mix with cat litter/coffee grounds, then seal in plastic bag and throw out in trash
- Flush down toilet: environmental issues
  - Fentanyl Patch: Flush only
- DO NOT throw out in trash in Rx bottle

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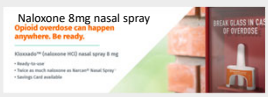
Co-Prescribe Naloxone Formulations



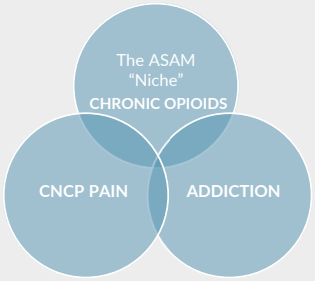


Naloxone 5mg

Nalmefene


33

Complex Intersection



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Pain and Addiction: Definitions

- "Pain is viewed as a biopsychosocial phenomenon that includes **sensory, emotional, cognitive, developmental, behavioral, spiritual and cultural components."** (IASP website)

- Addiction is a treatable, chronic medical disease involving **complex interactions among brain circuits, genetics, the environment, and an individual's life experiences.** People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences.

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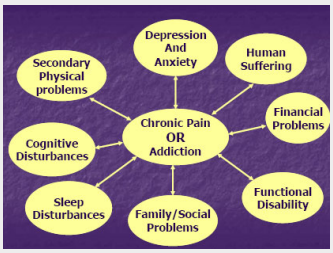
Pain and Addiction



Ann Quinlan-Colwell, PhD, PCSS-O Webinar, 2011.

36

Pain and Addiction
Limited (e.g., UDT) Objective Measurements

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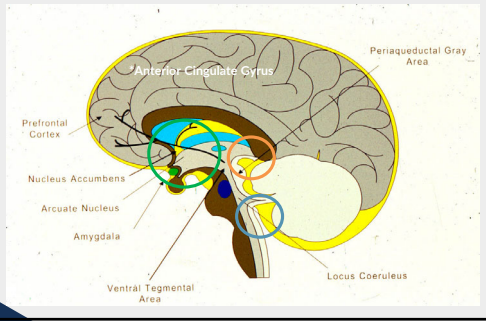
Opioid Sites of Action in the Brain



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"Exaggerated Response"
What Did It Feel Like The First Few Times?

- "All my problems disappeared."
- "Felt like I was under a warm blanket."
- "Thought this is how normal people feel."
- "Forgot about all the abuse."
- "Felt like the world was at peace."
- "Totally relaxed." "Not shy."
- "Looking at a beautiful sunset."
- "I was energized!"
- *Liking opioids: this is a vulnerability.*

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Treating Pain in the Addicted Patient

- "Pain patients with a coexisting SUD are among the most challenging patients in medicine."
- Universal Precautions
- "Real Pain" may make opioids less rewarding/euphorogenic
- Addicted Patients Have Pain: Trauma, Lower Thresholds, Medical
- Screening Tests: ORT, SOAPP, others
- Untreated Pain is a trigger for relapse:
- Address both pain and addiction: **Consider the Bupe Formulations approved for OUD**

- Significant other to secure and dispense opioid meds
- Psychiatric Co-morbidity
- Active Addiction recovery program
- UDS, pill counts, agreements, etc.
- Multidisciplinary Pain Program

Bailey, et al. Pain Medicine 2010; 11: 1803-1818

40

Buprenorphine Formulations: FDA Approved for Pain not OUD

- Buprenex® Parenteral (IV, IM)
- Butrans® Transdermal (7 Day)
- Belbuca® Buccal Film (75—900mcg q12h)

- Approved for pain but **NOT** OUDs
- Can **NOT** be used OFF LABEL for OUDs: Violates DATA 2000

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JAMA Network Open. JAMA Network Open. 2021;4(9)

Original Investigation | Substance Use and Addiction

Evaluation of Buprenorphine Rotation in Patients Receiving Long-term Opioids for Chronic Pain
A Systematic Review

Victoria D. Powell, MD; Jack M. Rosenberg, MD; Avani Yagnik, BS; Claire Garpestad, MD; Pooja Lagisetty, MD, MSc; Carol Shannon, MPH; Maria J. Silveira, MD, MA; [illegible]

CONCLUSIONS AND RELEVANCE: In this systematic review, buprenorphine was associated with reduced chronic pain intensity without precipitating opioid withdrawal in individuals with chronic pain who were receiving LTOT. Future studies are necessary to ascertain the ideal starting dose, formulation, and administration frequency of buprenorphine as well as the best approach to buprenorphine rotation.

MEANING: These findings suggest that buprenorphine rotation may be a viable option for mitigating the harms of long-term opioid therapy in individuals with chronic pain who were receiving unsafe opioid analgesic regimens; further studies are needed to examine the best way to accomplish buprenorphine rotation.

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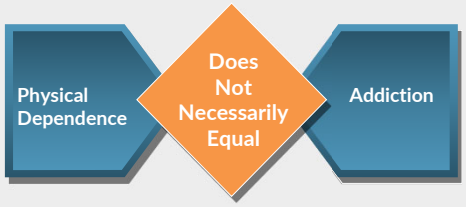
Pain and Addiction



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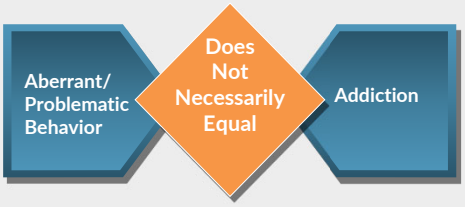
Definitions: Complex Physical Dependence

"Dependence on opioid pain treatment is not, as we once believed, easily reversible; it is a complex physical and psychological state that may require therapy similar to addiction treatment, consisting of structure, monitoring, and counseling, and possibly continued prescription of opioid agonists. Whether or not it is called addiction, **complex persistent prescription opioid dependence** is a serious consequence of long-term pain treatment that requires consideration when deciding whether to embark on long term opioid pain therapy as well as during the course of such therapy."

Opioid Dependence vs Addiction: A Distinction Without a Difference?
Ballantyne J, Sullivan M, Kolodny A, Arch Intern Med, 2012

44

Pain and Addiction



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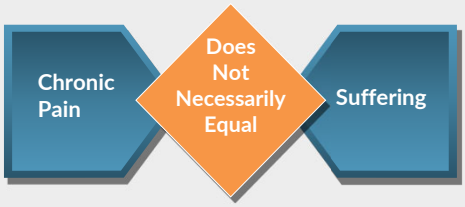
Pain and Addiction



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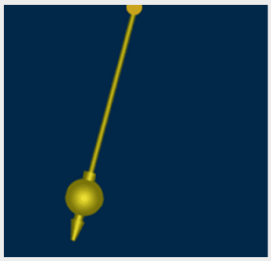
Evolution Of Opioid Prescribing

Opioid Phobia



Opioid Philia

Opioid Cautious
Multidimensional Pain Treatment

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Pain Quotes

- "To have great pain is to have certainty. To hear that another person has pain is to have doubt." "Seeing Pain," Nicola Twilley (2018)
- "Physical Pain does not simply resist language, but actively destroys it." -"The Body in Pain" by Elaine Scarry (1985)
- "Morphine is God's own medicine" Sir William Osler
- We can't live without opioids; we have to learn to live with them.

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Good luck on the exam and in your careers!

REVIEW COURSE 2024

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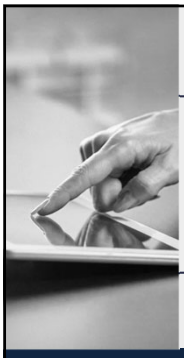

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JULY 2024

REVIEW COURSE 2024

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Sedative Use Disorder: Research and Practice

Ricardo Restrepo, MD, MPH
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Substance Abuse Treatment Program-SATP
Buprenorphine Clinic Medical Director
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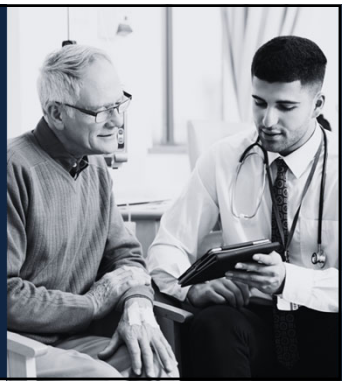

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Financial Disclosure

Ricardo Restrepo, MD, MPH

- No relevant disclosures

REVIEW COURSE 2024

2

Outline

1. Historical View
2. Neurobiology
3. Epidemiology
4. Risk and Benefits of Benzodiazepines
5. Phases of Sedative-Hypnotic Treatment and related Syndromes
6. Selective nonbenzodiazepine hypnotic agents
7. Barbiturates
8. GHB
9. Conclusions

3

Historical View

- First half of XX century Barbiturates (starting with Barbital)
- 1950 Meprobomate
- 1950s Benzodiazepine were introduced as substitute for barbiturates (starting with Chlordiazepoxide)
- 1960s Benzodiazepines widely available and prescribed
- 1970s Benzodiazepines became the most commonly prescribed of all medications around the world

4

Historical View

- 1980s Identification of medication losing efficacy over time and became associated with adverse effects
- 1990s Short acting benzodiazepines
- 2000s (drug tolerance and withdrawal) Not sufficient for dependence and nonbenzodiazepine hypnotic agents; elderly population risks
- 2014-present DSM 5 (sedative use disorder); guidelines adopted regarding use

5

Types of Sedatives

- BZ- receptor agonist (BZRA)
  - Benzodiazepines
  - Selective non-benzodiazepine hypnotics (Z-drugs)
- Barbiturates
- Others: GHB and Paraldehyde, chloral hydrate, meprobomate

6

7

Case: RR

A year later, Mr. RR, now 59-year-old Latino male with a past history of ETOH use disorder, anxiety, insomnia, and past medical history of HTN, GERD, and pancreatitis, arrives in the emergency department with a friend for confusion and diaphoresis.

8

Neurobiology (GABAA Receptor)

- GABA - the primary inhibitory neurotransmitter system in the CNS
- Transmembrane pentamer composed of:

2α , 2β

1γ

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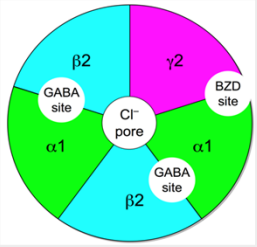
Neurobiology (GABAA Receptor)



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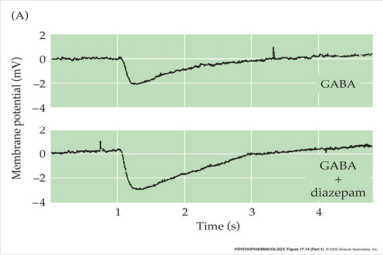
Neurobiology (GABAA Receptor)

- GABA is estimated to be present in 40% of all synapses in the human brain
- It is an inhibitory neurotransmitter, opposed to excitatory neurotransmitters such as glutamate.
- It reduces the excitability of the post synaptic side of the synapse
- 2 types : GABAA ionotropic (prominent target for drugs) and GABA B metabotropic
- BZDs increase the number of time the Cl- channel opens (frequency)
- BBTs increase the duration of the opening of the Cl-channel

11

Effects of GABA and diazepam (benzodiazepine) on membrane potentials and chloride flux



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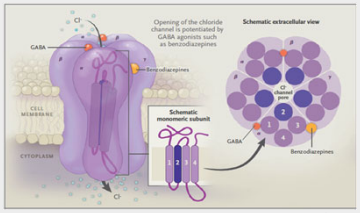
Neurobiology (GABAA Receptor)

Benzodiazepines require the presence of GABA

Barbiturates do not require the presence of GABA

Flumazenil blocks effects of benzodiazepine and zolpidem but not Barbiturates



Soyka, N Engl J Med 2017; 376:1147-1157

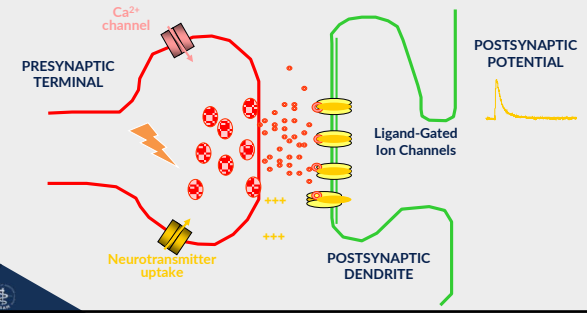
13

Neurobiology (GABAA Receptor)

- Benzodiazepines
  - Bind a cleft of α and γ subunits
  - Increase the affinity of the receptor for GABA (frequency) : Chloride channel opening
  - BZD needs GABA
- Barbiturates (propofol):
  - Bind α subunit
  - Increase duration of channel opening
  - BBT does need GABA

14

Steps in Synaptic Transmission



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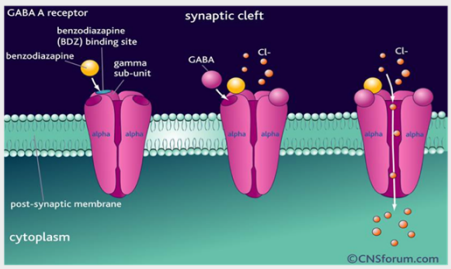
Neurobiology ($GABA_A$ Receptor)



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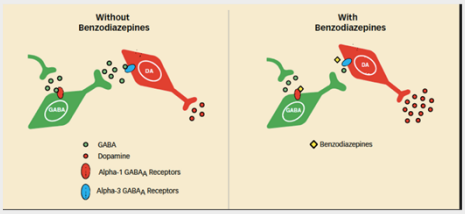
Mechanism of Benzodiazepine Addiction (hypothesis)



NIDA NOTES APRIL 19, 2012

17

Epidemiology

- 80% of pts with benzo use disorder use other drugs
- 30-50% of pts with ETOH use disorders in detox and 44% of IV drug user also use BZD
- Average benzodiazepine use is about 2 :: 1

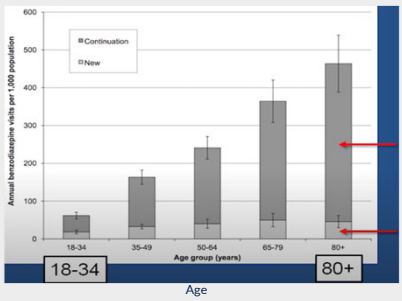
- Approximately 5.2 % of adults in U.S use benzos
- Use of benzodiazepines increases with age
- In the US, roughly 9 of 10 older adults who use benzodiazepines on a long-term basis are prescribed by PCP

18

Epidemiology

Use of Benzodiazepine accumulates with age

Annual BZD visits per 1,000 population



Continuation

New

18-34

80+

Age

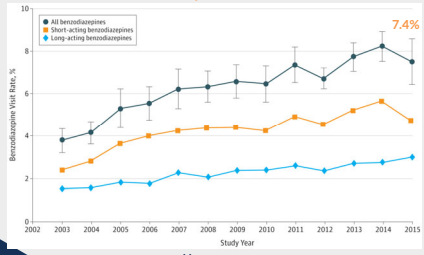
Maus et al. JAGS 2016

19

Epidemiology

Benzodiazepine Visit Rate in United States

Benzo visit Rate %



7.4%

95% increase in BZD-related visits in 12 years

Year

Agarwal SD, Landon BE. JAMA Netw Open. 2019 Jan 4:2(1)

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Concurrent use of other Substances

- Rarely the initial or primary substance of abuse
- Rarely used alone to produced intoxication
- Usually abuse with other substances
- Healthy patients prefer placebo to benzodiazepines

- *ETOH use disorder patients and their offspring are more likely to experience mood elevation with benzodiazepines*

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Concurrent use of other Substances

- A high percentage of alcohol dependent patients use benzodiazepines regularly (29-76%)
- 70-96% of patients admitted to inpatient addiction treatment on high dose benzodiazepine use have concurrent dependence on other substances
- It is uncommon to see patients with substance use disorder just on benzodiazepines. Concurrent use with other drugs is common just with benzodiazepine use
- BNZD are prescribed in 1 out of 5 patients on opioids
- ↑ Lethality when sedatives-hypnotics are combined with:
  - ETOH + BNZ
  - methadone + BNZ
  - buprenorphine + BNZ
  - Other CNS depressants + BNZ

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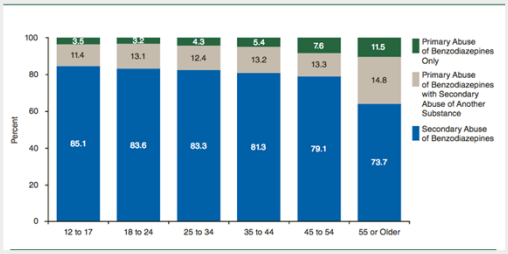
Epidemiology

Primary and Secondary Benzodiazepine Admissions, by Age in 2008



Note: Percentages may not sum to 100% due to rounding
Source: SAMHSA Treatment Episode Data Set (TEDS) 2008

23

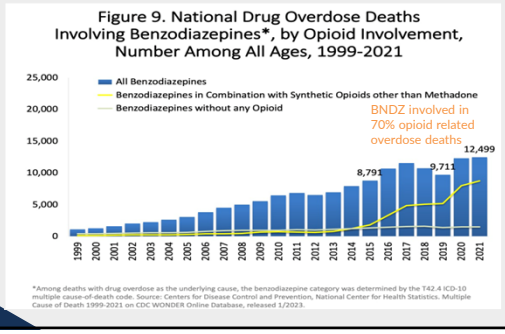
Benzodiazepines + Opioids

- Benzodiazepines (BZs) are the most frequently cited co-intoxicants involved in opioid-related morbidity and mortality.
- In 2010, the CDC reported 16,651 pharmaceutical opioid-related overdose deaths based on death certificate data- almost one of every three opioid-related deaths in 2010 also involved BZs
- On August 31, 2016, FDA issued a drug-safety communication about risks when opioid pain or cough meds are combined with BZs.

(Hwang et al., 2016; Jones, Mack & Paulozzi, 2013; DEA 2013)

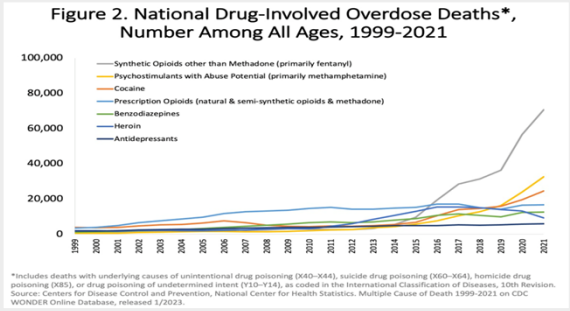
24

BZDs, by Opioid Involvement, Number among All Ages, 1999-2021



25

National Drug Overdose Involving Overdose Deaths, Number Among All ages, 1999-2021



26

ED Visits: Risk of Serious Outcomes

	12-34 yo	35-44 yo	45-64 yo	65+
BZD alone	28%	30%	37%	39%
BZD + opioids	37%	43%	47%	59%
BZD + alcohol	35%	43%	51%	55%
BZD + opioids + alcohol	39%	47%	57%	70%

SAMHSA, DAWN Report, 12/18/2014

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Epidemiology

- Most frequent abused pharmaceutical second only to opioids
- Alprazolam is the most frequently abused followed by Clonazepam, Lorazepam, and Diazepam
- BZDs are prescribed at about 65.9 million office-based doctor visits. That's a rate of 27 annual visits per 100 adults

National Health Statistics Report that examined data from the 2014-2016 National Ambulatory Medical Care Survey (NAMCS) 2020.

28

Prevalence of Benzodiazepine Use

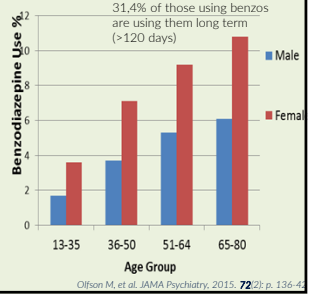
Benzodiazepines:

- Use is nearly twice as prevalent in women
- Increased utilization with increasing age
- Proportion of long-term use increases with age
- Prescribed at greater rates than antidepressants for the treatment of depression and anxiety

*Bernardy NC, et al. J Gen Intern Med, 2013. 28(S2): p S542-8; Demyttenaere, K., et al., J Affect Disord, 2008. **110**(1-2): p. 84-93.; Benitez, C.I., et al., Am J Geriatr Psychiatry, 2008. **16**(1): p. 5-13.; Maudsley Prescribing Guidelines in Psychiatry 12th Edition. 2015*

Figure 1. Prevalence of benzodiazepine use in the United States

In the oldest group (65-80)- 31,4% of those using benzos are using them long term (>120 days)



*Olfson M, et al. JAMA Psychiatry, 2015. **72**(2): p. 136-42*

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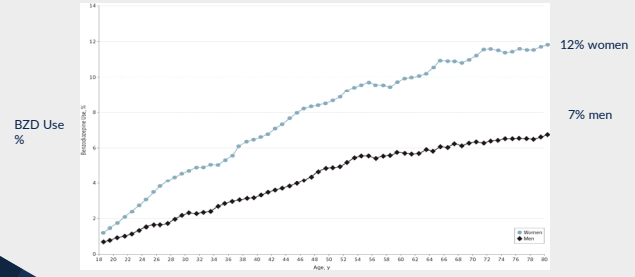
Epidemiology

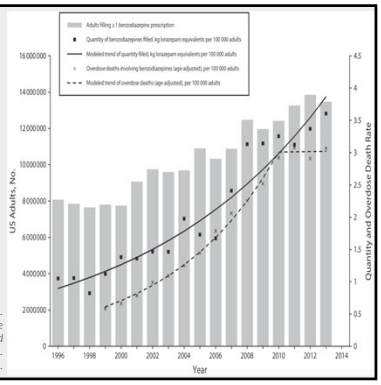


Olfson M, et al. JAMA Psychiatry 2015;72(2):136-142.

30

Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996–2013

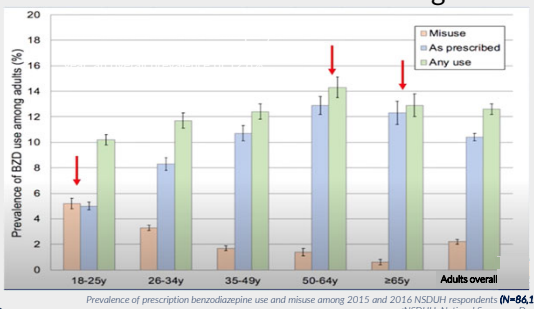
- Between 1996 and 2013, the number of adults who filled a benzodiazepine prescription increased by 67 percent, from 8.1 million to 13.5 million.



Olfson M. JAMA Psychiatry, 2015. 72(2): p. 136-42. Bachhuber MA et al Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996-2013. Am J Public Health. 2016;106(4):686–688.

31

BZD use accumulates with age



Prevalence of prescription benzodiazepine use and misuse among 2015 and 2016 NSDUH respondents (N=86,186), by age group. aNSDUH, National Survey on Drug Use and Health

Maust DT, Lin LA, Blow FC. Benzodiazepine Use and Misuse Among Adults in the United States. Psychiatr Serv. 2019;70(2):97-106. doi:10.1176/appi.ps.201800321

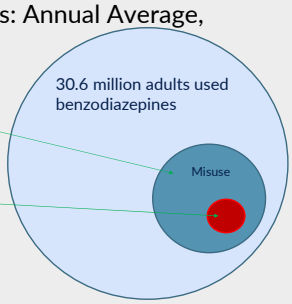
32

Benzodiazepine Use, Misuse, and Use Disorder Among Adults in the United States: Annual Average, 2015-2016

5.3 million adults misused benzodiazepines

0.5 million adults had benzodiazepine use disorders:

- 0.3 million had benzodiazepine dependence
- 0.2 million had benzodiazepine abuse



Maust DT et al, Benzodiazepine Use and Misuse Among Adults in the United States. Psychiatr Serv. 2019 Feb 1;70(2):97-106

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Case: RR

- Mr. RR did not receive his alprazolam refill from his PCP because, after taper, patient returned to his original dose and ran out of the prescription sooner. Mr. RR is upset and decided to see a psychiatrist who had planned to prescribe medication if ROI to contact PCP is signed.

34

Case: RR

- Mr. RR reports that his heart has been racing and his insomnia has worsened; his friend states that, for the past four days, he has been having difficulty following conversations and focusing on daily tasks. He has been off alprazolam for seven days. Mr. RR denies any recent psychosocial stressors and does not endorse feelings of guilt, helplessness, or hopelessness. Furthermore, he denies any fever, nausea, vomiting, diarrhea, myalgia, abdominal cramps, or seizures. He denies any recent alcohol or illicit drug use.

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Factors associated with prescribing benzos

- Anxiety
- Insomnia
- Pain
- Chronic Medical Condition
- Female
- White
- Retirement Low income
- Elderly
- Smoking
- Poor Health
- >1 Prescriber
- Computer prescribing

Agarwal SD, Landon BE. JAMA Netw Open. 2019 Jan 4;2(1)

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Benzodiazepines and Addiction

Benzodiazepines are often not the primary substance abused and, when combined with other substances (e.g. alcohol, opioids), can have fatal consequences

- 5-10% - Patients newly started on benzodiazepines develop a substance use disorder
- 50% - Patients with substance use disorder history will develop a benzodiazepine use disorder
- 58-100% - Patients prescribed chronic benzodiazepines become physically dependent

Guina, J., et al., J Psychiatr Pract, 2015. 21(4): p. 281-303.; Substance Abuse: A Comprehensive Textbook (4th ed.). Baltimore, MD: Lippincott. Williams & Wilkins. 2004. pp. 302-312.; Substance Abuse and Mental Health Services Administration. The TEDS Report: Substance Abuse Treatment Admissions for Abuse of Benzodiazepines. . Rockville, MD., June 2, 2011.

37

Benefits and Risks

- Population
  - Therapeutic dose dependent
  - Prescribed high-dose dependent (sedative use disorder)
  - Recreational benzodiazepine use
- Risk factors for benzo use disorder:
  - Longer duration of BNZ use
  - Higher Benzodiazepine doses
  - Lower level of education
  - Greater insomnia severity
  - Current antidepressant use

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Benefits and Risks

ACTION		CLINICAL USE
Anxiolytic	Relief of anxiety	Anxiety and panic disorders, phobias
		Agitated Psychosis
Hypnotic	Promotion of sleep	Insomnia
Myorelaxant	Muscle relaxation	Muscle spasms, spastic disorders
Anticonvulsant	Stop fits, convulsions	Fits to drug poisoning, some form of epilepsy, alcohol withdrawal
Amnesia	Impairment of short-term memory	Premedication for operations, sedation for minor surgical operations

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Benefits and Risks
–prior prescribing benzodiazepines-

TOLERANCE and DOSE ESCALATION = WITHDRAWAL

- Examine the risk-benefit ratio
- Avoid nonbenzodiazepine hypnotic
- Short term use (4 weeks)

Royal College of Psychiatrists and The British Association for Psychopharmacology 2013

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Benefits and Risks (concerns)

- Long term use have shown deficits in: learning, memory, attention and visual spatial ability
- Anterograde Amnesia
- Adverse effects:
  - May contribute to psychomotor impairment and increase the risk of falls and automobile accidents
  - Psychomotor impairment is characterized by:
    - Slow reaction time
    - Diminish speed and accuracy for motor tasks
- Increase risk of hip fractures (50% increase risk) and recurrent falls in the elderly population
- OD with Benzodiazepine alone are almost never lethal (high therapeutic index) but OD with BBT alone can be
- Withdrawal symptoms prolong sedative overuse

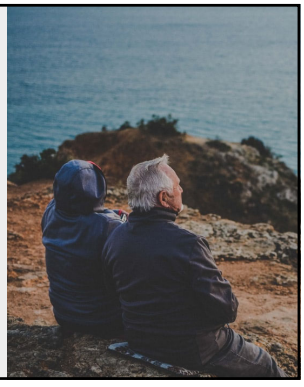
Falls | Hip Fractures | Sedation | Cognitive impairment

Cumming et al. Benzodiazepines and Risk of Hip Fractures in Older People. CNS Drugs17,2003

41

Benefits and Risks (concerns)

- The 2015 American Geriatrics Society Beers Criteria recommend avoiding benzodiazepines in this population. Despite these consensus recommendations and known risk factors:
  - Benzodiazepine use is three times more prevalent in older adults compared to younger adults
  - Roughly one-quarter of long-term benzodiazepine use is in patients ≥65 years of age



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Considerations when prescribing BZs

- Examine the risk-benefit ratio
- Avoid nonbenzodiazepine hypnotic (Alternative)
- Inform patient of planned duration of therapy
- Prescribe for brief periods
- No refills without follow up
- Use random urine toxicology
- Attempt to taper dose
- Always check the Prescription Drug Monitoring Program (PDMP) before and during the treatment
- Formalize written treatment agreement

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Phases of Sedative-Hypnotic Treatment and Related Syndromes

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Equivalent Doses and Elimination half-lives of benzodiazepines

BENZODIAZEPINES	APPROXIMATELY EQUIVALENT DOSAGE (mg)	ELIMINATION HALF-LIFE (hrs)- (active metabolite)
Alprazolam *	0.5	6-12
Chlordiazepoxide	25	5-30 (36-200)
Clonazepam*	0.5	18-50
Diazepam	10	20-100 (36-200)
Flunitrazepam	1	18-26 (36-200)
Flurazepam	15-30	(40-250)
Lorazepam*	1	10-20
Oxazepam	20	4-15
Temazepam	20	8-22
Triazolam*	0.5	2

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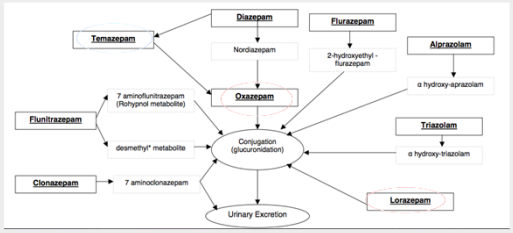
Benzodiazepine Metabolism



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Types of Benzodiazepines

- 2-Keto benzodiazepines (Clonazepam, Diazepam, Chlordiazepoxide)
  - All have long half-lives (23-100 hours)
  - All have active metabolites (commonly desmethyldiazepam)
  - Some administered as Prodrug
- 3-Hydroxy Benzodiazepines (Oxazepam, Temazepam, Lorazepam)
  - Intermediate half-lives (most 10-15 hours)
  - No active metabolites (better in elderly/hepatic impaired)
  - Metabolized outside the liver (only need glucoronidation)
- Triazolo Benzodiazepines (Alprazolam, Triazolam)
  - Short to Intermediate half lives (anywhere from <12 hours)
  - Some have active metabolites

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Pharmacokinetics

BZDs are differentiated by their pharmacokinetic profiles, based on lipophilicity and metabolism:

- **Half-life** (short, intermediate, long)
- **Onset-of-action** (rapid, intermediate, slow)
- **Metabolic pathways** (with or without active metabolites, with or without P450 involvement)
- Pharmacokinetics are affected by:
  - Routes of administration
  - Rates of absorption
  - Rates of elimination

Clinical Pharmacology 2017

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Pharmacokinetics

LONG ACTING	MEDIUM ACTING	SHORT ACTING
• Chlordiazepoxide	• Lorazepam	• Alprazolam
• Diazepam	• Oxazepam	• Triazolam
• Clonazepam	• Temazepam	• Midazolam

49

Case: RR

PE: He was found to be tachycardic (pulse, 110 beats/min) and hypertensive (blood pressure, 170/90 mm Hg). His medical workup, including CBC count, electrolyte panel, liver function tests, blood glucose level, and urine toxicology screen were within normal limits.

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Case: RR

MSE: Casually dressed male who appeared to be restless and irritable with twitches in his face and complains about tinnitus. He was oriented to time, place, and person. His speech was normal in rate and content. His mood was subjectively anxious and objectively dysphoric, and his affect was congruent with mood. His thought form was linear and goal directed. There was no evidence of paranoid ideations/delusions. He denied any auditory or visual hallucinations. He scored 30/30 on the Mini-Mental State Examination. He had good insight and judgment. He endorsed passive suicidal ideations, no plan. He denied any homicidal ideations

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Management of Benzodiazepine Withdrawal

Variable presentation:

- There are no pathognomonic signs and symptoms of benzodiazepine withdrawal
- Assess for subjective and objective symptoms
- May have few concurrently observable hyper-adrenergic signs or vital sign fluctuations (unlike acute alcohol withdrawal)

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Symptoms of anxiety state	Symptoms less common in anxiety states-relatively specific to benzodiazepine withdrawal
Anxiety, panic attacks, agoraphobia	Perceptual distortions, sense of movement
Insomnia, nightmares	Depersonalization, derealization
Depression, dysphoria	Hallucinations (visual, auditory)
Excitability, restlessness	Distortion of body image
Poor memory and concentration	Tingling, numbness, altered sensation
Dizziness, light headedness	Formication (skin "crawling")
Weakness "jelly legs"	Sensory hypersensitivity (light, sound, taste, smell)
Tremor	Muscle twitches, jerks, fasciculation
Muscle pain, stiffness	Tinnitus
Sweating, night sweats	Psychotic Symptoms
Palpitations	Confusion, delirium
Blurred or double vision	Convulsions

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Management of Benzodiazepine Taper

Challenging process for both patients and doctors if you do not have a treatment plan

Strategies:

- Gradual dosage tapering (avoid prn dosing)
- Psychological Support
- Reasons for prescribing
- Lifestyle
- Personality

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Management of Benzodiazepine Taper

- Take into account dosage and type of benzodiazepine
- Environment stresses
- Amount of available support
- Prepare for months or a year for the taper
- Individualize treatment adjusted to patient's needs (personalized treatment)

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Management of Benzodiazepine Withdrawal /Taper

Time course and severity are influenced by:

- Duration of use: short vs. long term use
- Dose: low/therapeutic dose vs. high dose
- Pharmacokinetics: short vs. long acting
- Host factors: comorbid pathology or substance use disorder

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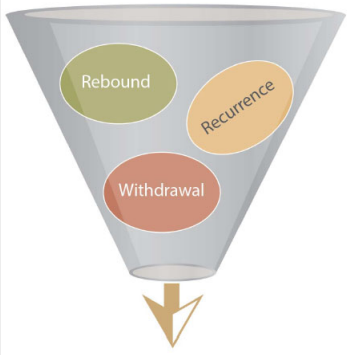
What is the difference between withdrawal, rebound and recurrence?

- Recurrence: the person experiences the same symptoms and severity of symptoms that existed prior to treatment
- Rebound: occurs when a drug is withdrawn and the individual experiences anxiety symptoms that are more severe than those experience prior treatment
- Withdrawal: the time-limited development of unique symptoms as the result of discontinuing or decreasing the use of a psychoactive drug



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Management of Benzodiazepine Withdrawal

Time and Severity can vary

- Short Acting BZs and those with active metabolites when stopped, can lead to WD sx within hours
- Long Acting BZs with active metabolites can take 48 hours – 7 days for WD sx to emerge
- Severe WD from BZs can be accompanied by delirium

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Management of Benzodiazepine Withdrawal

Duration of use and therapeutic dose:

- >10 days use with therapeutic dose: some experience transient insomnia
- <2 weeks with therapeutic dose: Most experience rebound
- >2 months with therapeutic dose: Most experience mild withdrawal

Of patients who take a benzodiazepine for more than a month, 47% (n=1048) become dependent

De Las Cuevas et al 2003

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Management of Benzodiazepine Withdrawal

Duration of use and therapeutic dose:

- >4 to 6 months with therapeutic dose;
- Most experience mild to moderate withdrawal
- >12 months with therapeutic dose:
- 20-80% experience moderate to severe withdrawal

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Management of Benzodiazepine Withdrawal: When to Taper

- Over-sedation
- Cognitive impairment
- Concurrent Rxs or use of high-risk CNS depressants medications
  - Other BZs, non-BZ hypnotics, and OPIOIDS
- Alcohol use disorder and other SUDs
- Overuse, misuse, or BZ use disorder
- Patient request
- Other

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MANAGEMENT/Systematic discontinuation

- Tapering
- Substitution and tapering

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MANAGEMENT/Systematic discontinuation

- Rate for dosage varies for different types of benzodiazepine pts:
- Withdrawal shows in 1- 7 days depending on half lives
- One-eight to one-tenth of the daily dose (10-25% weekly)
- Taper between 4 weeks to 6 months or even more

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Management of Benzodiazepine Withdrawal

Pharmacological /Strategies Treatment of Withdrawal

- Taper over months:
- Convert to longer acting agent like Clonazepam, Chlordiazepoxide, Diazepam)
- Taper gradually while starting alternative therapies if needed (months)
- Rebound psych meds for anxiety/sleep (Trazadone, Mirtazapine, Buspirone)
- Use of Anticonvulsant carbamazepine or valproate

Ashton H. The diagnosis and management of benzodiazepine dependence. Curr Opin Psychiatry. 2005; 18:249-255.

64

When do you see withdrawal symptoms?

- Short-acting BZD: oxazepam, triazolam, temazepam, alprazolam
- Short acting sedative-hypnotics: pentobarbital, secobarbital, meprobamate, metaqualone
  - Withdrawal onset in 12-24 hrs with
  - Peak of withdrawal intensity-day 1 to 5
  - Duration of acute withdrawal- 7 to 21 day

65

When do you see withdrawal symptoms?

- Long-acting BZD and sedative-hypnotics: diazepam, chlordiazepoxide, phenobarbital
  - Withdrawal Onset within 5 - 14 days of cessation
  - Peak of Withdrawal Intensity - Days 1 to 9
  - Duration of Acute Withdrawal - 10-28 days
    - Protracted withdrawal symptoms for months

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Phenobarbital Substitution and Taper

- Substitution of benzodiazepine with equipotent dose of phenobarbital
- For inpatient, medically monitored setting only
- Effective Strategy for:
  - High dose dependent
  - Poly-Substance Dependence
  - Concurrent Alcohol/other Sedative Hypnotic
  - Unknown or erratic polypharmacy drug use

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Phenobarbital Substitution and Taper

- Establish Stabilization Dose by Computing Phenobarbital equivalents
  - Alprazolam 1 mg=PB 30 mg
  - Clonazepam 2mg=PB 30 mg
  - Diazepam 10 mg=PB 30 mg
  - Lorazepam 2 mg=PB 30 mg
  - Carisoprodol 700 mg=PB 30 mg
- PB should be give TID or QID
- Maximum PB starting dose 500mg/day

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Phenobarbital Substitution and Taper

- Monitor patient for signs of toxicity before administering each dose
- Signs of PB toxicity are easy to observe:
  - Sustained horizontal nystagmus
  - Ataxia
  - Slurred Speech
- If intoxication observed:
  - If 1 sign of toxicity observed, skip one dose
  - If 2 signs of toxicity observed, skip 2 doses
  - Recalculate new daily dose

69

Phenobarbital Substitution and Taper

- Once stabilization dose is established: maintain patient on initial dose for two days
- If patient has neither signs of withdrawal or toxicity, then patient is moved to the withdrawal phase
- Decrease phenobarbital 30 mg/day unless signs of toxicity or withdrawal are seen
- If patient develops objective signs of withdrawal. Daily dose is adjusted upward by 50% and patient is stabilized before continuing withdrawal

70

Pregnancy

- Pregnant and lactating women are relatively contraindicated due to:
  - Ability of benzodiazepines to cross fetal placental barrier and to pass into breast milk
  - Teratogenic effects
  - Floppy baby syndrome
  - Neonatal withdrawal

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Flumazenil

- Reverse the sedation produced by a benzodiazepine (Acute O.D with benzodiazepine)
- Nonspecific competitive antagonist of benzodiazepine receptor
- May up regulate BZ receptors
- IV use 1 mg monitor pt every 30-60 minutes
- Adverse effects: seizures, cardiac arrhythmias and acute precipitated withdrawal

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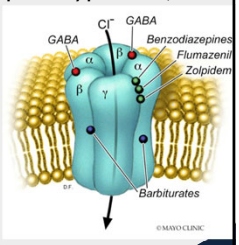
Z-Drugs (Selective nonbenzodiazepine hypnotics)

- Zaleplon
- Zolpidem
- Eszoplicone
- Zoplicone*
- Lower the risk for residual daytime drowsiness due to shorter duration of action
- Short term use
- Bind to sub-types of GABA A receptors – α1 subunit that specifically modulate sleep and therefore are thought to have less unwanted side effects
- SE: risk of increased sleep- related behaviors
- Apply the general principles prescribing benzodiazepines to the Z-drugs



73

Barbiturates

- The oldest sedative hypnotics
- Classified in three different pharmacokinetics category
- In the past used for treatment of anxiety disorders
- BBT: low therapeutic index
- Replaced by benzodiazepines
- BBT induce the synthesis of hepatic cytochrome P450, thus alter their own metabolism and the metabolism of other meds

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Barbiturates

Duration of Action	LS	Onset	Duration	Use
Ultrashort	H	10-20 s	20-30 min	IV anesthesia
Thiopental				
Methohexital				
Short/Intermediate	M	20-40 min	5-8 h	Surgical anesthesia and sleep induction
Amobarbital				
Secobarbital				
Pentobarbital				
Long	L	Over 1 h	10-12 h	Prolong sedation and seizure control
Phenorbarbital				
Meprobarbital				

75

GHB
Gamma-Hydroxy-Butyrate

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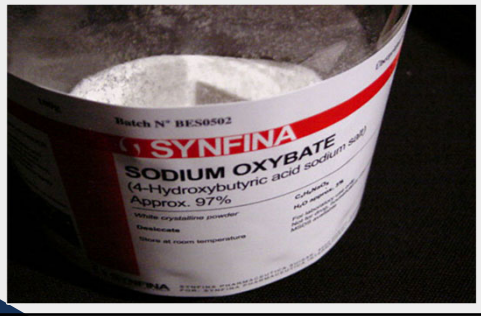
"When I wake up,
I feel completely refreshed.
In comparison to the other drugs that
are supposed to be 'clean,'
G really is clean."

77

FDA approved: Narcolepsy with cataplexy



78

Effects

- Sensual drug, like MDMA, but also resulting in "the greatest sex ever."
- Relaxation, tranquility, placidity, mild euphoria, disinhibition.
- Temporary amnesia (hence "the date rape drug").
- Has been used as a muscle developer and fat burner

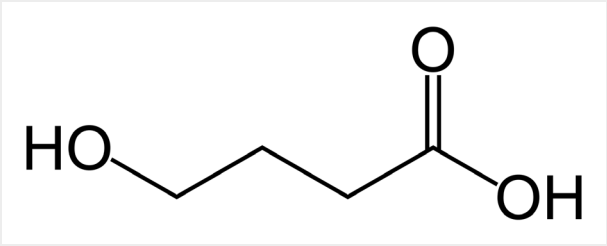
79

Neurobiology

- GHB is a neurotransmitter.
- Short half life (30 minutes)
- It is both a precursor and a metabolite of GABA.
- Activity on both the GABAB and the GHB binding sites, results in:
  - Temporary suppression of dopamine,
  - Subsequent marked release of dopamine, and
  - Increased release of endogenous opioids.
- Also it is a highly regulated Schedule III medication for narcolepsy (Xyrem).

80

The Molecular Structure



81

Intoxication

- Steep dose-response curve:
  - Ataxia, loss of coordination.
  - Respiratory depression, bradycardia, hypotension
  - Coma, persistent vegetative states, death
  - Overdose is a real danger (LD50 is only 5 times the recreational dose).
  - Synergistic effect with alcohol/other sedatives.
- Treat as a medical emergency:
  - ABCs, consider Intensive Care Unit admission.
  - Atropine for bradycardia.

82

Withdrawal

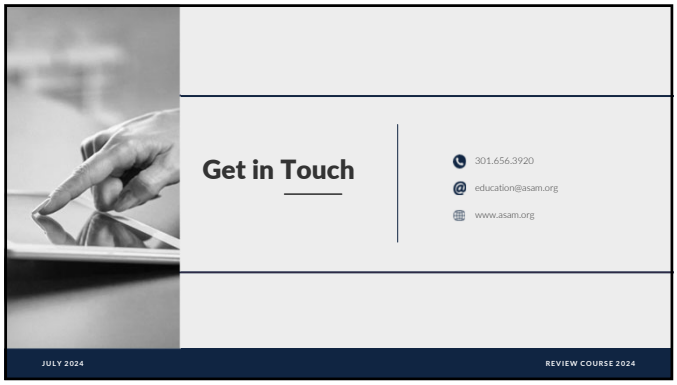
- Withdrawal is rare but severe.
- Mild withdrawal may persist for several weeks after cessation of use:
  - Anxiety, tremor, insomnia.
  - "Feelings of doom."
- Severe withdrawal resembles barbiturate withdrawal:
  - Treat with benzodiazepines.

83

Long Term Features

- Physiological dependence.
- Most patients who overdose on GHB recover completely.
- No FDA approved medications.
- MET and CBT are the major treatment modalities.

84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JULY 2024
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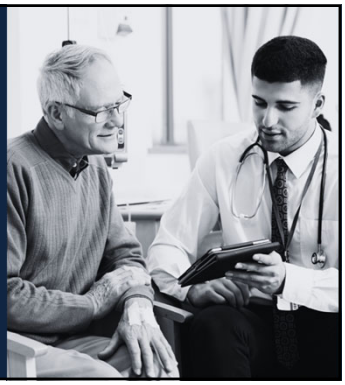
Stimulant Use Disorders: From Neurobiology to Public Health

Michael H. Baumann, PhD
Designer Drug Research Unit (DDRU),
Intramural Research Program, NIDA, NIH
Baltimore, MD



1

Financial Disclosure

Michael Baumann, PhD

- No relevant disclosures

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2

General Outline

- Cocaine
- Methamphetamine
- Ecstasy
- Bath Salts and RCs
- Summary

3

Topics Covered for Each Substance

- Drug Trafficking and Epidemiology of Use
- Formulations and Methods of Use
- Pharmacokinetics and Metabolism
- Desired and Adverse Effects
- Chronic and Withdrawal Effects
- Neurobiology
- Treatments

4

Cocaine

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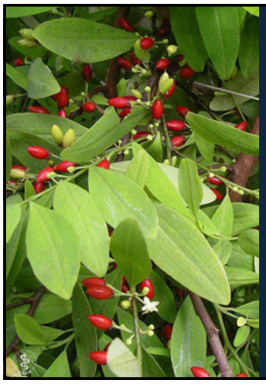
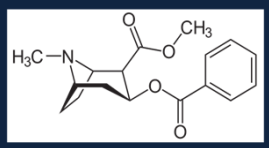
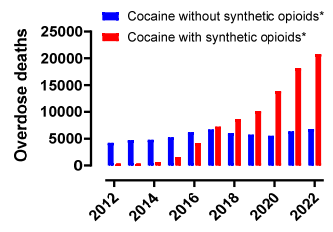


Cocaine is a Plant Based Alkaloid



6

Cocaine Overdose Deaths Are Increasing



*synthetic opioids other than methadone

CDC Wonder, 2024

7

Formulations and Methods of Use

- Cocaine Free Base (i.e., Crack)
  - Smoking of free base "rock" using pipes
- Cocaine HCl
  - Intravenous injection of solutions using needle and syringe
  - Intranasal snorting of powder

8

Pharmacokinetics and Metabolism

- Pharmacokinetics
  - Smoked drug reaches brain within seconds
  - Intravenous drug reaches brain within seconds
  - Intranasal drug reaches brain within minutes
- Metabolism
  - Ester hydrolysis to benzoylecgonine
  - Ecgonine methyl ester

Cone, 1995

9

Rate Hypothesis of Drug Reward

- Smoked and Intravenous Routes
  - Faster rate, and greater amount, of drug entry into the brain
  - Enhanced subjective and rewarding effects
- Intranasal and Oral Routes
  - Slower rate, and lesser amount, of drug entry into the brain
  - Reduced subjective and rewarding effects

10

Desired Effects

- Enhanced Mood and Euphoria
- Increased Attention and Alertness
- Decreased Need for Sleep
- Appetite Suppression
- Sexual Arousal

11

Adverse Effects

- Psychosis
- Tachycardia, Arrhythmias, Heart Attack
- Hypertension, Stroke
- Hyperthermia, Rhabdomyolysis
- Multisystem Organ Failure

12

Tolerance- Blunted Effects

- Acute Tachyphylaxis or "First Dose" Effect
  - Cardiovascular effects blunted within a dosing binge
  - Euphoria and sexual arousal diminished
- No longer-term tolerance

13

Sensitization- Enhanced Effects

- Seizures
- Psychosis
  - Paranoid delusions
  - Visual and auditory hallucinations
  - Indistinguishable from schizophrenia
- Stereotypical Behaviors
  - Compulsive skin picking or scratching
  - Involuntary movements

14

Withdrawal Effects

- Anhedonia and Depressed Mood
- Increased Appetite
- Anergia and Fatigue
- Vivid or Unpleasant Dreams
- Insomnia or Hypersomnia

15

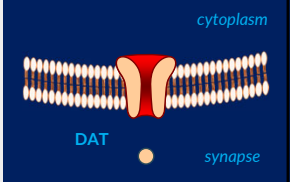
Molecular Sites of Action

- SLC6 Monoamine Transporters
  - Dopamine transporter (DAT)
  - Norepinephrine transporter (NET)
  - 5-HT transporter (SERT)
- Other sites
  - Sodium channels

16

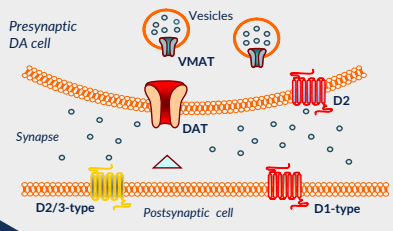
DATs Mediate DA Uptake

- DATs are membrane proteins responsible for uptake of released dopamine (DA)
- Drugs that disrupt DAT function increase extracellular (EC) DA
- Increases in EC DA are rewarding



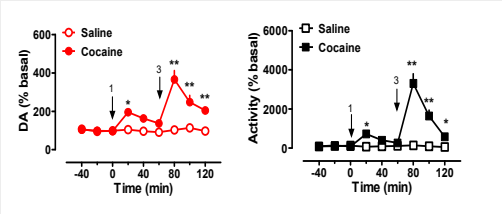
17

Cocaine is a DAT Blocker (DA Uptake Inhibitor)



18

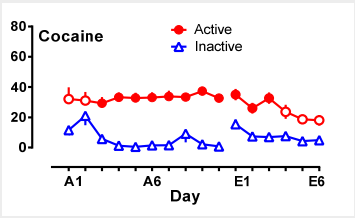
Cocaine Increases EC DA in Rat Brain



Baumann et al., 1994

19

Rats Learn to Self-Administer Cocaine



Schindler et al., 2016

20

Treatment for Cocaine Use Disorder (CUD)

- Pharmacotherapy
  - No FDA-approved medication for CUD
- Psychosocial Therapies
  - Contingency Management
  - Cognitive Behavioral Therapy
  - Group & Community Therapies

21

Experimental Pharmacotherapies for CUD

- Single agonist medications
  - Some positive results with stimulant medications, like mixed amphetamine salts (MAS) (*Tardelli et al., 2020*)
- Medication combinations
  - MAS + topiramate (*Levin et al., 2020*)

22

Methamphetamine

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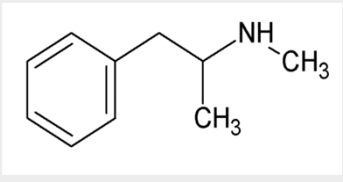
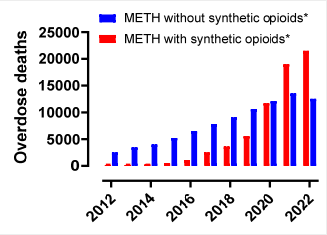
Methamphetamine (METH) is a Synthetic Amphetamine Derivative



24

METH Overdose Deaths are Increasing



*synthetic opioids other than methadone

CDC Wonder, 2023

25

Formulations and Methods of Use

- Methamphetamine (i.e., Ice or Crystal)
  - Smoking using pipes
- Methamphetamine HCl
  - Intravenous injection of solutions using needle and syringe
  - Intranasal snorting of crystals

26

Pharmacokinetics and Metabolism

- Pharmacokinetics
  - Smoked drug reaches brain within seconds
  - Intravenous drug reaches brain within seconds
  - Intranasal drug reaches brain within minutes
- Metabolism
  - *N*-demethylation to form amphetamine (bioactive)
  - Hydroxylation to form inactive metabolites

27

Desired Effects

- Enhanced Mood and Euphoria
- Increased Attention and Alertness
- Decreased Need for Sleep
- Appetite Suppression
- Sexual Arousal

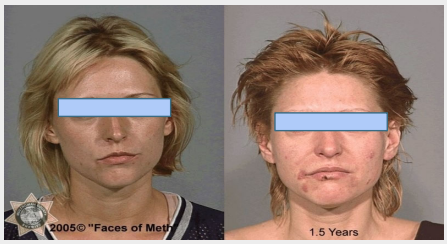
28

Adverse Effects

- Agitation, Psychosis
- Arrhythmias, Palpitations, Heart Attack
- Hypertension, Stroke
- Hyperthermia, Rhabdomyolysis
- Multisystem Organ Failure

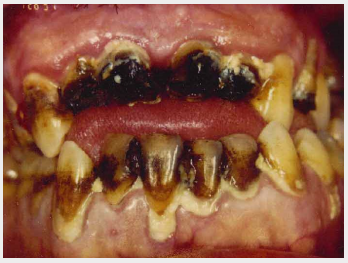
29

METH causes adverse health consequences



30

Chronic METH causes dental problems



31

Sensitization- Enhanced Effects

- Seizures
- Psychosis
  - Paranoid delusions
  - Visual and auditory hallucinations
  - Indistinguishable from schizophrenia
- Stereotypical Behaviors
  - Compulsive skin picking or scratching
  - Involuntary movements

32

Withdrawal Effects

- Anhedonia and Depressed Mood
- Increased Appetite
- Anergia and Fatigue
- Vivid or Unpleasant Dreams
- Insomnia or Hypersomnia

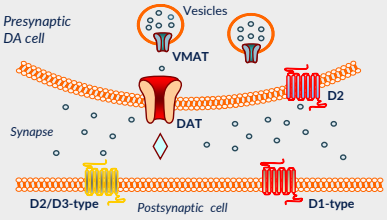
33

Molecular Sites of Action

- SLC6 Monoamine Transporters
  - Dopamine transporter (DAT)
  - Norepinephrine transporter (NET)
  - 5-HT transporter (SERT)
- Other sites
  - Vesicular Monoamine Transporter 2 (VMAT2)
  - Trace amine-associated receptors (TAAR1)

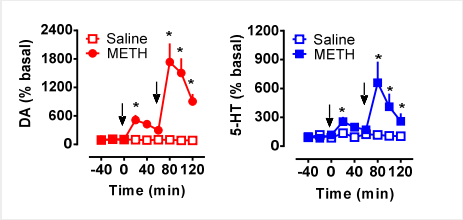
34

METH is a DAT substrate (DA releaser)



35

METH Increases EC DA More Than 5-HT



Baumann et al., 2002

36

Cocaine vs Methamphetamine

COCAINE

Inhibits DAT-mediated reuptake of EC DA

METH

Inhibits DAT-mediated reuptake of EC DA

Evokes DAT-mediated release of IC DA by reverse transport

37

Cocaine vs Methamphetamine

COCAINE

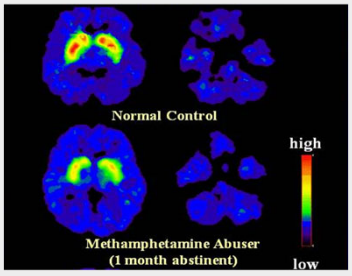
- Rapidly metabolized
- Effects last 1-2 hours
- Withdrawal lasts 1-2 days

METH

- Slowly metabolized
- Effects last 10-20 hours
- Withdrawal lasts many days

38

Chronic METH decreases DAT sites in brain



Volkow et al., 2001

39

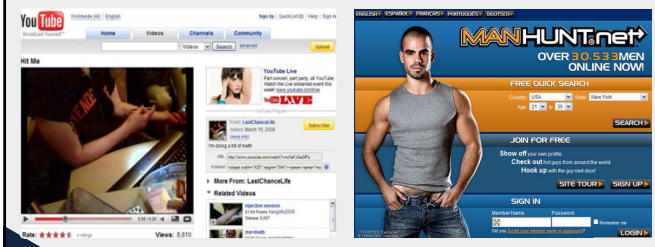
Role of METH in Gay Subculture

- METH intoxication
- Decreased inhibitions and judgment
- Increased sensation seeking and sexual arousal
- Unsafe sexual practices
- HIV transmission

Lee & Rawson, 2008

40

Internet Websites Foster Risky Behaviors



41

Treatment for METH Use Disorder (MUD)

- Pharmacotherapy
  - No FDA-approved medication for MUD
- Psychosocial Therapies
  - Contingency Management
  - Cognitive Behavioral Therapy
  - Group and Community Therapies

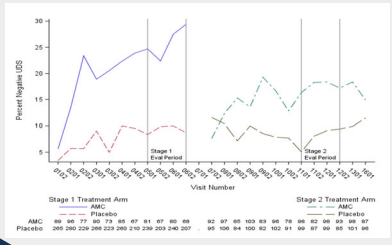
42

Experimental Pharmacotherapies for MUD

- Single medications
  - Some positive results with tetracyclic antidepressants, like mirtazapine (e.g., *Coffin et al., 2020*)
- Medication combinations
  - Bupropion + extended-release naltrexone (e.g, *Trivedi et al., 2021*)

43

Bupropion + Naltrexone Reduces METH Use



Trivedi et al. 2021

44

Ecstasy

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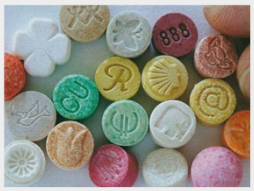
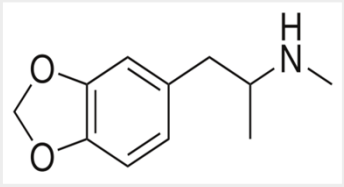
45

Ecstasy (MDMA) is a Synthetic Amphetamine Derivative

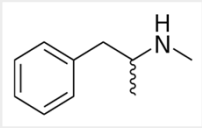




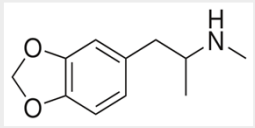
46

MDMA is a Ring-Substituted Amphetamine

Methamphetamine



3,4-Methylenedioxy Methamphetamine (MDMA)



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Formulations and Methods of Use

- Powders, capsules and tablets
  - Oral ingestion of tablets most common
  - Some intranasal and intravenous use
- "Bumping" or repeated intermittent dosing
- "Stacking" or taking multiple doses at once
- Binge and crash cycling

48

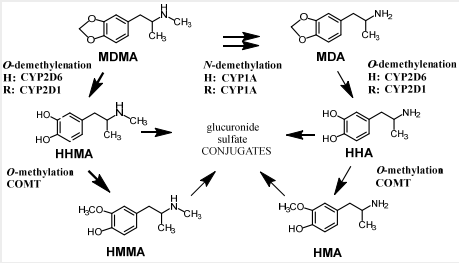
Pharmacokinetics And Metabolism

- Pharmacokinetics
  - Cmax reached within 2 h of oral ingestion
  - Non-linear drug accumulation at doses > 3 mg/kg
- Metabolism
  - *N*-demethylation to form MDA (bioactive)
  - O-demethylenation to form hydroxylated metabolites

de la Torre et al., 2004

49

MDMA Metabolism is Complex



Baumann et al., 2007

50

Desired Effects

- Combined effects of a stimulant and psychedelic
  - Enhanced mood and energy
  - Heightened or altered sensory perception
- Feelings of empathy and closeness to others
- Cardiovascular stimulation
- Appetite suppression

51

Adverse Effects

- Psychosis
- Sympathetic Stimulation
  - Palpitations and heart attack
  - Hypertension
- 5-HT Syndrome
  - Hyperthermia and dehydration
  - Treat with hydration, cooling, and sedation

52

Withdrawal

- Anhedonia and depressed mood
- Lethargy and fatigue for several days
- Sleep disturbances
- No indication for treatment

53

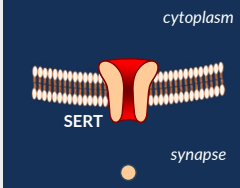
Molecular Sites of Action

- SLC6 Monoamine Transporters
  - 5-HT transporter (SERT)
  - Dopamine transporter (DAT)
  - Norepinephrine transporter (NET)
- Other sites
  - Vesicular Monoamine Transporter 2 (VMAT2)
  - 5-HT2B receptors

54

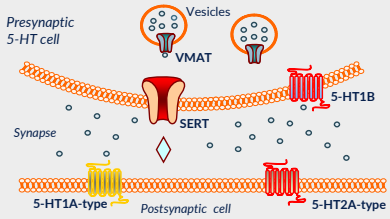
SERTs Mediate 5-HT Uptake

- SERTs are membrane proteins responsible for uptake of 5-HT
- Drugs that disrupt SERT function increase EC 5-HT
- Increases in 5-HT are not rewarding (e.g., SSRIs)



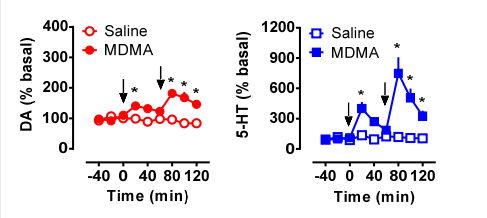
55

MDMA is a SERT substrate (5-HT releaser)



56

MDMA Increases EC 5-HT more than DA



Baumann et al., 2008

57

Neurotoxic Potential

- MDMA enters 5-HT neurons via SERT
  - Drug accumulates in 5-HT neurons
- MDMA chronically impairs 5-HT neurons
  - Depletion of 5-HT stores
  - Inhibition of 5-HT synthesis
  - Loss of SERT sites in brain
- Neurotoxicity?

58

MDMA for PTSD

- MDMA induces empathy and prosocial effects
  - SERT-mediated 5-HT release (*Oeri, 2021*)
- MDMA is efficacious as an adjunct for treating PTSD
  - Phase III trial (*Mitchell et al., 2023*)
  - Increased patient-provider alliance
  - Decreased PTSD symptoms

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Bath Salts

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Cathinone is a Plant-Based Alkaloid

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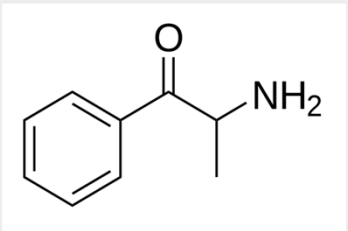
Khat Plant *Catha edulis*

62

Cathinone is β-Keto Amphetamine



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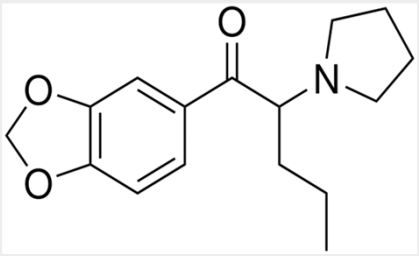
Psychoactive "Bath Salts" Products Contain Synthetic Cathinones

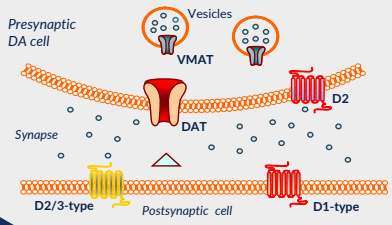
64

MDPV is an Analog of Pyrovalerone



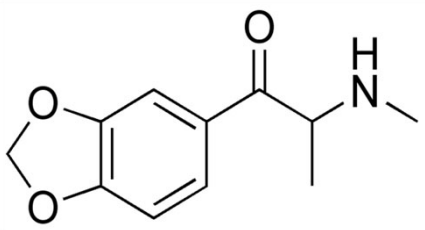
65

MDPV is a DAT Blocker (DA Uptake Inhibitor)



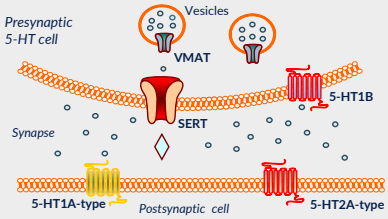
66

Methylone is β-Keto MDMA



67

Methylone is a SERT substrate (5-HT releaser)



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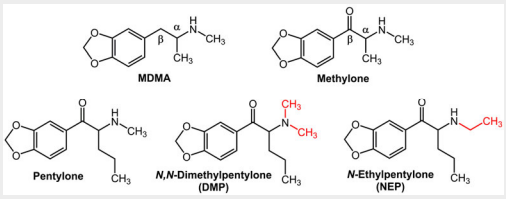
Methylone Analogs are Found as Counterfeit MDMA



69

Summary

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Overall Summary

1. Cocaine is a prototypical DAT inhibitor.
2. METH is a powerful stimulant, due to its DAT-mediated dopamine releasing action.
3. MDMA acts as a mild stimulant and psychedelic, due to its SERT-mediated 5-HT release.
4. MDPV is cocaine-like while methylone is MDMA-like.

71

Clinical Challenges

1. No FDA-approved medications for stimulant use disorders, so treatment is psychosocially-based.
2. No specific antidotes for stimulant intoxication, so treatment is supportive.
3. Stimulant-induced overdose deaths are increasing due to fentanyl co-use… intentional or accidental?

72


Thank You
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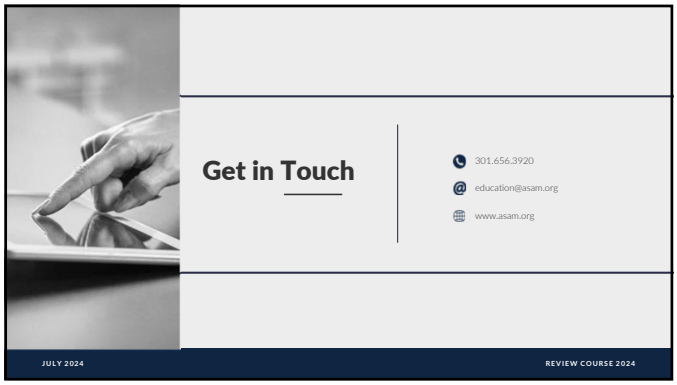
73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Nicotine Use Disorder: Public Health and Practice

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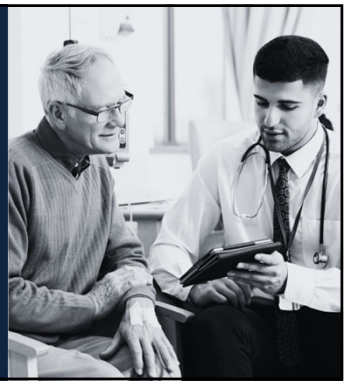

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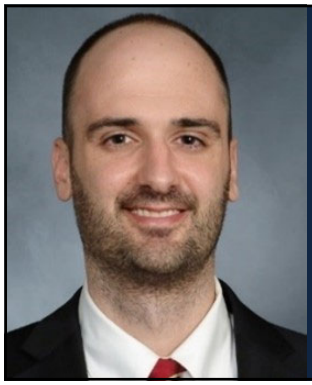

Financial Disclosure

Jonathan Avery, MD, FASAM

- No relevant disclosures

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2

History

- Native American tribes cultivated and used tobacco for many different purposes for thousands of years before the arrival of the Europeans. [1-2]
- Tobacco became an important economic influence in the British American colonies and the early United States. [1-2]
- The World Health Organization estimates that 1/3 adults smoke, and because tobacco use is on the rise in developing countries, it is one of the few causes of death that is increasing. (CDC, 2005) [3]
- Nicotine and the reinforcing sensory stimulation associated with tobacco use are responsive for the compulsive use of tobacco in the form of cigarettes, bidis, cigars, pipes, snuff, chewing tobacco, etc.

3

Epidemiology of Tobacco

- **Prevalence has declined** in the US from 42% in 1965 to 14% in 2017 [4,5]
- Men are more likely to be smokers than women (15.8% vs. 12.2%) [6]
- >16 million Americans have smoking-related disease
- Accounts for **20%** of coronary-artery disease [7]

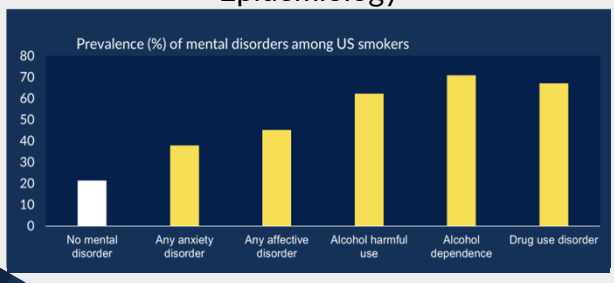
4

Morbidity and Mortality

- Leading cause of preventable death in the United States, accounting for about **440,000 premature deaths annually** [8]
  - **150K from CV disease**
  - **150K from cancer**
  - **150K from non-malignant pulmonary disease**
- Lost years of life: [9]
  - adult men: 13.2 yrs
  - adult women: 14.5 yrs

5

Epidemiology



[10] - Lawrence et al., 2009

6

Compounds in Tobacco Smoke

An estimated 4,800 compounds in tobacco smoke, including 11 proven human carcinogens [11]

Gases [12]	Particles [12]
• Carbon monoxide	• Nicotine
• Hydrogen cyanide	• Nitrosamines
• Ammonia	• Lead
• Benzene	• Cadmium
• Formaldehyde	• Polonium-120

Nicotine is the addictive component of tobacco products, but it does NOT cause the ill health effects of tobacco use.

7

Health Consequences

- Smokers **die 10 years earlier** than non-smokers on average
- **Cancer:** oral cavity, pharynx, larynx, bladder, esophagus, cervix, kidney, lung, pancreas, stomach, liver, bowel, acute myeloid leukemia [13]
- **Cardiovascular disease, DM type** [14]
- **COPD, Asthma** [15]
- Osteoporosis, cataracts and macular degeneration, early menopause, erectile dysfunction, gastric and duodenal ulcer disease, skin aging, periodontal disease [16]

8

Tobacco Associated Problems

- Barrier to Recovery
- Financial Hardships
- More Employment Difficulties
- More Housing Difficulties
- Poorer Mental Health
- More Relapse to Drugs and Alcohol
- Social Stigma
- Poorer Appearance
- More Fires in Home

9

Public Health Interventions [17]

- Anti-smoking advertisements
- Increasing taxes
- Age-restrictions
- Tobacco-free laws and policies
- Support for cessation

10

Pharmacology of Nicotine

- Naturally occurring alkaloid [3]
- Triggers the release of a variety of neuroactive hormones
- Acts as a **nicotinic acetylcholine receptor (nAChR) agonist** [3]
- **Stimulant-like effect** in the CNS: enhances concentration, alertness, arousal [3]
- Increase of dopamine in brain's reward circuitry [18]
- Enters the CNS in rapidly after inhalation [19]
- Rapid effect on CNS contributes to reinforcement and dependence

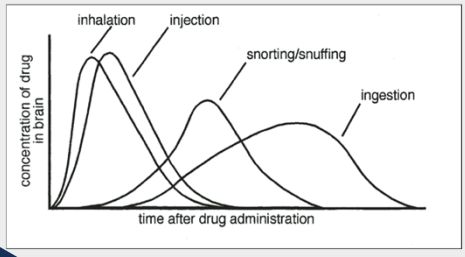
11

Routes of Use

- Nicotine and reinforcing sensory stimulation associated are responsible for the compulsive use of tobacco [20-23]
- Method of administration modifies the addictive potential associated with use [24]
- Compulsive use increases with rapid administration: smoking/vaping >> dermal patch, chewing

12

Smoking is the Fastest Route of Drug Administration



25 - https://science.education.nih.gov/supplements/nih2/addiction/guide/lesson3-1.html

13

Nicotine

- Reaches the brain 20 seconds after inhalation + gradually increases occupancy of the nAChRs over minutes [19]
- Smoking 1 cigarette leads to significant occupancy of alpha4beta2 containing nAChRs for >3 hrs [19]
- The initial relatively rapid rate of rise of nicotine occurs within minutes, though levels of nicotine-bound receptors continue to rise slowly/are maintained for hours [19]
- Rapid onset = allows smokers to control nicotine intake (by # of puffs, intensity of puffs, depth of inhalation)

14

Pharmacology of Nicotine

- Half-life is 2 hours [25, 26]
- Accumulation in various tissues throughout the body during the day [27]
- Continue to be release from tissues for 6-8 hours after smoking ceases during sleep [25, 26]
- Metabolized in the liver via cytochrome P450 enzymes [26]
- Major metabolite is cotinine [26]
- Crosses placenta and is found is breast milk [27]

15

Pharmacology

- Undergoes 1st pass metabolism [26]
- Oral bioavailability is 45% [26]
- Poorly absorbed from stomach 2/2 acidity of gastric fluid, but well absorbed in small intestine 2/2 alkaline environment [26]
- Renal clearance accounts for 2% to 35% (about 10%) of total nicotine clearance [28]
- Nicotine obtained via tobacco reaches high initial concentrations in arterial blood and lungs
  - Nicotine is then distributed to brain, storage adipose, muscle tissue from arterial blood
  - Avg steady-state concentration in body tissue is 2.6x that of the blood [26]

16

Pharmacology

- Once absorbed in bloodstream, nicotine has a volume of distribution of about 180 liters, with less than 5% of it binding to plasma proteins [26]
- Crosses placenta freely
- Found in the amniotic fluid and in the umbilical cord blood of neonates
- Found in breast milk at concentrations approximately 2x those found in blood

17

Sex and Race on Metabolism

- Women metabolize nicotine faster than men, 2/2 estrogen effect on CYP2A6 [29]
  - Even faster during pregnancy
- Related to CYP2A6 gene variants, African Americans obtain on average 30% more nicotine per cigarette, and they clear nicotine and cotinine more slowly than Caucasians. [30]
- Chinese American have a lower nicotine intake per cigarette, and slower metabolism (vs. Caucasians or Hispanics) 2/2 having a higher prevalence of CYP2A6 alleles (associated with slow metabolism) [31, 32]
  - Suggest why Chinese American smokers have lower rates of lung cancer than either African Americans or Caucasians [31, 32]

18

Biochemical Assessment

- Blood, salivary, and plasma cotinine can be used [33, 34]
  - others include expired breath CO, blood carboxyhemoglobin, + plasma/salivary thiocyanate concentrations
- 16-hr ½ life of cotinine makes it useful as a plasma and salivary marker of nicotine intake [35]
- The gold standard for estimating daily nicotine intake from tobacco use is the sum of nicotine and its metabolites in urine. [36]
- Measurement of the minor tobacco alkaloids anabasine and anatabine in urine can be used as a biomarker of tobacco use in individuals who are using nicotine medications. [37]

19

Drug Interactions from Tobacco Smoke

- Affects the pharmacokinetics or pharmacodynamic mechanisms
- absorption, distribution, metabolism, or elimination
- potentially causing altered response or toxicity
- Accelerates metabolism of many drugs, esp. those metabolize by CYP1A2 [38]
- Might increase CYP2E1 and inhibit CYP2A6 enzymatic activity [38]
- When smokes discontinue abruptly (i.e., when hospitalized) doses of such meds may need to be lowered to avoid toxicity [38]

20

Drug Interactions from Tobacco Smoke

Drugs that may have a decreased effect due to induction of CYP1A2 by tobacco smoke: [39]

- Caffeine
- **Clozapine**
- **Olanzapine**
- **Haloperidol**
- **Chlorpromazine**
- Fluvoxamine
- Theophyline

21

Quitting Smoking Effects on CYP1A2

- Risk for medication toxicity
- May ↑ levels acutely
- Consider dose adjustment
- Clozapine toxicity
- Seizures
- Reduce caffeine intake

- Nicotine (or NRT) Does Not Change Medication Levels
- Nicotine metabolized by CYP2A6

22

Pharmacodynamic Interactions: OCPs

- Alter the expected response or action of a drug
- Combined OCPs (estrogen + progestin) w/ smoking is very important
  - Increased risk of serious cardiovascular effects (stroke, MI, thromboembolism) [40]
- Recommended that OCPs are **contraindicated** in women > 35 yrs old AND are a heavy smoker (>15cigs/day) [40]

23

Pharmacodynamic Interactions

- Appear to enhance the procoagulant effect of **estrogens** [41]
- Results in less sedation from benzodiazepines and less analgesia from some opioids [42]
- Impairs the therapeutic effects of histamine H2 -receptor antagonists used in treating **peptic ulcers** [42]
- Cutaneous vasoconstriction by nicotine can slow the rate of absorption of subcutaneously administered **insulin** [43]

24

Pharmacologic Actions: CNS [44, 45]

- Acts on sympathetic system: increase BP, HR, cardiac output, and cutaneous vasoconstriction
- Causes muscle relaxation via simulation of Renshaw cells, via inhibition of motor neurons
- Higher doses: produces ganglionic stimulation -> releases adrenal catecholamines
- Very high doses cause hypotension, slowing of HR

25

Psychoactive Effects

- Causes arousal, relaxation, enhancement of mood/attention/rxn time [46-48]
- Results in relief of withdrawal sx of dependent smokers, rather than direct-enhancing effects [46-48]
  - Smokers may need regular doses of nicotine to feel normal rather than to enhance their capabilities/cognitive effects
- Psychoactive effects dependent on route, speed of administration, environmental factors
  - Subjective effects depend on pre-drug state, level of genetics, history, expectancy [49,50]

26

Genetic Predisposition

- GWAS: single nucleotide polymorphisms on... [51]
  - **CHRNA5-CHRNA3- CHRNB4 nAChR** subunit cluster on chromosome 15q25
    - associated w/ # of cigs/day, serum cotinine levels, lung cancer, peripheral artery disease, chronic lung dz
  - **CYP2A6,** primary enzyme responsible for the oxidation of nicotine and cotinine. [52-53]
    - Reduced function variants of the gene are associated with smoking fewer cigarettes per day and a lower risk of lung cancer
  - **Cell adhesion and ECM molecules** [54]
    - neural plasticity and learning are key determinants of individual differences in vulnerability to drug addictions
- Twin studies: [55-56]
  - monozygotic twins are more similar than dizygotic twins w/ smoking behavior
  - ½ of the total variance (28% to 84%) in smoking behavior are due to genetic effects
  - There is genetic influence on nicotine withdrawal symptoms as well

27

Psychiatric Comorbidities

- **37%** of those w/ a mental illness are smokers vs. **20%** of smokers who do not carry a mental illness. [57]
- Those with Sz, depression, ADHD have **higher prevalence** of cig smoking compared with general population

Sz: 70-88% are smokers [58]
- Diminished sensory gating to repeated stimuli, smoking can relieve negative sx (blunted affect, emotional withdrawal, lack of spontaneity)
- Smokers experience fewer side effects from antipsychotics (2/2 stimulating effects of nicotine), which might contribute to greater prevalence of smoking in ppl w/ Sz

ADHD: 40% are smokers [59]
- Associated with early initiation of regular cigarette smoking, even after controlling for confounding variables such as socioeconomic status, IQ, and psychiatric comorbidity
- transdermal patches improve the attentional symptoms of ADHD

28

Best Measure of Nicotine Dependence Severity

Heaviness of Smoking Index

- AM (upon awakening) Time to First Cigarette (TTFC) [46]
  - < 30 minutes = moderate
  - < 5 minutes = severe
- Implications for Treatment Outcome
- Need for Medications
- Implications for Dose

29

Tobacco Tolerance

- Causes effects of individual cigarettes tend to lessen throughout the day.
- Overnight abstinence allows considerable, but not complete, re-sensitization of nicotinic receptors to non-desensitized states
- Populations of nAChR subtypes that begin to change as other molecular mechanisms involving neuroadaptations come into play after days and weeks of tobacco use [47,48]

30

Tobacco Cravings

- Powerfully conditioned cues = cravings become associated with everyday events, become linked with mood
- High rates of relapse: [49]
  - Population surveys find that up to 75% of adults who smoke want to stop, but only 1/3 try to stop, and only 3% of those do without aids
  - 50% of individuals w/ past hx of MI, COPD, and other sequelae of smoking, revert to cig smoking days or weeks after leaving the hospital

31

Which of the following is a symptom of tobacco withdrawal?

A. Irritability

B. Hypersomnia

C. Elated Mood

D. Decreased Appetite

32

Tobacco Withdrawal

- Nicotine use is continued to avoid the negative sx associated with withdrawal (known as negative reinforcement)
- Majority of withdrawal sx are distressing, but not life-threatening
- Acute withdrawal sxs reach max. Intensity 24 - 48 hrs after cessation and then gradually diminish over weeks [50-51]
- Extrahypothalamic corticotropin-releasing factor (CRF-1) contributes to negative affect during withdrawal [52]
- CRF released in central amygdala following nicotine withdrawal -> produces anxiety behavior
- Pharmacological blockade of CRF1 receptors inhibits the anxiogenic effects in withdrawal

33

Tobacco Withdrawal Symptoms [53]

Emerge hours after last cigarette

Can last up to (4) weeks

- Depressed mood
- Insomnia
- Irritability, frustration or anger
- Anxiety
- Difficulty concentrating
- Restlessness
- Increased appetite or weight gain

34

MAO and Nicotine Dependence

- Cig smoking is associated w/ inhibition of monoamine oxidase A + B [54-56]
  - Not caused by nicotine itself, but the condensation products of acetaldehyde with biogenic amines, such as benzoquinones, 2-naphthylamine, harman, + others
- MAOs = metabolize catecholamines, including dopamine
- Rat studies: [57]
  - Pre-tx with MAO-I makes nicotine more rewarding and increases the likelihood and rate of acquisition of nicotine self-administration
  - Important consideration: anti-depressants also inhibit MAOs, therefore smoking-induced inhibition of MAO might contribute to the perceived benefit of smoking by some depressed patients

35

Systemic Toxicities

- **Tobacco smoke =** carries volatile and particulate phases that contain substances that are primarily responsible for the human morbidity and mortality [58]
  - Volatile = 500 compounds (nitrogen, CO, carbon dioxide, ammonia, hydrogen cyanide, and benzene)
  - Particulates = >3,500 (alkaloids nornicotine, anabasine, anatabine, myosmine, nicotyrine, and nicotine)
- **Tar:** contains many carcinogens, including polynuclear aromatic hydrocarbons, N-nitrosamines, and aromatic amines [58]

36

Toxicities: Pulmonary

- Causes imbalance between proteolytic and antiproteolytic forces in the lung [59]
- Heightens airway responsiveness
- High rates of COPD in tobacco smokers linked to: [59]
  - Exposure to tar, nitrogen oxides, hydrogen cyanide, and volatile aldehydes
  - These exposures results in oxidative stress and generation of superoxide radicals and hydrogen peroxide and lung damage
- Smokers with DNA damage from polynuclear aromatic hydrocarbons in the WBCs are 3x more likely to be dz with lung cancer than smokers with lower concentrations [60]

37

Toxicities: Cardiovascular

- **Increased risk** of CV toxicity 61
  - Related to exposure to oxidant chemicals and CO, + hydrogen cyanide, carbon disulfide, cadmium, and zinc
  - CO reduces oxygen delivery to the heart
  - Oxidant chemicals are primarily responsible for endothelial dysfunction, platelet activation, thrombosis, and coronary vasoconstriction

38

Other Effects and Toxicities

- **For women:** [62]
  - lower levels of estrogen
  - earlier menopause
  - increased risk of osteoporosis
  - alkaloids in tobacco smoke decrease estrogen formation by inhibiting an aromatase enzyme in granulosa cells or placental tissue
- **Skin changes:** [63]
  - yellow staining of fingers
  - precancerous and squamous cell carcinomas on the lips and oral mucosa
  - vasospasm and obliteration of small skin vessels
  - enhanced facial skin wrinkling

39

Predictors of Abstinence [64-66]

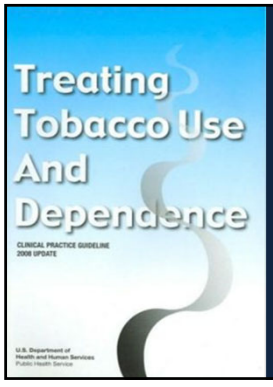
- Lower level of dependence
- Higher socioeconomic status: education, insured
- Older age
- Male gender
- No behavioral health comorbidity
- Fewer smokers in social networks
- Quit in first 7 days / # days quit
- Use of cessation treatment

40

Why is it so hard to quit?

- Smoking a drug is highly addicting
- **Treatment options are limited**
  - Few medication types
  - Limited (brief) counseling support
  - No levels of care
- **Utilization of treatment is poor**
  - Most don't use counseling
  - Medications-too low dose, not enough time

41



Brief Intervention

2As and R (Ask, Advise, and Refer)

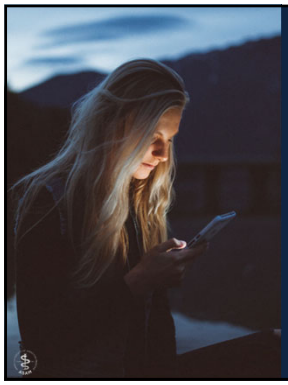
- Do you use Tobacco?
  - How much? What kinds?
  - Document tobacco use at visits
- How do you feel about quitting?
  - Can I give your name to someone to get more information?

42

Why Not Quit For One Day?
Or Six Hours?

- Save money
- Try free NRT
- Feel better
- Master a new skill
- Try other coping
- Not go outside in bad weather

43



Quitline
1-800-QUIT-NOW

- Telephone counseling
- Toll-free / state funded
- Assessment
- 4 follow-up calls
- Good for transportation issues
- Scheduled calls from tobacco specialist
- Success rate in smoking cessation
- Many languages, free NRT

44

Pharmacologic Treatments

- First line (FDA-approved): [67]
  - Nicotine replacement therapy (NRT)
  - Bupropion
  - Varenicline
- Second line (not FDA-approved): [67]
  - Nortriptyline

Counseling + Medications= Best Treatment Plan

45

Which of the following is TRUE of nicotine replacement therapies (NRT)?

A. Most people who use NRT become long term users of it

B. These medications produce serum nicotine levels, which are higher than that of a smoked cigarette

C. Most people use NRT incorrectly or at too low a dose

D. Medicaid insurance never pays for coverage over the counter products like nicotine patch or gum

46

Nicotine Medications [68]

- Use high enough dose
- Scheduled better than PRN
- Use long enough time period
- Can be combined with bupropion
- Can be combined with each other
- Have almost no contraindications
- Have no drug-drug interactions
- Safe enough to be OTC

47

Oral Nicotine Spray [69,70]

- Approved Sept 2019; OTC (Canada & Europe)
- Faster absorption
- 1-2 to two sprays (140/ container; each 1mg nic). Max 4/ hour, 64/ day (most 10-14/ day)
- No evidence product abuse
- Real world and efficacy trials 2X placebo
- Contains tiny amount ethanol. At 64 doses/d, <one tsp (~ 5ml) of wine with 12% alcohol)
- Side effects: hiccups, headache, nausea, mouth/throat irritation, dyspepsia, dizziness

48

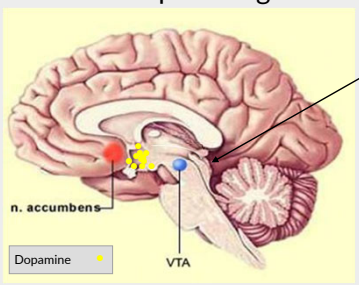
Combination Therapies [71,72]

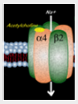
- Improve abstinence rates
- Decrease withdrawal
- Well tolerated

	OR
Patch + gum or spray	**1.9** (1.3-2.7)
Patch + bupropion	**1.3** (1.0-1.85)

49

Varenicline: A selective a4B2 nicotinic receptor partial agonist



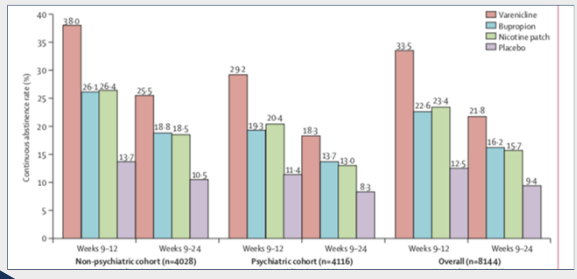


Partial Agonist [73]
- Partially stimulates receptor
- Some dopamine release
- Prevents withdrawal

"Antagonist"
- Blocks nicotine binding

50

EAGLES study [74]



51

Results from 2013 Cochrane Review [75]

Medication	Versus Placebo OR (95% Credible Interval)	Versus other medication OR (95% Credible Interval)
NRT	1.84 (1.71-1.99)	Combination outperformed single formulations
Bupropion	1.82 (1.60-2.06)	NRT: 0.99 (0.86-1.13)
Varenicline	2.88 (2.40-3.47)	Nicotine patches: 1.51 (1.22-1.87) Nicotine gums: 1.72 (1.38-2.13) Other NRT: 1.42 (1.12-1.79) Combination NRT: 1.06 (0.75-1.48)

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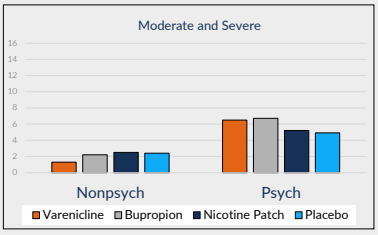
Neuropsychiatric Adverse Events



- FDA Approves Removal of Boxed Warning Regarding Serious Neuropsychiatric Events from CHANTIX® (varenicline) Labeling [90]
- Based on a U.S. Food and Drug Administration (FDA) review of a large clinical trial that we required the drug companies to conduct, we have determined the risk of serious side effects on mood, behavior, or thinking with the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion) is lower than previously suspected. The results of the trial confirm that the benefits of stopping smoking outweigh the risks of these medicines (December 2016) [76]

Varenicline ↑ Side effects: Nausea, insomnia, abnormal dreams, headaches

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Summary of Treatment

- All tobacco users should be offered treatment to try to stop
- Counseling + Medications = Best treatment plan
- Better outcomes
  - Education to use medication effectively
  - Combinations of NRT or Varenicline as first line
  - Longer durations (6 mos) effective for relapse prevention

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Gender Issues

- In any given quit-attempt, women are less likely to successfully quit smoking than men [77]
  - Negative affect/ depression/ socioeconomic issues/ less likely meds
- Women in placebo group less likely than men to quit
- Varenicline was more effective than TNP for women (OR=1.51; 95%CI=0.12,2.05; p=0.007) but not men (OR=0.92; 95%CI=0.65,1.31; p=0.64). [78]
- The advantage of varenicline over bupropion SR and TN is greater for women than men
- Clinical trials and epidemiologic studies

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Combination Therapy Of Varenicline and Bupropion

- Meta Analysis: 4 RCTs with 1230 smokers.
- Compared with varenicline, combination treatment with varenicline and bupropion could significantly improve the abstinence rate at the end of treatment (RR 1.153, 95% CI 1.019 to 1.305, P = 0.024). [79]

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Combination Therapy Of Varenicline and Bupropion

- The benefit existed at 6 months follow-up (RR 1.231, 95% CI 1.017 to 1.490, P = 0.033), and was mainly concentrated in highly dependent smokers (RR 1.631, 95% CI 1.290 to 2.061, P < 0.001) and heavy smokers (RR 1.515, 95% CI1.226 to 1.873, P < 0.001) [79]
- For safety outcomes, the combination treatment was associated with more anxiety (RR 1.717, 95% CI 1.176 to 2.505,P = 0.005) and insomnia (RR 1.268, 95% CI 1.076 to 1.494, P = 0.005) symptoms vs varenicline monotherapy. [79]

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Medication Interaction Tobacco Treatments [79]

Nicotine	CYP_2A6	None
Bupropion	CYP_2B6 CYP_2D6 inhibitor	Many
Varenicline	Excreted in urine	None

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Special Population: Pregnancy

In 2016, 7.2% of US women who gave birth smoked cigarettes during pregnancy. [80]

Smoking in pregnancy ↑ risks of:

- Spontaneous pregnancy loss
- Placenta abruption
- Ectopic pregnancy
- Placenta previa
- Preterm rupture of membranes
- Low birth weight
- Sudden infant death syndrome
- Low milk volume production and shorter duration of lactation

59

Special Population: Pregnancy [80]

- More likely to quit smoking in pregnancy
- Initiate intervention before conception
- Continue interventions during prenatal care visits
- Counseling is the first-line of treatment
- NRT or bupropion are acceptable second-line options (data lacking but supported by experts comities)
- Limited information regarding safety of varenicline

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Special Population: Adolescents

- Early intervention is important
- Counseling is the first-line of treatment
- If counseling fails NRT is an acceptable options
- Insufficient data regarding bupropion and varenicline

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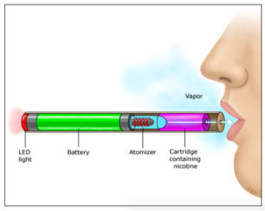

E-Cigarettes

- Battery-operated device
- Heats liquid containing nicotine
- Creates vapor that is inhaled
- Entered US market in 2006 [81]

Image from Rigotti N. et al. E cigarette chapter. Uptodte 2019.

62

Chemicals in Electronic Cigarettes [82,83]

- Propylene glycol, ethylene glycol and glycerin
- Nicotine
- Flavors (sweeteners)
- Most chemicals found at or below 1% of levels in tobacco smoke, and far below safety limits for occupational exposure.
  - Metals (cadmium, chromium, lead, manganese and nickel)
  - Formaldehyde
  - Other carcinogens
  - Solvents
  - Tobacco alkaloids

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Vaping and Youth

- Vaping" = nicotine, marijuana, just flavoring since 2017
- Increased dramatically in 2018 84
  - **Nicotine vaping largest ↑ ever recorded for any substance in the 44 years of MTF (2017-2018)**
    - 30% of 12th graders vaping nicotine (↑ 11%)
  - Marijuana vaping increased (1-3%) among 8, 10, 12th graders 4%, 12% and 13%
  - Just flavoring increased among 8, 10, 12th graders
    - 15%, 25% and 26%

65

Association of Electronic Cigarette Use With Subsequent Initiation of Tobacco Cigarettes in US Youths

- Prospective cohort (6123=N), mean age 13.4
- Cigarette use at wave 3 was higher among prior e-cigarette users (20.5%) vs no prior tobacco (3.8%). 85
- Prior e-cigarette use was associated with more than 4 times the odds of ever cigarette use (odds ratio, 4.09; 95%CI, 2.97-5.63) and nearly 3 times the odds of current cigarette use (odds ratio, 2.75; 95%CI, 1.60-4.73) vs no prior tobacco use.
- Supports that e-cigarette use is associated with increased risk for cigarette initiation and use, particularly among low-risk youths.

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E-cigarette or Vaping Associated Lung Injury (EVALI) [86]

- Lung injury cases associated with e-cigarette, or vaping, to CDC
- **Vitamin E acetate** -bronchoalveolar lavage (BAL) fluid samples
- Thickening agent in THC-containing e-cigarette
- **Most (86%) involved THC products**; some (11%) nicotine alone
- 70% of patients are male; 79% are < 35 years old

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E-Cigarettes

- More frequently used by Americans than other FDA-approved treatments for smoking cessation
- Safer than combustible products, but long-term effects are unknown
- Controversial whether e-cigarette should be used as a first line of treatment, although this is common in UK

68

Select the one TRUE statement about nicotine dependence.

A. Smokers that report smoking within 30 minutes of waking are moderately nicotine dependent and may need medications to succeed in quitting

B. Smokers who use less than 10 cigarettes per day are not nicotine dependent

C. Users of electronic cigarettes almost never become addicted to nicotine

D. Treatment for tobacco dependence should not be initiated until the primary mental disorder is in remission and all symptoms have abated

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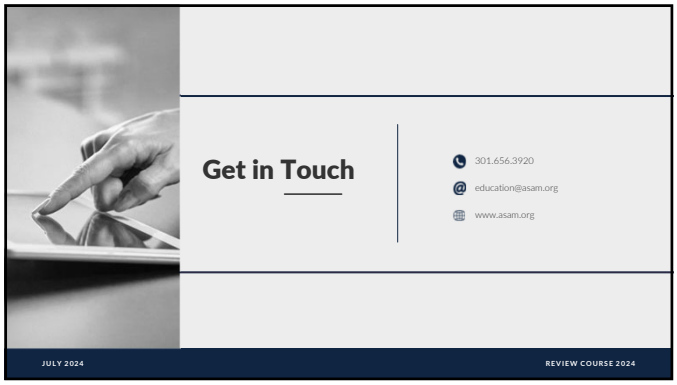
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REVIEW COURSE 2024

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Cannabis Use Disorder: Science, Trends, and Clinical Implications

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Financial Disclosure

Mashal Khan, MD

- No relevant disclosures

REVIEW COURSE 2024

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Learning Objectives

- Increase knowledge about current epidemiological trends in cannabis use in the United States.
- Name the different formulations of cannabis that impact individuals today.
- Review medications that have an evidence base for treating cannabis withdrawal and cannabis use disorder.

3

Presentation Outline

- Epidemiology
- Cannabis formulations
- Effects of Cannabis
- Cannabis Potency (THC concentration)
- Special Populations and Cannabis
- Cannabis Use Disorder Treatment
- Medicinal Uses of Cannabis/Cannabinoids
- Board Review Questions / Wrap Up

4

Epidemiology

REVIEW COURSE 2024

5

Cannabis Use/Misuse

- In 2021, an estimated 65.2 million Americans- **27.1%** of the population aged 12 years or older had used cannabis in the preceding month.
- In 2015, it was 22.2 million (**8.9%**) Americans aged 12 years and older.
- Cannabis use peaks in the late teens to early 20s, then declines.

6

Increased Risk for Use Disorder

- 9% of users develop Cannabis Use Disorder
- The risk increases to 17% in people who start using in adolescence.
- The risk increases to 25 to 50% in people who are daily users (most of whom started using marijuana early in adolescence).

7

Cannabis Basics

- The cannabis plant has 104 cannabinoids; only 2 (THC and CBD) have been extensively studied for potential therapeutic applications.
- THC is the most psychoactive component – (*inhaled, ingested*)
- CBD is postulated to have other mechanisms of action (anti-inflammatory, analgesic, etc.).

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Cannabis Plant

9

Natural, Plant - Derived Cannabinoids

- Cannabis
- Sativa, Indica, or Hybrid
- Subspecies of the hemp plant

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Natural, Plant - Derived Cannabinoids

Most common preparations:

*Marijuana

*Hashish

*Hash Oil

THC Concentrations vary—

For example, extraction of THC with butane ("dabs") can contain up to 90% THC.

11

Synthetic Cannabinoids

- Higher affinity for cannabinoid receptors than THC
- Have active metabolites that prolong their durations of action
- Increased potential for toxicity
- "Spice" or "K2"
- Not detected on standard UDS

12

Synthetic Cannabinoids

Seely et al. Spice Drugs are More than Harmless Herbal Blends: A Review of the Pharmacology and Toxicology of Synthetic Cannabinoids. Prog Neuropsychopharmacol Biol Psychiatry. 2012;39(2):234-243.

Spice/K2, Synthetic Marijuana, dea.gov

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Cannabinoid Receptor Neurobiology

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14

The Cannabinoid System

- THC activates the CB1 and CB2 cannabinoid receptors:
  - CB1 has high density in cerebellum, basal ganglia, hippocampus, cerebral cortex. *G protein mediated system.*
  - CB1 has low density in the brainstem, hence low risk of respiratory depression.
  - CB2 is found in spleen, hematopoietic cell lines, mast cells.

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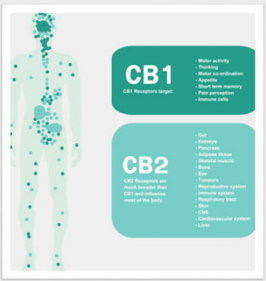
Cannabinoid Receptors

- CB1 – CNS site of CB binding
  - Memory, learning, problem solving, coordination
  - Activated by anandamide, other CBs
  - Modulates neurotransmitters
- CB2 – immune cells outside CNS
  - Anti-inflammatory effects



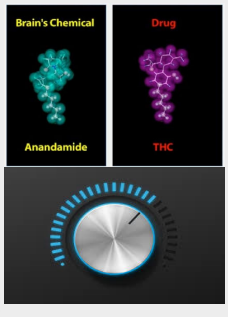
16

Cannabinoids (CBs)

- > 400 chemicals, ↓ neurotransmitter release
- Natural CBs
  - **Endogenous** – Anandamide, 2-Arachidonoylglycerol (AEA, 2-AG)
  - **Exogenous** – Sativa or Indica plant (marijuana)
    - Tetrahydrocannabinol (THC) – psychoactive
    - Cannabidiol (CBD) – no effect in brain

17

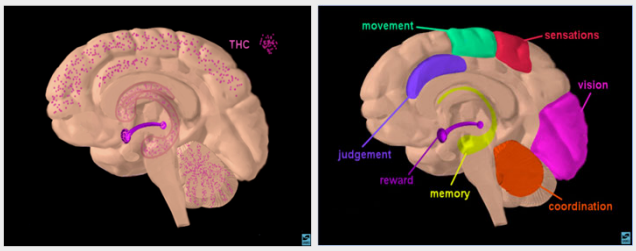
9-tetrahydrocannabinol (THC)



- Primary psychoactive constituent
- Endocannabinoid system
  - Brain development
- Mimics anandamide
  - Dial down neuron activity

18

CB1 Receptor Locations in the Brain



19

Neurotransmitter modulation

- Dopamine – euphoria, reward, pleasure
- GABA- muscle relaxation and sleepiness
- ↓ Glutamate- relaxation, ↓ memory

20

Cannabis Intoxication

- *Desired effects*: relaxation, euphoria, slowed time perception, altered sensory perception, increased appetite.
- *Undesired effects*: impaired concentration, anterograde amnesia, anxiety, panic attacks, paranoia, derealization/depersonalization, psychosis (visual – not auditory hallucinations).

21

Synthetic Cannabinoid Toxicity

Central Nervous System	Seizures	*Cardiovascular*	Tachycardia
	Agitation		Hypertension
	Irritation		Chest pain
	Loss of consciousness		Cardiac Ischemia
	Anxiety		
	Confusion	*Gastrointestinal*	Nausea
	Paranoia		Vomiting
Metabolic	Hypokalemia	*Autonomic*	Fever
	Hyperglycemia		Mydriasis
		Other	Conjunctivitis

Seely et al. Marijuana-based Drugs: Innovative Therapeutics or Designer Drugs of Abuse? Mol Interv. 2011;11(1):36-51.

22

Routes of Administration

- Smoked:
  - Reaches the brain in minutes
  - Effects last 1 - 3 hours
  - Delivers significant amount of THC into the bloodstream

Smoked	*Vaporized*	*Eaten/Drunk*
Smoked in a pipe, bowl, cigarette	Inhaled through machine that converts active compounds into inhalable form	Consumed as ingredient in baked goods, candies, sodas
Rapid effects	Rapid effects	Takes time to reach brain, so effects are delayed

23

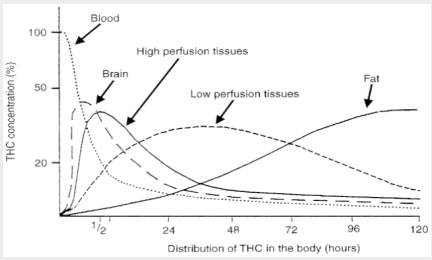
Routes of Administration

- Eating or drinking marijuana:
  - Takes ½ - 1 hour to have an effect
  - Effects last up to 4 hours
  - THC is metabolized by the liver into 11-hydroxy-THC
  - 11-Hydroxy-THC is more lipophilic, potent and has a longer half-life.

Smoked	*Vaporized*	*Eaten/Drunk*
Smoked in a pipe, bowl, cigarette	Inhaled through machine that converts active compounds into inhalable form	Consumed as ingredient in baked goods, candies, sodas
Rapid effects	Rapid effects	Takes time to reach brain, so effects are delayed

24

Biphasic distribution



2019 National Drug Threat Assessment. US Department of Justice Drug Enforcement Administration. December 2019.

25

Toxicology Testing

- Casual use:
  - Up to 10 days in urine
  - 50% positive in hair samples
- Heavy use:
  - Up to 30 days in urine
  - 85% positive in hair samples
- Measures THC
- Weight loss gives serial UTox spike
- Dronabinol gives positive test
- Passive inhalation gives negative test

26

Cannabis Withdrawal

- Reported by up to 1/3 of persons who use cannabis frequently.
- Cannabis withdrawal is recognized by the DSM 5.
- Clinical trials – show reduction of withdrawal symptoms with synthetic THC (dronabinol), nabilone, nabiximol, and gabapentin.

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Cannabis Withdrawal

Causing distress & ≥ 3 of the following:

- Irritability
- Anxiety
- Sleep problems
- ↓ Appetite/weight loss
- Depressed Mood
- Restlessness

AND ≥ 1 of the following:

- Abdominal pain
- Sweating
- Shakiness/tremors
- Fever/chills
- Headache

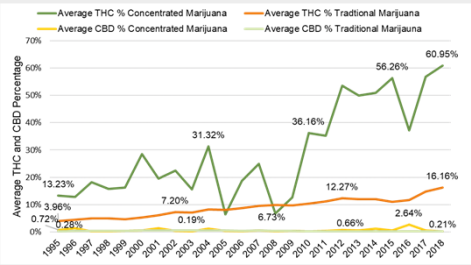
28

THC Potency is Increasing

- Up to 31 % in products
- Widespread availability of THC edibles (food and beverage products) and butane-extracted hash oil products ("dabs", "budder", "shatter", "wax")
- Rate of ED visits per 100,000 for cannabis-related adverse reactions has dramatically risen: 96.2 to 146.2 (2004 in 2011).

29

THC Percent is Increasing



2019 National Drug Threat Assessment. US Department of Justice Drug Enforcement Administration. December 2019.

30

Special Populations and Cannabis

- Adolescents
- Pregnant persons

31

Decreased Harm Perception: Adolescents

- 36% of teens think cannabis is harmless
  - 43% favor legalization
  - 80s: 15%
  - 90s-00s: 30%
- Harm perception lowest in 40 yrs
  - Often precedes ↑ prevalence

32

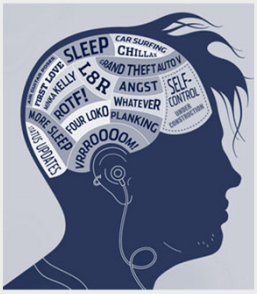
Rates ↑ Across Adolescence

- Ever tried
  - ~17% 8th graders
  - ~50%12th graders
- Past year use
  - 12% 8th graders
  - 35% 12th graders
- Current use (past month)
  - 7% 8th graders
  - 21% 12th graders
  - Surpasses current alcohol and tobacco use

33

Adolescent Brain

- May be vulnerable to the addictive nature of cannabis and neurotoxic effects, including development of psychiatric disorders.
- One study showed decline in IQ among cannabis users before the age of 18, with much less recovery of neuro-psych functioning.
- NSDUH data: risk for cannabis dependence is higher if use begins before age 16 (17% versus 9%)
- Most and latest change in areas of:
  - Reward and motivation
  - Cognition



34

Pregnancy

- Endocannabinoid system plays a role in the control of brain maturation, particularly emotional responses
- THC crosses the placenta (also note effect of smoking)

35

Pregnancy

- Babies exposed to THC:
  - Neurological development effects
  - Reduction in fetal growth, also other negative effects on the infant

36

Pregnancy

- Children exposed to THC:
  - Problem-solving skills, memory, attention deficit
- THC-specific vs. associated environmental factors hard to sort out; ongoing debate and research.

37

Effects of Use

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Physiological Effects

- Adrenergic look-alike:
  - Tachycardia
  - Hypertension (but orthostatic hypotension)
  - Tachypnea
  - Dry mouth
- Conjunctival injection
- Appetite increase

39

Impaired Cognition

- ↓ Ability to learn
- ↓ Attention, concentration
- ↓ Abstract reasoning and decision-making
- ↓ Memory

40

Neurocognitive Effects

- Short-term memory impairment
- Judgment impairment
- Motor coordination impairment (increased risk of MVA)

41

Impaired Driving

- Acute THC
  - → ↓ Peripheral vision
  - → ↓ Motor coordination
    - → ↑ reaction time
    - → ↓ time/distance judgment
- #1 reported illicit drug in accidents/fatalities
  - 2x accident risk
  - 3-7x risk of causing accident

42

Physical Health

- Respiratory
  - ↓ Function
  - ↑ Infections
- ↑ Stroke/Temporary brain blood constriction

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Psychiatric

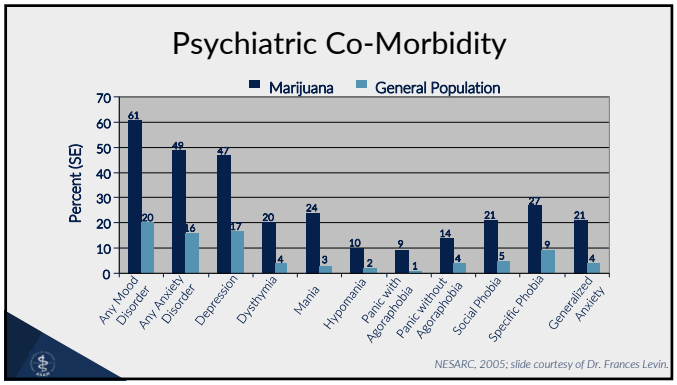
- Anxiety
  - Acute THC → ↓ anxiety
  - Long-term THC → ↑ anxiety
- ↑ Depression
- ↑ Psychosis

44

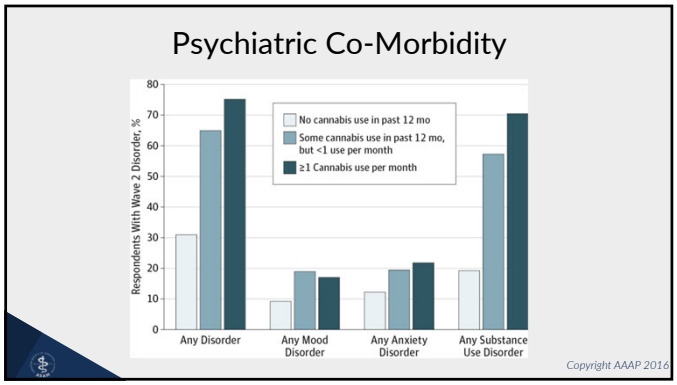
Amotivational Syndrome

- Mental slowing
- ↓ Planning ability
- ↓ Judgment, concentration, memory
- Apathy, ↓ pursuit of goals

45


Psychiatric Co-Morbidity
Marijuana
General Population
Percent (SE)
70
60
50
40
30
20
10
0
61
20
49
16
47
17
20
4
24
3
10
2
9
1
14
4
21
5
27
9
21
4
Any Mood Disorder
Any Anxiety Disorder
Depression
Dysthymia
Mania
Hypomania
Panic with Agoraphobia
Panic without Agoraphobia
Social Phobia
Specific Phobia
Generalized Anxiety
NESARC, 2005; slide courtesy of Dr. Frances Levin.

46


Psychiatric Co-Morbidity
Respondents With Wave 2 Disorder, %
80
70
60
50
40
30
20
10
0
No cannabis use in past 12 mo
Some cannabis use in past 12 mo, but <1 use per month
≥1 Cannabis use per month
Any Disorder
Any Mood Disorder
Any Anxiety Disorder
Any Substance Use Disorder
Copyright AAAP 2016

47


Diagnosis
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Substance Use Disorder

In Same Year, ≥2 of:

- Tolerance
- Withdrawal
- Use more/longer
- Unable to ↓ use
- Use despite problems
- Craving
- Failed roles
- Hazardous use
- Social problems
- ↓ Activities
- Lots time use

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Cognitive Effects

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50

Residual Cognitive Effects

- Memory
  - Learning & retaining new information
- Attention and concentration
  - Response speed & variability
- Executive functioning
  - Working memory
  - Verbal fluency

51

Likely Reversible with Abstinence

- Biological markers normalize ~4wks
  - CB receptor density in brain
  - Cortical blood volumes
- Especially in cognitive areas

52

Treatment

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53

Treatment for CUD is Challenging

- Few evidence-based supported approaches
- ~ 50% achieve remission
- ~ 70% return to use
- No FDA-approved medications

54

Psychosocial Treatments

- Motivational Enhancement Therapy
- Cognitive Behavior Therapy
- Contingency Management
- Family-Based Programs

55

Pharmacologic Treatment Options

Medication	Mechanism	Comments	Literature in Adolescents?
Atomoxetine	Norepinephrine reuptake inhibitor	• No change in cannabis use • Worsened irritability and GI side effects	• Thurstone et al., 2010[7]
Bupropion	Norepinephrine reuptake inhibitor	• Exacerbated withdrawal (irritability, insomnia)	• Riggs, et al., 2013[8]
Buspirone	Serotonin partial agonist	• Conflicting evidence on cravings and irritability	--
Dronabinol	CB1 receptor agonist	• **Reduced symptoms of withdrawal** • Contains THC	--
Gabapentin	GABA modulation	• **Decrease self-reported cannabis use** • **Reduced withdrawal symptoms**	--
N-acetylcysteine	Correct glutamate dysregulation	• Decreased use in adolescents • Did not show same benefit in adults	• Gray et al., 2012[9]
Naltrexone	Mu-opioid receptor antagonist	• Enhanced subjective effects of cannabis • No change in frequency of cannabis use	--

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Medication for CUD

- N-acetylcysteine (NAC)
  - Amino acid derivative, OTC supplement
  - Restores normal glutamate activity
  - Pros: ↓ use in Non-Treatment Seeking adolescents, *not in adults*
  - Cons: did not ↓ craving

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N-acetylcysteine (NAC)

Risks	• Nausea/vomiting • Drowsiness/insomnia • Vivid reams • *Anaphylactoid reactions seen with IV admin, not PO*
Pharmacokinetics	• Bioavailability for oral: 9% • Metabolized to cysteine and glutathione • Half-life: ~ 18 hours

58

Gabapentin

Mechanism of Action	• Blocks alpha-2d subunit of the voltage-gated calcium channel which modulates GABA in the amygdala
Notes	• FDA approved for multiple indications, including partial seizures in ages 3-12
Doses	• Goal of ~1200mg/day Mason (2012) [10]: 50 cannabis-dependent adults (18-65 years old) • Gabapentin 1200mg vs placebo for 12 weeks • Titrated up to 300mg / 300mg / 600mg over the course of 4 days
Clinical benefit	• Increase in negative UDS • Decrease self-reported cannabis use • Reduction in withdrawal symptoms (mood disturbance, craving, and sleep disturbances)

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Gabapentin

Risks	Well tolerated ☺ Headache, nausea, insomnia and depression

Pharmacokinetics	• Bioavailability: inversely proportional due to saturable absorption
	  • Immediate release
	  • 900mg/day: 60%
	  • 1200mg/day: 47%
	  • 3600mg/day: 33%
	  • 4800mg/day: 27%
	  • Extended release: increased with higher fat content
	• Half-life:
	  • ≤ 12 years old: 5hr
	  • > 12 years: 5-7hr
	  • **Longer in patients with decreased renal function**

60

CB1 Receptor Agonists

Cannabidiol (CBD) Epidiolex ®	Dronabinol (THC) Marinol® Syndros® Nabilone (THC) Cesamet®	Nabixmols (THC + CBD) Stavivex® *not FDA approved*


61

Medicinal Uses of Cannabis/Cannabinoids

- Dronabinol: FDA approved for treatment of anorexia associated with weight loss in patients with AIDS, chemotherapy-induced nausea/vomiting.
- Nabilone: FDA approved for treatment of chemotherapy-induced nausea/vomiting.
- Studies also ongoing re: effects on other disease states (epilepsy, MS).

62

Therapeutic Potential

- Pain (cancer, multiple sclerosis)
- Nausea (cancer)
- Loss of appetite and wasting (HIV/AIDS)
- Increased ocular pressure (glaucoma)
- Inflammation (rheumatoid arthritis, Crohn's disease, ulcerative colitis)
- Epilepsy

63

In Summary

- Cannabis includes plants and synthetic cannabinoids.
- Cannabis use is common, risk of a use disorder increases with earlier onset of use.
- Cannabis contains more THC now than in the past.
- Cannabis can affect cognition, but this is reversible in adults, impacts on adolescents less clear.
- Most treatment is psychosocial, but several drug targets are being investigated.

64

Which of the following trends in youth from the Monitoring the Future study about marijuana use and perception of harm is true?

A. Since the early 1990's, the percentage with perceived risk of harm from marijuana has been higher than past year use of marijuana.
B. Since about 2009, there has been a growing gap between decreased perception of harm and increased past year use of cannabis.
C. The lowest past year cannabis use was in the late 1970's.
D. The perceived risk of harm for cannabis fell throughout the 1980's.

65

Which of the following medications has a trial supporting efficacy in cannabis use disorder in adolescents?

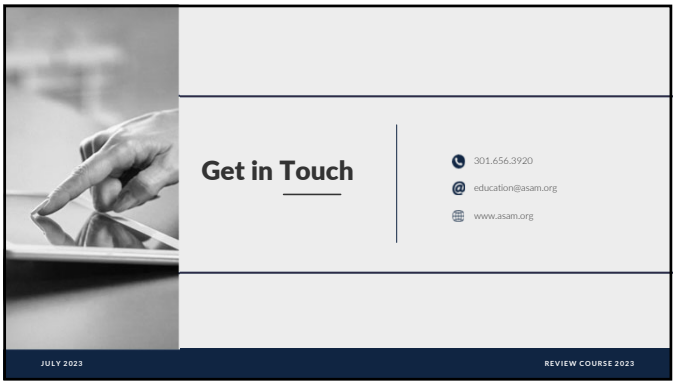
A. N-acetylcysteine
B. Baclofen
C. Quetiapine
D. Mirtazapine

66

Cannabis use is reported in greater than 10% of pregnancies. Which correctly lists the reasons cannabis users who are planning to become pregnant should be cautioned against cannabis use:

A. THC easily passes into breast milk and crosses membranes and is transferred to the developing fetus, and therefore impacts pregnancy success in females only.
B. While THC does not pass into breast milk, studies show that it does easily crosses membranes and is transferred to the developing fetus.
C. While human studies on the effect of prenatal THC exposure on the developing brain are preliminary, they correlate with studies carried out in animals and show that THC easily passes into breast milk and crosses membranes and is transferred to the developing fetus.
D. While no human studies have been done on the effect of prenatal THC exposure, animal studies show that it does easily pass into breast milk, crosses membranes, and is transferred to the developing fetus.

67



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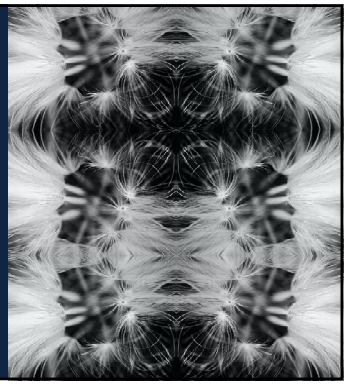
Other Classes of Drugs: Pharmacology and Epidemiology

Annie Lévesque, MD, MSc
Assistant Professor
Mount Sinai West Hospital, Icahn School of Medicine
New York, NY



1

Financial Disclosure

Annie Lévesque, MD, MSc

- No relevant disclosures

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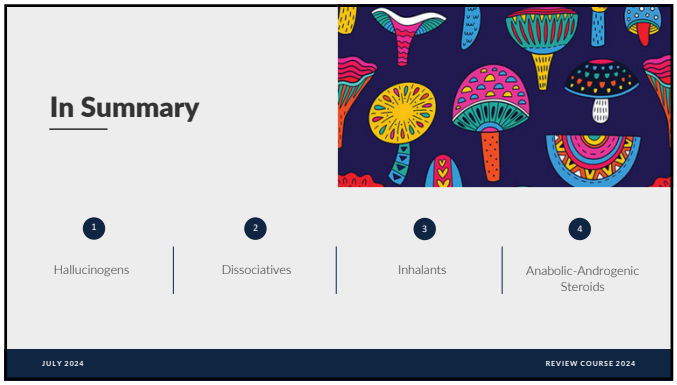
2

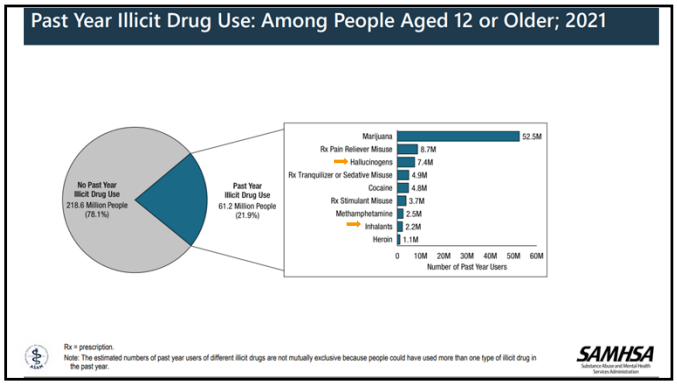
LEARNING OBJECTIVE

Identify other classes of drugs, their physiological impacts, and treatment considerations.

3


In Summary
1
Hallucinogens
2
Dissociatives
3
Inhalants
4
Anabolic-Androgenic Steroids
JULY 2024
REVIEW COURSE 2024

4


Past Year Illicit Drug Use: Among People Aged 12 or Older; 2021
No Past Year Illicit Drug Use 218.6 Million People (78.1%)
Past Year Illicit Drug Use 61.2 Million People (21.9%)
Marijuana 52.5M
Rx Pain Reliever Misuse 8.7M
Hallucinogens 7.4M
Rx Tranquilizer or Sedative Misuse 4.9M
Cocaine 4.8M
Rx Stimulant Misuse 3.7M
Methamphetamine 2.5M
Inhalants 2.2M
Heroin 1.1M
0 10M 20M 30M 40M 50M 60M
Number of Past Year Users
Rx = prescription.
Note: The estimated numbers of past year users of different illicit drugs are not mutually exclusive because people could have used more than one type of illicit drug in the past year.
SAMHSA

5

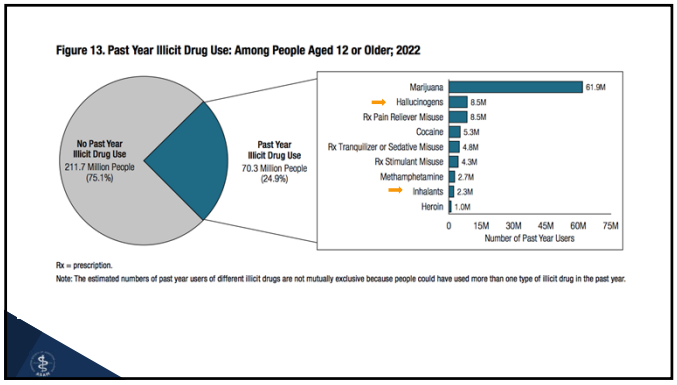
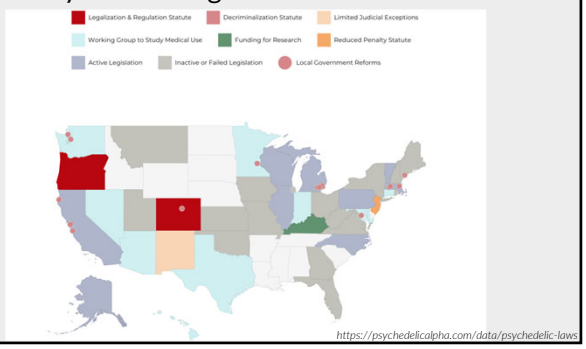


Figure 13. Past Year Illicit Drug Use: Among People Aged 12 or Older; 2022
No Past Year Illicit Drug Use 211.7 Million People (75.1%)
Past Year Illicit Drug Use 70.3 Million People (24.9%)
Marijuana 61.9M
Hallucinogens 8.5M
Rx Pain Reliever Misuse 8.5M
Cocaine 5.3M
Rx Tranquilizer or Sedative Misuse 4.8M
Rx Stimulant Misuse 4.3M
Methamphetamine 2.7M
Inhalants 2.3M
Heroin 1.0M
0 15M 30M 45M 60M 75M
Number of Past Year Users
Rx = prescription.
Note: The estimated numbers of past year users of different illicit drugs are not mutually exclusive because people could have used more than one type of illicit drug in the past year.

6

Psychedelic legal status in the USA



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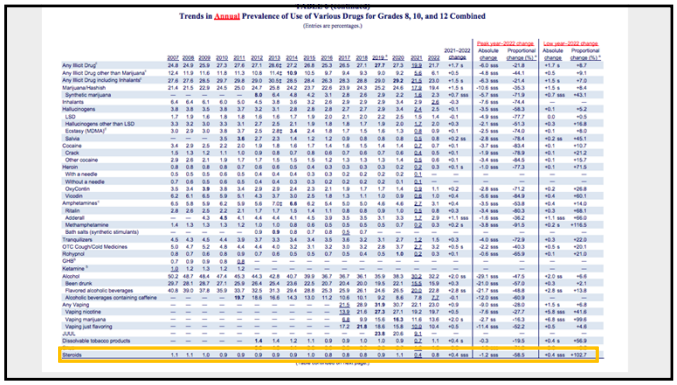

Trends in Annual Prevalence of Use of Various Drugs for Grades 8, 10, and 12 Combined

(Entries are percentages.)

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019 †	2020	2021	2022	2021–2022 change	Peak year–2022 change		Low year–2022 change	
																		Absolute change	Proportional change (%) *	Absolute change	Proportional change (%) *
Any Illicit Drug[1]	24.8	24.9	25.9	27.3	27.6	27.1	28.02	27.2	26.8	25.3	26.5	27.1	27.7	27.3	32.8	21.7	+1.7 s	-6.0 sss	-21.8	+1.7 s	+8.7
Any Illicit Drug other than Marijuana[1]	12.4	11.9	11.6	11.8	11.3	10.8	11.42	10.9	10.5	9.7	9.4	9.3	9.0	9.2	9.6	8.1	+0.5 s	-4.8 sss	-44.1	+0.5 s	+9.1
Any Illicit Drug including Inhalants[1]	27.6	27.6	28.5	29.7	29.8	29.0	30.52	29.5	28.4	26.3	28.3	28.8	29.0	29.2	31.5	23.0	+1.5 s	-6.3 sss	-21.4	+1.5 s	+7.0
Marijuana/Hashish	21.4	21.5	22.9	24.5	25.0	24.7	25.8	24.2	23.7	22.6	23.9	24.3	25.2	24.6	17.8	19.4	+1.5 s	-10.6 sss	-35.3	+1.5 s	+8.4
Synthetic marijuana	—	—	—	—	—	8.0	6.4	4.8	4.2	3.1	2.8	2.6	2.9	2.2	1.6	2.3	+0.7 sss	-5.7 sss	-71.9	+0.7 sss	+43.1
Inhalants	6.4	6.4	6.1	6.0	5.0	4.5	3.8	3.6	3.2	2.6	2.9	2.9	3.4	2.9	2.6	2.3	-0.3	-7.6 sss	-74.4	—	—
Hallucinogens	3.8	3.8	3.5	3.9	3.7	3.2	3.1	2.9	2.8	2.8	2.7	2.7	2.9	3.4	2.4	2.5	+0.1	-3.5 sss	-58.3	+0.1	+5.2
LSD	1.7	1.9	1.6	1.9	1.8	1.8	1.6	1.7	1.9	2.0	2.1	2.2	2.5	1.5	1.4	1.1	-0.1	-4.9 sss	-77.7	0.0	+0.5
Hallucinogens other than LSD	3.3	3.2	3.0	3.3	3.1	2.7	2.5	2.1	1.9	1.8	1.8	1.7	1.9	2.0	1.2	2.0	+0.3	-2.1 sss	-51.3	+0.3	+16.8
Ecstasy (MDMA)[1]	3.0	2.9	3.0	3.9	3.7	2.5	2.82	3.4	2.4	1.8	1.7	1.5	1.8	1.3	0.8	0.9	+0.1	-2.5 sss	-74.0	+0.1	+8.0
Salvia	—	—	—	3.5	3.6	2.7	2.3	1.4	1.2	1.2	0.9	0.6	0.8	0.5	0.5	0.9	+0.2 sss	-2.6 sss	-76.4	+0.2 sss	+45.1
Cocaine	3.4	2.9	2.5	2.2	2.0	1.9	1.8	1.6	1.7	1.4	1.6	1.5	1.4	1.4	0.7	0.7	+0.1	-3.7 sss	-83.4	+0.1	+10.7
Crack	1.6	1.3	1.2	1.1	1.0	0.9	0.8	0.7	0.8	0.6	0.7	0.6	0.7	0.6	0.4	0.5	+0.1	-1.9 sss	-78.9	+0.1	+21.2
Other cocaine	2.9	2.6	2.1	1.9	1.7	1.7	1.5	1.5	1.5	1.2	1.3	1.3	1.3	1.4	0.8	0.8	+0.1	-3.4 sss	-84.5	+0.1	+15.7
Heroin	0.8	0.8	0.8	0.8	0.7	0.6	0.6	0.6	0.4	0.3	0.3	0.3	0.3	0.2	0.2	0.3	+0.1 s	-1.0 sss	-77.3	+0.1	+71.5
With a needle	0.5	0.5	0.5	0.6	0.5	0.4	0.4	0.4	0.3	0.3	0.2	0.2	0.2	0.2	0.1	—	—	—	—	—	—
Without a needle	0.7	0.6	0.6	0.6	0.5	0.4	0.4	0.3	0.3	0.2	0.2	0.2	0.2	0.1	0.1	—	—	—	—	—	—
OxyContin	3.5	3.4	3.9	3.9	3.4	2.9	2.9	2.4	2.3	2.1	1.9	1.7	1.7	1.4	0.9	1.1	+0.2	-2.8 sss	-71.2	+0.2	+26.8
Vicodin	6.2	6.1	6.0	5.9	5.1	4.3	3.7	3.0	2.5	1.8	1.3	1.1	1.0	0.9	0.6	1.0	+0.4	-5.6 sss	-84.9	+0.4	+60.1
Amphetamines[1]	6.3	6.8	5.9	6.2	5.9	5.6	7.02	6.6	6.2	5.4	5.0	5.0	4.6	4.6	2.7	3.1	+0.4	-3.5 sss	-53.8	+0.4	+14.0
Ritalin	2.8	2.6	2.5	2.2	2.1	1.7	1.7	1.5	1.4	1.1	0.8	0.8	0.9	1.0	0.5	0.8	+0.3	-3.4 sss	-80.3	+0.3	+68.1
Adderall	—	—	4.3	4.5	4.1	4.4	4.4	4.1	4.5	3.9	3.5	3.5	3.1	3.3	1.7	2.9	+1.1 sss	-1.6 sss	-36.2	+1.1 sss	+66.0
Methamphetamine	1.4	1.3	1.3	1.3	1.2	1.0	1.0	0.8	0.6	0.5	0.5	0.5	0.5	0.7	0.2	0.3	+0.2 s	-3.8 sss	-91.5	+0.2 s	+116.5
Bath salts (synthetic stimulants)	—	—	—	—	—	0.9	0.9	0.7	0.8	0.5	0.7	—	—	—	—	—	—	—	—	—	—
Tranquilizers	4.5	4.3	4.5	4.4	3.9	3.7	3.5	3.4	3.4	3.5	3.6	3.2	3.1	2.7	1.2	1.5	+0.3	-4.0 sss	-72.9	+0.3	+22.0
OTC Cough/Cold Medicines	5.0	4.7	5.2	4.8	4.4	4.4	4.0	3.2	3.1	3.2	3.0	3.2	2.8	3.7	2.7	3.2	+0.5 s	-2.2 sss	-40.3	+0.5 s	+20.1
Rohypnol	0.8	0.7	0.6	0.8	0.9	0.7	0.6	0.5	0.5	0.7	0.5	0.4	0.5	1.0	1.2	0.3	+0.1	-0.6 sss	-66.9	+0.1	+21.0
GHB[1]	0.7	0.9	0.9	0.8	0.8	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Ketamine †	1.0	1.2	1.3	1.2	1.2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Alcohol	50.2	48.7	48.4	47.4	45.3	44.3	42.8	40.7	39.9	36.7	36.7	36.1	35.9	36.3	30.2	32.2	+2.0 ss	-29.1 sss	-47.5	+2.0 ss	+6.6
Been drunk	29.7	28.1	28.7	27.1	25.9	26.4	25.4	23.6	22.5	20.7	20.4	20.0	19.5	22.1	15.5	15.9	+0.3	-21.0 sss	-57.0	+0.3	+2.1
Flavored alcoholic beverages	40.8	39.0	37.8	35.9	33.7	32.5	31.3	29.4	28.8	25.3	25.9	26.1	24.6	26.5	20.0	22.8	+2.8 ss	-21.7 sss	-48.8	+2.8 ss	+13.8
Alcoholic beverages containing caffeine	—	—	—	—	19.7	18.6	16.6	14.3	13.0	11.2	10.6	10.1	9.2	8.6	7.6	7.7	-0.1	-12.0 sss	-60.8	—	—
Any Vaping	—	—	—	—	—	—	—	—	—	21.5	28.9	31.9	30.7	22.1	23.0	+0.9		-9.0 sss	-28.0	+1.5 s	+6.8
Vaping nicotine	—	—	—	—	—	—	—	—	—	13.9	21.6	27.3	27.1	19.2	19.7	+0.5		-7.6 sss	-27.7	+0.5 sss	+41.6
Vaping marijuana	—	—	—	—	—	—	—	—	—	6.8	9.9	15.6	16.3	11.6	13.6	+2.0 s		-2.7 ss	-16.3	+0.8 sss	+99.6
Vaping just flavoring	—	—	—	—	—	—	—	—	—	17.2	21.9	19.6	15.8	10.0	10.4	+0.5 †		-11.4 sss	-52.2	+0.5	+4.8
JUUL	—	—	—	—	—	—	—	—	—	—	—	23.8	20.6	8.1	—	—		—	—	—	—
Dissolvable tobacco products	—	—	—	—	—	1.4	1.3	1.1	0.9	0.9	1.0	1.0	0.9	0.7	1.1	+0.4 s		-0.3	-19.6	+0.4 s	+56.9
Steroids	1.1	1.1	1.0	0.9	0.9	0.9	0.9	0.9	1.0	0.8	0.8	0.8	1.0	1.1	0.4	0.8	+0.4 sss	-1.2 sss	-58.0	+0.4 sss	+102.7

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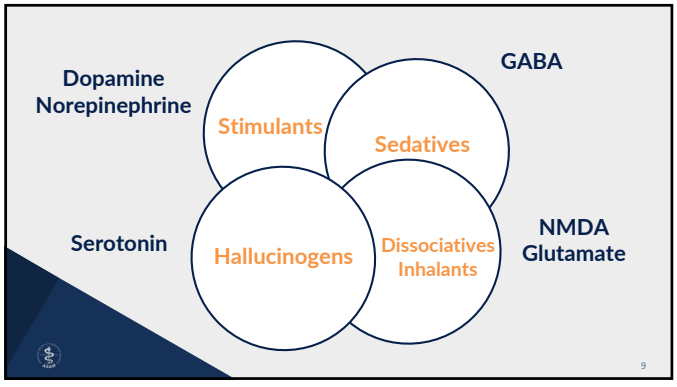

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Hallucinogens

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LSD and Psilocybin are:

A. Serotonin 5HT-2A receptor agonists
B. Dopamine transporter reuptake inhibitors
C. NMDA receptor antagonists
D. Opioid mu-receptor agonists

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LSD and Psilocybin are:

A. Serotonin 5HT-2A receptor agonists
B. Dopamine transporter reuptake inhibitors
C. NMDA receptor antagonists
D. Opioid mu-receptor agonists

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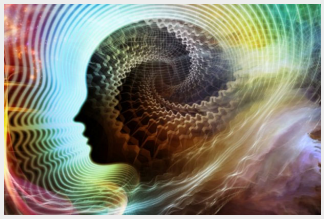
Hallucinogens

- Alterations in cognition, perception, and emotion
- Minimal autonomic side effects or craving



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"Illusionogen"

- Illusions = alteration or enhancement of existing sensory perception
- May be more accurate term
  - Reality testing is generally intact
  - Effect varies greatly with expectations and environment

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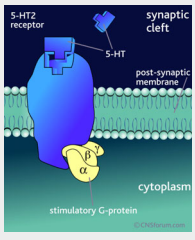
Hallucinogens

Classical Hallucinogens:
- 5HT-2A agonists or partial agonists
- LSD, DMT, psilocybin, mescaline

Empathogens:
- Creates a sense of connection to others
- MDMA and related substances

Others:
- Salvia, Ibogaine



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Effects of Hallucinogens

- Altered shapes and colors
- Synesthesia
- Alterations in mood (can be tension and anxiety)
- Distorted sense of time
- Difficulty expressing thoughts
- Depersonalization
- Dreamlike feeling

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Effects of Hallucinogens
Somatic

- Dizziness
- Weakness
- Tremors
- Nausea
- Drowsiness
- Paresthesias
- Blurred Vision

Most hallucinogens induce rapid tolerance

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DMT

Naturally occurring (plants, toad)

- Inhalation (smoking) or injection (rare)
- Can be taken orally, but requires MAOI
- Rapid onset (<5 min), short duration of action (30 min)

In contrast to other classical hallucinogens, DMT does not induce tolerance in humans.

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Ayahuasca

- Brew containing DMT, MAOIs, and other hallucinogens
- Used ceremonially in some traditional religious ceremonies
- Can cause significant vomiting
- High dose may lead to seizure

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Psilocybin

Pro-drug: Psilocybin → psilocin

- Found as naturally occurring tryptamine in certain varieties of mushrooms
- Inability to discern fantasy from reality
  - Can lead to panic attacks, psychosis
- Duration: 4-6 hours

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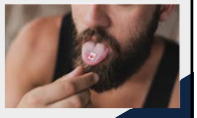
Lysergic Acid Diethylamide (LSD)

- First hallucinogen to be synthesized
- Blotter paper with dried solution of LSD
- Breath mints, sugar cubes, pressed into pills or thin gelatin squares
- Onset: 30-60 min, Peak: 2-4 hours, Duration 8-12 hours



Effects

✓ Altered shapes and colors, heightened sense of hearing
✓ Depersonalization, visual hallucinations, alterations in mood

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Mescaline/Peyote

Buttons from top of peyote cactus
- 6-10 buttons for intoxication

Slow onset (30-60 min)

First hour:
- Minor perceptual changes
- Increased respiratory rate,
- Nausea

Next several hours (5-10):
- Visual illusions/hallucinations
- Synesthesia

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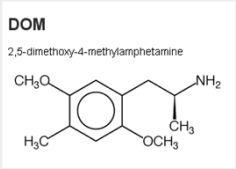
DOM

- Results from structural modification of mescaline-like substances
- Extremely potent
- Used as model hallucinogen in drug discrimination studies



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MDA (*Sass*)

- Powder or pill – swallowed or sniffed
- Produces stimulant, empathogen and hallucinogenic effects
- Increases release of serotonin, norepinephrine and dopamine
- Closely related to MDMA (Ecstazy)
- Is sometimes used as an adulterant and falsely sold as MDMA

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Salvia

- Naturally grows in the US
- Can be ingested or smoked
- Active ingredient: salvinorin A (kappa opioid agonist)
- Changes in visual perception
- Decreased ability to interact with surroundings
- Intense and short-lived
  - Onset < 1 minute, Duration < 30 minutes

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Hallucinogen Intoxication

- Anxiety, "Bad Trip"
- Usually self-limited and returns to baseline without treatment
- Treatment
  - First line: Low stimulus environment, reassurance
  - Second line: Benzo
  - Third line: Antipsychotic

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Summary: Hallucinogen Intoxication

- Clear Sensorium
- Intact Memory
- Hyperalert
- Tolerance
- Intact reality testing
- Visual Hallucinations >> Auditory

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Hallucinogen Persisting Perception Disorder (HPPD)

- Re-experiencing of perceptual symptoms experienced while intoxicated following cessation of use (flashbacks)

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Hallucinogen Persisting Perception Disorder (HPPD)

- Unrelated to dose or number of exposures
- Usually resolves within 1-2 years of last use
- Can be triggered by other substance use

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Dissociatives

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PCP and Ketamine are:

A. Serotonin 5HT-2A receptor agonists
B. Dopamine transporter reuptake inhibitors
C. NMDA receptor antagonists
D. Opioid mu-receptor agonists

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PCP and Ketamine are:

A. Serotonin 5HT-2A receptor agonists
B. Dopamine transporter reuptake inhibitors
C. NMDA receptor antagonists
D. Opioid mu-receptor agonists

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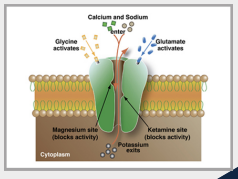
Definition

- NMDA receptor antagonists
  - Glutamate activates NMDA receptors to filter sensory stimuli
  - Dissociatives noncompetitively block NMDA receptors → sensory overflow



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Effects

- Dissociation
- Sensory Isolation
- Mental Distortions
- Increased HR, BP, Temp

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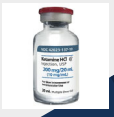
Members of the Class

- PCP
- Ketamine
- Dextromethorphan (DXM)
- Nitrous Oxide



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Phencyclidine (PCP, Angel dust)

- Developed as IV anesthetic
  - No longer FDA-approved
  - Associated with prolonged delirium
  - Risk of seizures or death
- Available as powder, tablets, liquid, and sprayed onto plant leaves and then smoked

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PCP Effects

Confusion, delirium, psychosis

↓

Semi-coma and coma (less common)

↓

Coma with seizures (rare)

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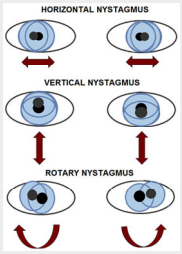
PCP

- PCP Intoxication
  - Nystagmus (rotary, vertical, horizontal)
  - Hyperreflexia
  - HTN
  - Feelings of invulnerability
  - Management of intoxication: low stimulus environment, benzos/antipsychotics as indicated



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Ketamine (K, Special K)

- FDA-approved for general anesthesia and treatment-resistant depression
- Administered as IV, IM or as nasal spray in medical settings
- Misused by inhalation, smoking, or oral administration
- Less potent, shorter-acting than PCP

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Effects of Ketamine

- Analgesia / numbness
- Spacey feeling ("K-hole")
- Amnesia
- Delirium (higher doses)
- Nystagmus (vertical and/or horizontal)
- Urinary complications

40

Dextromethorphan (DXM)

- OTC cough medicines
- FDA-approved for the treatment of depression (combo drug with bupropion)
- Anti-tussive dose: <120mg daily; recommended dose 10-20mg q4hours
- 300-1800mg produces PCP-like effects
  - Euphoria and hallucinations
  - Drowsiness, blurred vision, slurred speech
  - N/V, hypertension, diaphoresis

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Effects of DXM

- In addition to antagonism at NMDA receptor, DXM has significant serotonergic properties
  - ↑ serotonin synthesis and release
  - ↓ reuptake
- Deaths have been reported with large doses (200x dose)
  - CNS & respiratory depression, seizure, arrhythmias

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Therapeutic use of psychedelics

- Research mostly stopped in the 70s with war on drugs
- More recently:
  - Ketamine for depression
  - MDMA for the treatment for PTSD
  - Research currently conducted to use of some hallucinogen and dissociative drugs for the treatment of SUD but nothing approved

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Inhalants

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Many abused inhalants produce an intoxication that most closely resembles which of the following?

A. Alcohol
B. Cocaine
C. Cannabis
D. LSD

45

Many abused inhalants produce an intoxication that most closely resembles which of the following?

A. Alcohol
B. Cocaine
C. Cannabis
D. LSD

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Inhalants

Breathable chemicals that can be self-administered, also known as:

- Whippets
- Poppers
- Huff
- Bang
- Kick
- Sniff

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Terminology

- Sniffing = inhaling from an open container
- Huffing = holding fabric soaked in substance to the nose or mouth and inhaling
- Bagging = concentrating vapors in a bag and inhaling

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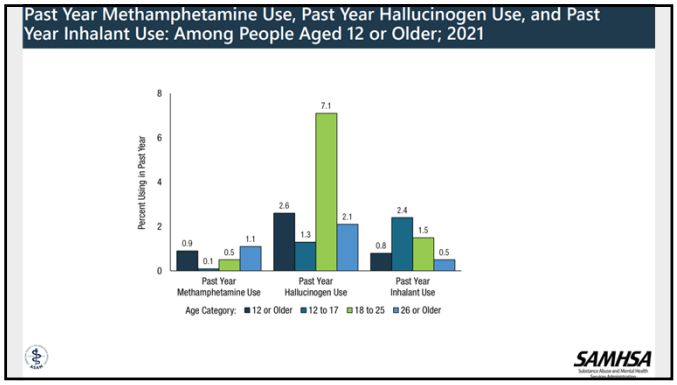

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Source of Inhalants: Products

Air freshener	Lighter fluid	Household cleaners	Gasoline
Hair spray	Mothballs	Nail polish remover	Paint thinner
Markers	Refrigerant	Rubber cement	Spray paint
	Video head cleaner	Whipped cream canisters	

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Abuse Liability

- Number of factors increase abuse potential
  - Free or low cost
  - Readily available
  - Difficult to test for
  - Perceived as low risk
- Inquire about inhalant use, especially when working with adolescent population
- Provide education regarding consequences of use

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Inhalant Pharmacology

- Highly lipophilic
- Rapidly absorbed through the lungs
- Crosses blood-brain barrier
- Accumulates in brain, liver and fatty tissue
- Rapid onset, short duration
- Synergistic effect: alcohol, benzos

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Effects of Inhalants

Acute Effects	Toxic Effects and Overdose
• Euphoria • Disinhibition • Dizziness / lightheadedness • Slurred speech • Ataxia	• Respiratory depression • Arrhythmias • Asphyxia, cardiac arrest and death can occur

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Chronic Effects of Inhalants

CARDIAC arrhythmia cardiomyopathy	DERMATOLOGICAL perioral infection rash
GASTROINTESTINAL hepatorenal failure	MUSCULOSKELETAL Rhabdomyolysis

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Chronic Effects of Inhalants

PULMONARY
emphysema
hypoxia
aspiration pneumonia

GENITOURINARY
glomerulonephritis
hypokalemia

HEMATOPOIETIC
aplastic anemia
leukemia
bone marrow suppression

NEUROLOGICAL
peripheral neuropathy
delirium/dementia
cerebellar atrophy
irreversible white matter changes

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Treatment Considerations

- User may experience prolonged residual effects because chemicals are stored in fatty tissue
- Neurological impairment is often present
  - Talk therapy / group therapy may not be appropriate

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Anabolic-androgenic Steroids

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Which of the following is a side effect of anabolic steroid use?

A. Mania
B. ↓LDL,↑HDL
C. Hypersomnia
D. Weight loss

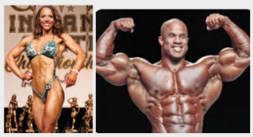
58

Which of the following is a side effect of anabolic steroid use?

A. Mania
B. Depression
C. Hypersomnia
D. Weight loss

59

Anabolic - Androgenic Steroids (AAS)



- Anabolic = skeletal muscle-building
- Androgenic = masculinizing
- Includes testosterone and related synthetic substances
- Enhance performance and/or improve physical appearance
- May be taken at 10-100x the intended dose

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Addiction Liability

- Rarely seek treatment
- Not euphorigenic; no immediate high
- Goal is long-term reward associated with physical changes
- May be seen as socially acceptable or positive
- Often missed by clinicians

61

Epidemiology

- 3 most common populations:
  - Athletes
    - Performance enhancement
  - Aesthetes
    - Improve physical appearance (often adolescents)
  - Fighting Elite
    - Increase aggression and/or job performance (security, law enforcement)

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Terminology

Stacking: use of combinations of multiple drugs at the same time

Cycling: use of steroid combinations for weeks to months with abstinent rest periods before resumption of different steroid or combinations in order to avoid tolerance

Pyramiding: starting with a low dose and gradually increasing the dose until peak levels are achieved a number of weeks before a competition and then tapering so the individual will be drug free when tested

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Medical Indications for AAS

- Hypogonadism
- Hereditary angioedema prophylaxis
- Acquired aplastic anemia and myelofibrosis treatment
- Muscle wasting secondary to starvation, weight loss following extensive surgery, chronic infections (advanced HIV), or severe trauma
- Secondary treatment of bone metastases from breast cancer in postmenopausal women
- Menopause with methyltestosterone combined with estrogen to alleviate symptoms
- Patients on dialysis to increase lean body mass
- Female-to-male gender change

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Steroid Side Effects

Women	Men
• Deepening of voice	• Testicular atrophy
• Facial hair	• Prostatic hypertrophy
• Menstrual changes	• Gynecomastia
• Male-pattern baldness	• Baldness
• Genital hypertrophy	• Infertility

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Steroid Side Effects

Acne	Liver damage	↑LDL, ↓HDL	Complications of Injections
Tendon rupture	Cardiac complications	Sexual dysfunction	Polycythemia

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Psychiatric Side Effects

- Aggressive / violent behavior
- Hypomania or Mania (high doses)
- Paranoia
- Extreme irritability
- Impaired judgment
- Delusions

- Treatment:
- Remove AAS
- Use mood stabilizers or anti-psychotics as needed
- Generally, resolves within 1-2 weeks after cessation

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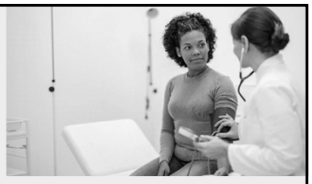
Other Associated Syndromes & Treatment

- Steroid Withdrawal-Associated Depression
  - Can be responsive to SSRIs
- Comorbid SUD, especially opioid
- Body Dysmorphic Disorder / Muscle Dysmorphia

68

In Summary



1. Diverse group of substances with relatively low prevalence, but high abuse liability

2. Varied but significant effects from use and misuse, including long-term consequences

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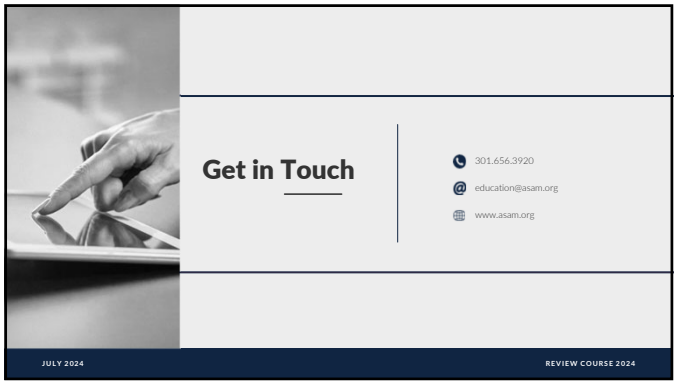
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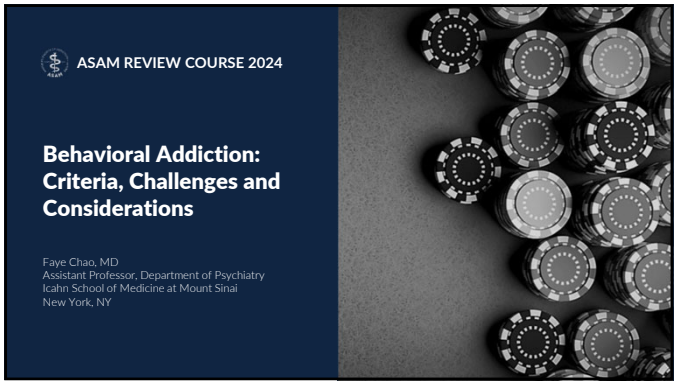
ASAM REVIEW COURSE 2024
Behavioral Addiction: Criteria, Challenges and Considerations
Faye Chao, MD
Assistant Professor, Department of Psychiatry
Icahn School of Medicine at Mount Sinai
New York, NY

1


Financial Disclosure
Faye Chao, MD
• No relevant disclosures
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2


LEARNING OBJECTIVE
Describe the theoretical framework for behavioral addiction, criteria for diagnosis and evidence-based treatment strategies.

3

Presentation Outline

- History
- Impulsivity/Compulsivity Spectrum
- Gambling Disorder
- Internet Gaming Disorder

4

History

- Classified as:
  - Obsessive-compulsive spectrum disorders
  - Impulse-control disorders
  - By-products of mood disorders
  - Now: substance-related and addictive disorder

5

DSM-5

- Substance-related and Addictive Disorders
  - Gambling disorder
- Conditions for Further Study
  - Internet gaming disorder
- Not included at all ("insufficient evidence")
  - Other internet or technology-related behaviors (social media, TV, etc.)
  - Sex, exercise, shopping, food, etc.

Potenza, M: Non-substance addictive behaviors in the context of DSM-5. Addict Behav 2014.

6

Essential Features

- Failure to resist an . . .
  - impulse
  - drive
  - temptation

. . . to perform an act that is harmful to oneself or others.

Potenza, M: Non-substance addictive behaviors in the context of DSM-5. Addict Behav 2014.

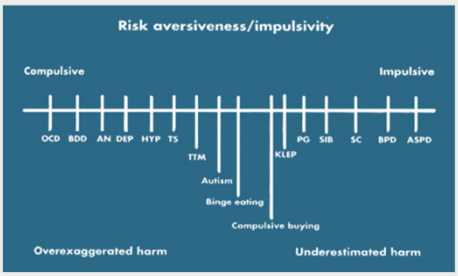
7

Impulsivity vs. Compulsivity

- Both show inability to refrain from repetitive behaviors.
- Impulsivity is driven by an effort to obtain arousal and gratification.
- Compulsivity is driven by an effort to reduce anxiety.

8

Dimensional Approach



Adapted from: Hollander E, Clinical Manual of Impulse-Control Disorders, 2006.

9

Gender Differences

Women	Men
• Anorexia	• Body Dysmorphic
• Binge Eating	• Sexual Compulsion
• Kleptomania	• Pyromania
• Compulsive Buying	• Gambling
• Trichotillomania	• Problematic gaming

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Gambling Disorder

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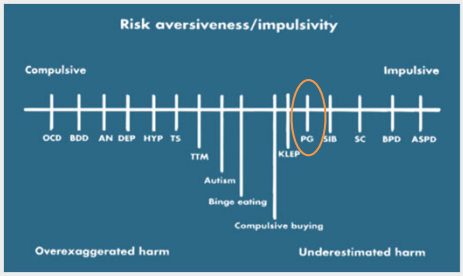
Gambling Disorder



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Gambling Disorder

DSM-IV-TR	DSM-5
Pathological Gambling as Impulse-Control Disorder	Gambling Disorder as Substance-Related and Addictive Disorder

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Washington, DC: American Psychiatric Association, 2013.

13

Substance-Related and Addictive Disorder

Alcohol	Caffeine	Cannabis
Hallucinogen	Inhalant	Opioid
Sedative	Stimulant	Tobacco
	Gambling Disorder	

14

Clinical Presentation for GD

- *Five DSM-5 Addiction Criteria*

Plus

- "Chases" one's losses
- Lies to conceal the extent of their gambling
- Relies on others for money
- Gambles when feeling distressed (Specifiers: episodic or persistent)

Phases

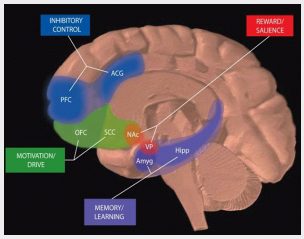
- Winning Phase
- Loss Phase
- Desperation Phase
- Hopelessness Phase

Blanco C, Cohen O, Luján JJ, et al: Pathological gambling and substance use disorders, in Substance Dependence and Co-Occurring Psychiatric Disorders: Best Practices for Diagnosis and Treatment. Edited by Nunes EV, Selzer J, Levounis P, Davies CA. New York, Civic Research Institute, 2010

15

Neurobiology of GD

- Gambling affects:
  - DA
  - NE
  - Cortisol
  - 5HT
- Neurobiological similarities with substance use disorders



16

Epidemiology

- US Gambling Statistics:
  - $110 billion commercial gaming revenue in 2023
    - $14.4 billion in revenue from gambling taxes
  - 49% of residents have gambled in the past year
  - ~0.5% of the adult population meets criteria for GD


State forecasts dip, stagnation of casino tax aid

Projections show state will no longer be able to count on more money from slots, table game for schools

By Lauren Stanforth Published 12:32 pm EDT, Wednesday, March 13, 2019

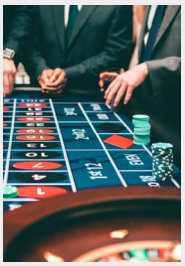
www.americangaming.org;

Stefanovics E, Potenza M: Update on Gambling Disorder. Psych Clin of N Am 45(3): 483-502, 2022.

17

Epidemiology

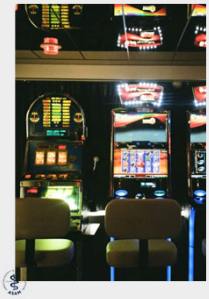
- High rate of co-occurrence with other psychiatric disorders
  - 96% of individuals with GD have one or more co-occurring psychiatric disorders
  - 64% have 3 or more
  - Substance use disorders, mood disorders, anxiety disorders, and impulse control disorders are most common
  - Co-occurring disorders may help guide treatment



Kessler RC, et al: DSM-IV pathological gambling in the National Comorbidity Survey Replication. Psych Med 38(9): 1351-1360, 2008.

18

What's Available in Your State?

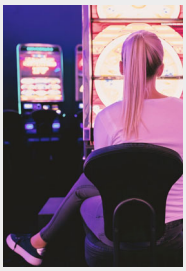


- Opportunities in US:
  - Land-based casinos
  - Internet gambling
  - Nonregulated gambling
  - Online fantasy sports
- More available and accessible now than ever before

19

Screening Tools

- The Lie/Bet Test
  - Have you ever felt the need to bet more and more money?
  - Have you ever had to lie to people important to you about how much you gambled?
    - *99% sensitivity, 91% specificity*



Johnson EE, Hamer R, Nora RM, et al: The lie/bet questionnaire for screening pathological gamblers. Psychological Reports 80:83-88, 1997.

20

Gambling Cognitive Distortions

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21

The Odds are Never in Your Favor

- "The house always wins"
- House edge is the ratio of the average loss to the initial bet, essentially the average gross profit the casino expects to make from each game
  - Keno – house edge 25-29%
  - Any craps – 11.11%
  - Ultimate Texas Hold 'Em – 2.19%
  - Blackjack (liberal Vegas rules) – 0.28%
- The longer you play, the greater the odds are that the result of your play will match up with the house edge

www.wizardofodds.com/gambling/house-edge

22

Interpretative Biases

- Attributing wins to skill, losses to flukes
- Wrongly believing that a series of losses increases the chance of subsequent win
- Near misses ("*I was only one number away!*")

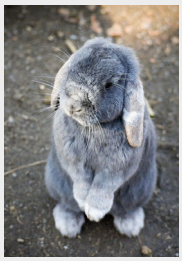
23

The "Sunk-Cost" Effect

24

Superstitious Beliefs

- Believing in:
  - Good luck objects (like animal parts)
  - Behaviors
  - Routines



Gaboury A, Ladouceur R: Erroneous perceptions and gambling. Journal of Social Behaviors and Personality 4:411-420, 1989.

25

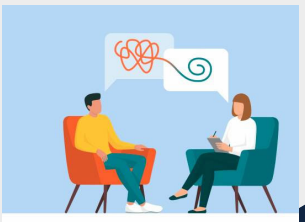
Selective Memory

- Remembering wins while ignoring losses
- Totaling wins without correcting for amounts lost

26

Treatment

- Evidence-based therapies
  - CBT, Motivational Interviewing, Imaginal Desensitization all appear efficacious
- NO FDA-approved medication for GD
  - opioid antagonists, SSRIs, and lithium show some positive effect
- Mutual-help groups (Gamblers Anonymous)



27

Treatment: Opioid Antagonists

- Naltrexone and Nalmefene
- GD conceptualized as an impulsive disorder
- Block opioid receptors, decrease dopamine function, and reduce "reward cravings"

28

Treatment: Opioid Antagonists

- Reductions in gambling outcomes and urges to gamble with daily naltrexone
- Results for "as-needed" use of naltrexone more mixed
- Naltrexone 50 mg PO daily seems to be as effective as higher doses though some studies dose up to 250 mg PO daily
- Appears to work best in patients with either a personal or family history of alcohol use disorder

Grant JE, Kim SW, Hollander E, et al: Predicting treatment response to opiate antagonists and placebo in the treatment of pathological gambling. Psychopharmacol 200:521-527, 2008.
Grant JE, Potenza MN: Pathological Gambling: A Clinical Guide to Treatment. Washington, DC, American Psychiatric Publishing, 2004.
Ward S, Smith N, Bowden-Jones H: The use of naltrexone in pathological and problem gambling: A UK case series. J of Behav Addictions 7(3): 827-833, 2018

29

Treatment: Lithium

- Mood stabilizer
- GD conceptualized as an impulsive disorder
- Shown to decrease both urges to gamble and gambling behavior in people with co-morbid bipolar-spectrum illness
- May also have some efficacy for those with GD but no bipolar illness

Pallanti S, Quercioli L, Sood E, Hollander E: Lithium and valproate treatment of pathological gambling: A randomized single-blind study. J Clin Psych.63: 559-564, 2002.
Hollander E et al: Does sustained-release lithium reduce impulsive gambling and affective instability versus placebo in pathological gamblers with bipolar spectrum disorders? Am J Psychiatry 162(1): 137-145, 2005.

30

Treatment: SSRIs

- Frequently investigated for compulsive disorders (e.g. OCD, hoarding, trichotillomania)
- Gambling conceptualized as a compulsive disorder
- Block serotonin reuptake, increase serotonin function, used for treatment of mood and anxiety disorders

Hollander E, Sood E, Pallanti S, et al: Pharmacological treatments of pathological gambling. Journal of Gambling Studies 21:101-110, 2005.

31

Treatment: SSRIs

- Fluvoxamine, paroxetine, escitalopram most studied
- Unclear if they help decrease urges but may reduce "self-medication" behavior
- May require higher-than-usual doses
- Work best with co-occurring depression or anxiety

Grant JE, Kim SW. Medication management of pathological gambling. Minn Med. 2006 Sep;89(9):44-8.

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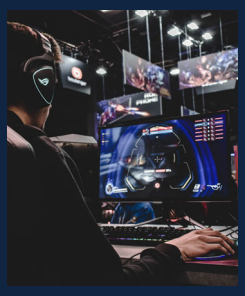

Internet Gaming Disorder

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The Evolution of IGD

DSM-IV-TR	DSM-5
Not Found	→ Conditions for Further Study

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Washington, DC: American Psychiatric Association, 2013.

34

Proposed Criteria

- Seven DSM-5 Addiction Criteria, plus
  - Has deceived family, therapists or others about the amount of gaming
  - Uses games to escape/relieve negative mood
    - (*Excludes Internet gambling, recreational/social Internet use, sexual websites*)

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Washington, DC: American Psychiatric Association, 2013.

35

ICD-11 Criteria

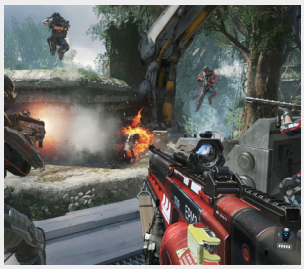
- A pattern of persistent or recurrent gaming behavior ('digital gaming' or 'video-gaming'), which may be online (i.e., over the internet) or offline, manifested by:
  - 1) impaired control over gaming (e.g., onset, frequency, intensity, duration, termination, context)
  - 2) increasing priority given to gaming to the extent that gaming takes precedence over other life interests and daily activities
  - 3) continuation or escalation of gaming despite the occurrence of negative consequences.
  - The behavior pattern is of sufficient severity to result in significant impairment in personal, family, social, educational, occupational or other important areas of functioning.
- Modifiers are "predominantly online" and "predominantly offline."
- "Hazardous gaming" also exists as a diagnosis

World Health Organization: International Statistical Classification of Diseases and Related Health Problems, 11th Edition. Retrieved from https://icd.who.int/, 2019.

36

Who's Playing?

- ESA (Entertainment Software Association) 2022 survey
  - 215.5 million Americans play video games
  - 83% of gamers play with others on-line or in person at least weekly (up from 77% in 2021 and 65% in 2020)
  - Players spend an average of 13 hours a week playing video games and 41% of that time is spent playing with others



2022 Essential Facts about the Computer and Video Game Industry. Entertainment Software Association. https://www.theesa.com/. Published June 2022. Accessed April 2023.

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The Average Player

- Is white (71%)
- May be of either gender
  - Gender breakdown: 52% identify as male, 48% identify as female (nearly 1% identify as "other")
- Is age 33
  - 76% of players are over 18 years old
  - 27% of those who play video games are over the age of 45.

2022 Essential Facts about the Computer and Video Game Industry. Entertainment Software Association. https://www.theesa.com/. Published June 2022. Accessed April 2023.

38

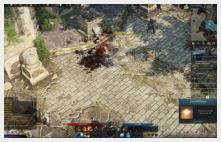
Clinical Presentation of IGD

- Has more to do with life impact than amount of time played (though this is controversial)
- Often, but not always, occurs in patients with other co-morbidities (especially SUDs and mood disorders)
- Prevalence: Global prevalence appears to be ~2-3% and males 2.5 times as likely to be diagnosed
  - More common in Asian countries esp. China, Taiwan, South Korea

39

Problematic Play

- Risk factors include:
  - Personality traits (neuroticism, aggression and hostility, and sensation seeking)
  - Motivations for play (escapism, control, avoiding dissatisfaction)
  - Structural game characteristics (online games, ability to customize virtual game persona, game reinforcement structure).
    - MMORPGs a particular area of interest



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Imaging studies

- Executive control networks are altered
  - Internet gaming addicts showed lower resting-state functional connectivity between VTA and mOFC (Han 2018)
  - Impaired task performance in Stroop test (Dong 2015)
- Decreased gray matter volume in brain regions involved in self-control and motivation in patients with gaming disorder (Yao 2017)

41

Imaging studies

- Several studies show increased activity in the ACC and mOFC in response to gaming cues in subjects with gaming disorder (Han 2010, Ko 2009)

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Bottom Line

- Imaging studies suggest that the brains of people with problematic play are similar to those of people with substance use disorders
  - Gaming and gaming-related cues trigger activation of reward pathway
  - Gaming cues acquire increased salience over other activities
- Clinically this may manifest in other impulse control problems
- Problematic play is frequently co-morbid with other psychiatric disorders including mood disorders and substance use disorders

43

Treatment

- Therapy modalities consist mainly of CBT, behavior therapy, and 12-Step approaches
- Psychopharmacologic management is off-label and has poor to middling evidence base for efficacy
  - Potential agents mainly selected from the same medications that are researched for SUDs
- Treatment centers initially arose in Asia and then Europe but now exist in North America as well

44

In Summary

- Behavioral addictions fall within an impulsivity-compulsivity spectrum of illness.
- DSM-5 only recognizes one disorder officially though one other is included as a condition for further study.
- Psychosocial treatments work.
- Medications have fallen short so far.

45

Which of the following behavioral addictions is included in the DSM-5 under "Substance-Related and Addictive Disorders"?

A. Internet Use Disorder
B. Gambling Disorder
C. Internet Gaming Disorder
D. Hypersexual Disorder

46

Research shows that gambling disorder involves the strongest effect on which of the following neurotransmitters?

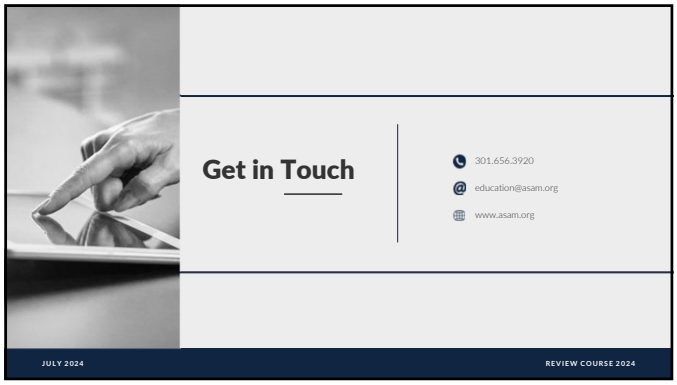
A. Dopamine
B. GABA
C. Acetylcholine
D. Serotonin

47

Which of the following medications has some evidence for the treatment of gambling disorder?

A. Memantine
B. Naltrexone
C. Aripiprazole
D. Clonidine

48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Genetics and Gender: Impacts on Diagnosis and Care

Leslie Hayes, MD
Family Physician and Addiction Medicine
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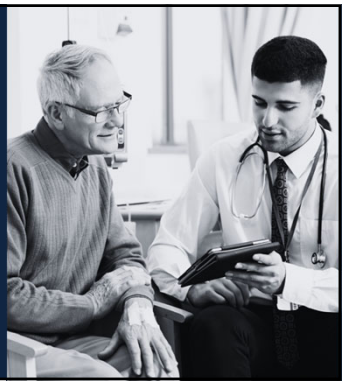

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Financial Disclosure

Leslie Hayes, MD

- No relevant disclosures

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2

LEARNING OBJECTIVE

Describe genetic and gender differences impacting the assessment and treatment of substance use disorder.

3

Presentation Outline

- Genetics and substance use disorder
- Gender differences in substance use disorder

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Genetics and Substance Use Disorder

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Three ways that genetics influences substance use disorder

- Direct effect of genes on susceptibility to substance use disorder
- Pharmacogenetics affects how drugs affect individuals differently
- Epigenetics affects which genes are expressed

6

Twin Studies

- Both the Swedish and Vietnam twin studies showed significantly higher concordance rates for substance use disorder in monozygotic twins than in dizygotic twins.[1,2]

[1]Gelernter et Kranzler. Chapter 2. Genetics of Addiction in Galanter et al. Textbook of Substance Abuse Treatment. The American Psychiatric Publishing 2015 pp. 26-45
[2]Bevilacqua and Goldman. Genes and Addictions. Clin Pharmacol Ther. 2009 April; 85(4) pp 359-361

7

Genetics of substance use disorder

- SUD is likely polygenic. Multiple genes, each having a small effect contribute to risk of developing SUD.[1]
- Environment has stronger influence on initiation, whereas genetic factors are more important in progression and development of SUD.[2]

1. Prom-Wormley EC, Ebejer J, Dick DM, Bowers MS. The genetic epidemiology of substance use disorder: A review. Drug Alcohol Depend. 2017 Nov 1;180:241-259. doi: 10.1016/j.drugalcdep.2017.06.040. Epub 2017 Aug 1. PMID: 28938182; PMCID: PMC5911369
2. Bevilacqua and Goldman. Genes and Addictions. Clin Pharmacol Ther. 2009 APril; 85(4) pp 359-361

8

Pharmacogenetics

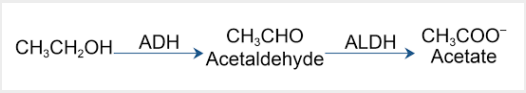
- Pharmacogenetics can be further divided into two different categories:
  - Pharmacokinetics: how the body metabolizes the drug
  - Pharmacodynamics: how the drug affects the body

Bugada D, Lorini LF, Fumagalli R, Allegri M. Genetics and Opioids: Towards More Appropriate Prescription in Cancer Pain. Cancers (Basel). 2020 Jul 18;12(7):1951. doi: 10.3390/cancers12071951. PMID: 32708424; PMCID: PMC7409218

9

Pharmacokinetics

- Metabolism of alcohol



https://www.niaaa.nih.gov/publications/alcohol-metabolism accessed 4/14/2024

10

Pharmacokinetics

- Both the ADH1 B2-His47 ARG allele of Alcohol Dehydrogenase 1B and ALDH-Glu487 Lys allele of Aldehyde Dehydrogenase 2 can cause flushing, nausea, and headache with alcohol, due to accumulation of acetaldehyde.[1]
  - More common in person of South Asian descent and those of Jewish ancestry.
  - Homozygotes nearly completely protected from alcohol use disorder.

[1]Zajicek and Karan. Pharmacokinetic and Pharmacodynamic Principles in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019. p. 97-98

11

Pharmacokinetics

- Opioids are mainly metabolized by the cytochrome P450 (CYP450) or by UDP-glucuronosyl-transferase (UGT) in the liver.
- Some opioids are pro-drugs and need to be converted into an active metabolite to be active. (Codeine to morphine, oxycodone to oxymorphone, hydrocodone to hydromorphone, tramadol to P-desmethyl-tramadol)
- Other opioids are already active and will be converted to inactive metabolites. (morphine, methadone)

Bugada D, Lorini LF, Fumagalli R, Allegri M. Genetics and Opioids: Towards More Appropriate Prescription in Cancer Pain. Cancers (Basel). 2020 Jul 18;12(7):1951. doi: 10.3390/cancers12071951. PMID: 32708424; PMCID: PMC7409018.

12

Pharmacokinetics

- CYP2D6 is characterized by extreme variability.
  - 4 phenotype groups: ultra-rapid metabolizer (UM), normal metabolizer (NM), intermediate metabolizer (IM), and poor metabolizer (PM)
- UM can have severe or even lethal effects when treated with pro-drugs, whereas poor metabolizers experience decreased analgesia after prodrug administration

Bugada D, Lorini LF, Fumagalli R, Allegri M. Genetics and Opioids: Towards More Appropriate Prescription in Cancer Pain. Cancers (Basel). 2020 Jul 18;12(7):1951. doi: 10.3390/cancers12071951. PMID: 32708424; PMCID: PMC7409018.

13

Pharmacogenetics of Medication Therapy of OUD

- Methadone is metabolized in part by CYP2D6.
  - Ultrarapid metabolizers do not do well on methadone. [1]

[1]*Haile et al. Pharmacogenetic Treatments for Drug Addiction: Alcohol and Opiates, The American Journal of Drug and Alcohol Abuse, 34:4, 355-381*

14

Pharmacodynamics

- The mu-1 opioid receptor (OPRM1) gene codes for the mu opioid receptor.
  - The G allele of the OPRM1 is related to a lower pain threshold and higher opioid consumption in the post-op period.
- The catchol-O-methyltransferase (COMT) gene regulates the expression of the mu-opioid receptor.
  - Some studies have suggested it may be involved with response to morphine.

Bugada D, Lorini LF, Fumagalli R, Allegri M. Genetics and Opioids: Towards More Appropriate Prescription in Cancer Pain. Cancers (Basel). 2020 Jul 18;12(7):1951. doi: 10.3390/cancers12071951. PMID: 32708424; PMCID: PMC7409018.

15

Epigenetics

- Epigenetics is the study of epigenomes which are markers that turn genes on or off or express them more or less strongly.
  - Changes to the epigenomes can be passed down anywhere from 2-12 generations.
  - Environmental factors like diet, stress, and prenatal drug use can cause epigenetic changes which predispose to substance use disorder.

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FDA Approves First Test to Help Identify Elevated Risk of Developing Opioid Use Disorder

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FOR IMMEDIATE RELEASE
Dec. 19, 2023

The following is attributed to Jeff Shuren, M.D., J.D., director of the FDA's Center for Devices and Radiological Health

Today, the U.S. Food and Drug Administration approved the first test that uses DNA in assessing whether certain individuals may have an elevated risk of developing opioid use disorder (OUD). As part of a clinical evaluation, the AutoGenomics, Inc. AvertD test is intended to be used prior to first exposure to oral opioid pain medications in patients being considered for a 4-30 day prescription for the treatment of acute pain, such as in patients scheduled to undergo a planned surgical procedure.

The AvertD test, a prescription-use only genetic laboratory test for patients 18 years and older, is to be used only with patients who consent to the test and have no prior use of oral opioid analgesics. The test is administered by a health care provider by swabbing the cheek of a patient to collect a DNA sample that will be used to determine if a patient has a combination of genetic variants that may be associated with an elevated risk of developing OUD. This information should be used as part of a complete clinical evaluation and risk assessment; it should not be used alone to make treatment decisions. The test is not intended to be used in patients being treated for chronic pain. AvertD may help patients

REVIEW COURSE 2024

17

Gender Differences in Substance Use Disorder

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18

A word about terminology

- None of the studies I found looking at gender and substance use disorder specified cis- or trans-gender.
- I have generally used the terms (female/male or woman/man) the study did.

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Gender Differences

- General differences
- Sex hormones and SUD
- Special health risks for women with alcohol
- LGBTQ community and alcohol
- Incarceration
- Sex work
- Violence
- Treatment

20

Gender differences and substance use disorder

- Men are more likely than women to use almost all types of illicit drugs.[1,2]
  - Women use prescription drugs at greater rates than men and have higher rates of prescription drug use disorder.[2]
  - Otherwise, men have higher rates of drug use disorder.[2]
- Men have higher rates of alcohol use, including binge drinking, than women1,2, except for teens, where rates were similar until recently.
- Men are more likely to engage in riskier types of drug use that elevate mortality, including taking greater amounts of drugs, using more lethal drugs, and sourcing drugs from riskier sources and unvetted dealers.[3]

1. *Substance Use in Women Research Report Sex and Gender Differences in Substance Use https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/sex-gender-differences-in-substance-use Accessed 2/18/2021*
2. *Center for Behavioral Health Statistics and Quality. (2023). Results from the 2022 National Survey on Drug Use and Health: Detailed tables. Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/report/2022-nsduh-detailed-tables*
3. *J. Ho. Cycles of Gender Convergence and Divergence in Drug Overdose Mortality. Population And Development Review 46(3): 443–470 (September 2020) 4*

21

Most recent study of teens showed higher rate of drug and alcohol use among girls

Behavior/Substance – current use	Male 2019 (%)	Male 2021 (%)	Female 2019 (%)	Female 2021 (%)
Alcohol	26.4	18.8	31.9	26.8
Marijuana	22.5	13.6	20.8	17.8
Binge drinking	12.7	9.0	14.6	12.2
Prescription opioid misuse	6.1	4.0	8.3	8.0

Hoots BE, Li J, Hertz MF, et al. Alcohol and Other Substance Use Before and During the COVID-19 Pandemic Among High School Students — Youth Risk Behavior Survey, United States, 2021. MMWR Suppl 2023;72(Suppl-1):84–92. DOI: http://dx.doi.org/10.15585/mmwr.su7201a10

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Gender differences and substance use disorder

- Women are more likely to be introduced to injection drug use by their male sexual partner, whereas men are more likely to be injected by a friend. [1]

[1] *Greenfield et al. Substance Abuse in Women. Psychiatr Clin Nort Am. 2010 June; 33(2): 339-355*

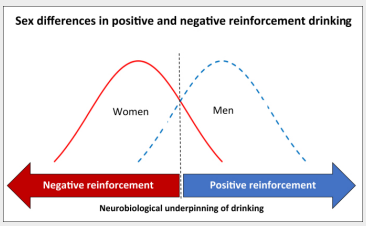
23

Gender differences and substance use disorder

- Women are more likely to use prescription opioids to self-medicate for anxiety or stress. [1] Men are more likely to use prescription opioids for experimentation or to get high. [2]
- Women are more likely to drink in response to stress and negative emotions whereas men are more like to drink to enhance positive emotions or conform to a group.[3]

[1] *Final Report: Opioid Use, Misuse, and Overdose in Women.. Office on Women's Health. July 19, 2017*
[2] *Greenfield et al. Substance Abuse in Women. Psychiatr Clin Nort Am. 2010 June; 33(2): 339-355*
[3] *Ibid*

24



Peltier MR, Verplaetse TL, Mineur YS, Petrakis IL, Cosgrove KP, Picciotto MR, McKee SA. Sex differences in stress-related alcohol use. Neurobiol Stress. 2019 Feb 8;10:100149. doi: 10.1016/j.ynstr.2019.100149. PMID: 30949562; PMCID: PMC6430771.

25

Special health risks for women from alcohol

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26

Women and alcohol

- Women get drunker faster than men:
  - Decreased body weight[1]
  - Decreased alcohol dehydrogenase[2]
  - Decreased volume of water compartment distribution[3]

[1] Zweben. Special Issues in Treatment: Women in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019 p. 529
[2] Ibid
[3] Ibid

27

Health risks for women with substance use disorder

- Women have "telescoped course" for alcohol use disorder. [1]
  - They develop pathologic effects of alcohol more rapidly.
- Women have a 50-100% higher death rate from alcohol use disorder, including deaths from suicide, alcohol-related accidents, heart disease, stroke, and liver damage.[2]

[1] Zweben. Special Issues in Treatment: Women in Miller et al. The ASAM Principles of Addiction Medicine, Sixth Edition. Wolters Kluwer 2019 p. 529

[2] Substance Use in Women Research Report Sex and Gender Differences in Substance Use https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/sex-gender-differences-in-substance-use Accessed 2/18/2021

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CDC guidelines for risky drinking[1]

- Excessive drinking (or risky drinking or at risk drinking) is defined as the following:
  - Binge drinking, the most common form of excessive drinking, is defined as consuming
    - For women, 4 or more drinks during a single occasion.
    - For men, 5 or more drinks during a single occasion.
  - Heavy drinking is defined as consuming
    - For women, or men over 65, 8 or more drinks per week.
    - For men, 15 or more drinks per week.
- Most people who drink excessively are not alcoholics or alcohol dependent.
- 2020 commentary by Lowik et al in the Journal of Addiction Medicine discussed whether adjustments are needed for these guidelines.[2]

[1] https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm accessed 2/17/2021

[2] Lowik et al. **Where is the Science? A Critical Interrogation of How Sex and Gender are Used to Inform Low-Risk Alcohol Use Guidelines.** J. Addict Med Vol 14, No. 5, Sept/Oct 2020

29

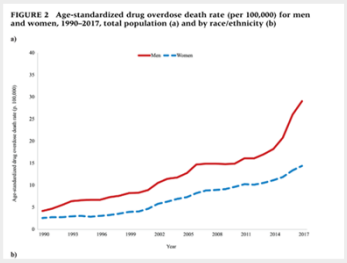
Men die at higher rates than women from alcohol

- Despite the higher risk for alcohol-related problems for women if they do drink, men still have much higher death rates from alcohol because they drink at higher rates
- A study from 2023 of alcohol-related deaths in the United states showed that **the mortality burden was higher among male individuals than female individuals, with male individuals being 2.88 (95% CI, 2.86-2.89) times more likely to die compared with female individuals.**

Karaye IM, Maleki N, Hassan N, Yunusa I. Trends in Alcohol-Related Deaths by Sex in the US, 1999-2020. JAMA Netw Open. 2023;6(7):e2326346. doi:10.1001/jamanetworkopen.2023.26346

30

Overdose death rate is higher in men



J. Ho. Cycles of Gender Convergence and Divergence in Drug Overdose Mortality. Population And Development Review 46(3): 443–470 (September 2020) 4

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Sex hormones and substance use disorder

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Menstrual cycle and substance use disorder

- Women who attempt to quit smoking during the luteal phase of their menstrual cycle had more favorable outcomes than women who attempted to quit during the follicular phase.[1]
- Progesterone may protect against cigarette smoking and nicotine addiction, whereas estradiol may underlie enhanced vulnerability.[2]
  - When progesterone levels are high, nicotine self-administration is decreased.[2]

1. *Allen et al. Menstrual phase effects on smoking relapse. Addiction. Volume 103. Issue 5. April 14, 2008.*
2. *Wetherill RR, Franklin TR, Allen SS. Ovarian hormones, menstrual cycle phase, and smoking: a review with recommendations for future studies. Curr Addict Rep. 2016 Mar 1;3(1):1-8. doi: 10.1007/s40429-016-0093-z. Epub 2016 Feb 1. PMID: 27134810; PMCID: PMC4847745*

33

Testosterone and substance use

- Testosterone levels in men are suppressed by both alcohol[1] and opioids.[2]

[1] Malabanan and Jack. Endocrine and Reproductive Disorders Related to Alcohol and Other Drug Use. The ASAM Principles of Addiction Medicine. Sixth Edition. Wolters Kluwer 2019 p. 1298

[2] Bawor et al. Testosterone suppression in opioid users: A systematic review and meta-analysis. Drug and Alcohol Dependence 149 (2015) 1–9

34

LGBTQ Persons and Substance Use

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LGBTQ People have higher rates of SUD

- Data from the 2020 National Survey on Drug Use and Health (NSDUH) suggest sexual minority adults report increased consumption and substance use disorders compared to heterosexual adults.
  - (In this survey, sexual minority adults include individuals who describe themselves as lesbian, gay, or bisexual.)
- Sexual minority adults had roughly double the rate of marijuana use, misuse of opioids, and alcohol use disorder compared to heterosexual adults.

https://nida.nih.gov/research-topics/substance-use-suds-in-lgbtq-populations Accessed 11/12/2023

36

Reasons for increased substance use and misuse among LBGTQ persons

- High levels of stress
- Lack of cultural competency and health care discrimination in the medical community
- Targeted marketing efforts by alcohol and tobacco companies
- Discrimination in employment
- Discrimination in housing

https://www.americanprogress.org/article/why-the-gay-and-transgender-population-experiences-higher-rates-of-substance-use/ Accessed 11/12/2023

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Gender Differences in Incarceration and Substance Use Disorder

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38

Incarceration and gender differences

- Men are far more likely than women to be incarcerated than women. 126/100,000 women were incarcerated in 2010 vs 1,352/100,000 men.[1]

Wagner, P. Incarceration is not an equal opportunity punishment. Updated August 28, 2012 on https://www.prisonpolicy.org/articles/notequal.html Accessed 11/15/19

39

Incarceration and substance use disorder

- An estimated 65% percent of the United States prison population has an active SUD.
- Another 20% percent did not meet the official criteria for an SUD but were under the influence of drugs or alcohol at the time of their crime.

https://nida.nih.gov/publications/drugfacts/criminal-justice Accessed 8/6/2023

40

Incarceration and substance use disorder

- A population-based study showed that 22% of patients with substance use disorder had been incarcerated before. 10.6% of the general population reported a history of incarceration.
- Men with SUD were 2.61 times as likely to have a history of incarceration as women with SUD.

Tsai, J., Gu, X. Utilization of addiction treatment among U.S. adults with history of incarceration and substance use disorders. Addict Sci Clin Pract **14,** 9 (2019).

41

Incarceration and gender differences

- Blacks and Latinos are far more likely to be incarcerated for drug law violations than whites, even though rates of drug use and drug selling are similar.[1]

http://www.drugpolicy.org/resource/drug-war-mass-incarceration-and-race-englishspanish Accessed 11/15/13

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Sex Work and Substance Use Disorder

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43

There is a significant correlation between sex work and substance use disorder

- A 2021 meta-analysis looked at 86 studies in 46 countries reported lifetime drug use among female sex workers (32 studies from 20 countries), and pooled prevalence in this sub-group was 29% (95% CI 24–34%).[1]
  - There was insufficient data for estimates for male and transgender sex workers.
- A 2008 cross-sectional, secondary data analysis of 1606 women and 3001 men entering substance use treatment in the United States found the incidence of sex work was 50.8% of women and 18.5% of men reported prostitution in their lifetime. 41.4% of women and 11.2% of men reported prostitution in the past year[2]

1. *Iversen J, Long P, Lutnick A, et al. Patterns and Epidemiology of Illicit Drug Use Among Sex Workers Globally: A Systematic Review. 2021 Apr 29. In: Goldenberg SM, Morgan Thomas R, Forbes A, et al., editors. Sex Work, Health, and Human Rights: Global Inequities, Challenges, and Opportunities for Action [Internet]. Cham (CH): Springer; 2021. Chapter 6. Available from: https://www.ncbi.nlm.nih.gov/books/NBK585687/ doi: 10.1007/978-3-030-64171-9_6*
2. *Burnette ML, Lucas E, Ilgen M, Frayne SM, Mayo J, Weitlauf JC. Prevalence and Health Correlates of Prostitution Among Patients Entering Treatment for Substance Use Disorders. Arch Gen Psychiatry. 2008;65(3):337–344. doi:10.1001/archpsyc.65.3.337*

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There is a significant correlation between sex work and substance use disorder

- It is often assumed that women who use drugs and participate in sex work began sex work to pay for drugs, but it is often the other way around. Many began using drugs to cope with the trauma of sex work.[1]
- A study in Chicago that interviewed 222 women doing sex work found that almost one-fourth of women in drug houses being raped more than 10 times.[2]
- Sex workers who are sexually assaulted often do not get good support from the medical system, the legal system, or family and friends because of their sex work.[3]

1. *https://www.caase.org/mental-health-impacts-of-sex-trade/ accessed 12/9/2023*
2. *Raphael J. and Shapiro D. Sisters speak out: the lives and needs of prostituted women in Chicago a research study Center for Impact Research. www.impactresearch.org August 2002*
3. *Natalie West with Tina Horn. We Too. Essays on Sex Work and Survival. Feminist Press. 2021*

45

Violence and Substance Use Disorder

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46

Women, violence, and SUD

- Girls with a history of childhood sexual abuse are 3 times as likely to develop an addictive disorder as girls without that history.[1]
- One study showed lifetime intimate partner violence victimization was reported by 46.7% of women and 9.5% of men entering SUD treatment.

1. *Zweben. Special Issues in Treatment: Women in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019 p. 532*
2. *Schneider et al. Violence and Victims, Volume 24, Number 6, 2009 744 © 2009 Prevalence and Correlates of Intimate Partner Violence Victimization Among Men and Women Entering Substance Use Disorder Treatment.*

47

Treatment Differences for SUD by Gender

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48

Treatment Differences

- Women have been found to do better in treatment programs that reduce barriers to treatment or address women's needs.
  - Provision of childcare
  - Prenatal care
  - Treatment for co-occurring mental health problems
  - Comprehensive approach to treatment
  - Supplemental services that address women-focused topics

McCrady BS, Epstein EE, Fokas KF. Treatment Interventions for Women With Alcohol Use Disorder. Alcohol Res. 2020 Jul 30;40(2):08. doi: 10.35946/arcr.v40.2.08. PMID: 32742894; PMCID: PMC7384374

49

In Summary

1. There is a substantial genetic component to substance use disorder.
2. Women are less likely than men to use drugs and alcohol but have worse outcomes when they do.

50

Which of the following is true regarding gender differences with respect to substance use disorder?

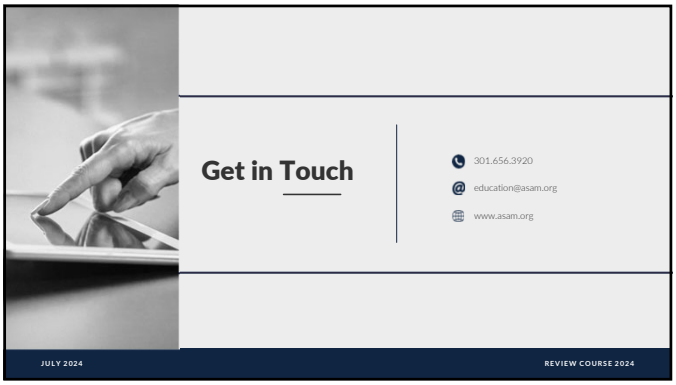
A. Men are less likely to use illicit drugs than women are
B. Women are more likely to use drugs to celebrate, whereas men are more likely to use to cope with physical or emotional pain
C. Women will suffer adverse effects from their use of similar levels of alcohol much sooner than men will
D. Women with substance use disorder are more likely to have a history of incarceration than men are

51

Which of the following is true about genetics and substance use disorder?

A. Some alleles of the ADH2 gene will cause flushing and nausea with alcohol ingestion. People who are homozygous for these alleles are protected against alcohol use disorder
B. There has been one gene found that completely determines the likelihood of developing SUD
C. Genetic factors influence whether people start using drugs, whereas environment influences how likely they are to continue.
D. People who are ultra rapid metabolizers of methadone will get a better response to it.

52



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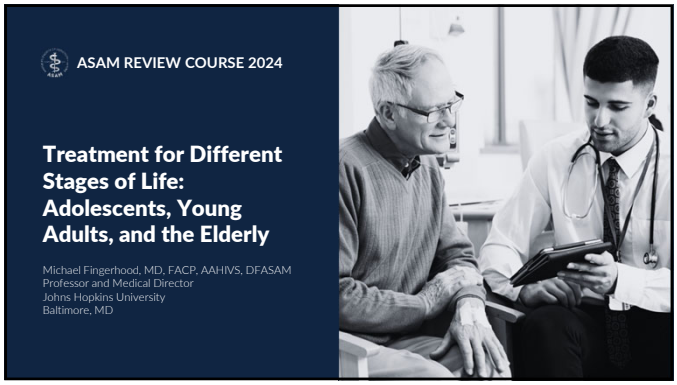
ASAM REVIEW COURSE 2024
Treatment for Different Stages of Life: Adolescents, Young Adults, and the Elderly
Michael Fingerhood, MD, FACP, AAHIVS, DFASAM
Professor and Medical Director
Johns Hopkins University
Baltimore, MD

1


Financial Disclosure
Michael Fingerhood, MD, FACP, DFASAM
• No relevant disclosures
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2


LEARNING OBJECTIVE
Describe how the different life stage of a patient can impact the development, diagnosis, and treatment of addiction.

3

Outline

1. Adolescents (10-19) and Young Adults (20-24 per World Health Organization)
2. Older adults (someone much older than yourself)

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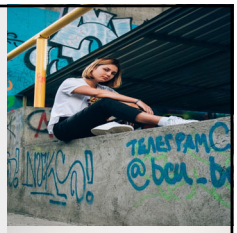
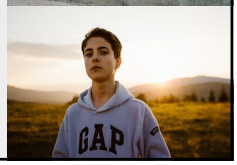
Adolescence

- Biologic growth and development
- Increased social pressures
- Increased decision making
- Search for self





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Substances

- Cannabis
- Alcohol
- Nicotine/vaping
- Opioids
- Cocaine
- Lots of experimenting- inhalants (nitrous and others), MDMA, synthetic cannabinoids, PCP, canthinones, stimulants, kratom, salvia

6

Adolescents Are Vulnerable

- Early substance use = high risk of addiction
- Adolescent immaturity during critical development period = vulnerability
  - Impulsiveness and excitement seeking
  - Difficulty delaying gratification
  - Poor executive function and inhibitory control

7

Associated Factors

- Having a parent with substance use disorder
- Mood disorder
- Learning disorder/poor school performance
- Low self-esteem
- Early sexual activity
- Substance using peers
- Availability of substances in community
- Poor family dynamics; family conflict

8

Recent Trends

- Overall, from 2020 to 2021, teen substance use declined.
  Johnston, L. D., Miech, R. A., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., & Patrick, M. E. (2022). Monitoring the Future national survey results on drug use 1975-2021: Overview, key findings on adolescent drug use. Ann Arbor: Institute for Social Research, University of Michigan.
- Overdose deaths increased 94% 2019 to 2020, largely due to fentanyl.
  Friedman J, Godvin M, Shover CL, Gone JP, Hansen H, Schriger DL. Trends in Drug Overdose Deaths Among US Adolescents, January 2010 to June 2021. JAMA. 2022;327(14):1398–1400. doi:10.1001/jama.2022.2847
- In a 2023 survey of 12 graders, 11.4% had used delta8-THC and 30.4% had used marijuana.
  Harlow AF, Miech RA, Leventhal AM. Adolescent Δ8-THC and Marijuana Use in the US. JAMA. 2024 Mar 12;331(10):861-865. doi: 10.1001/jama.2024.0865. PMID: 38470384; PMCID: PMC10933714.

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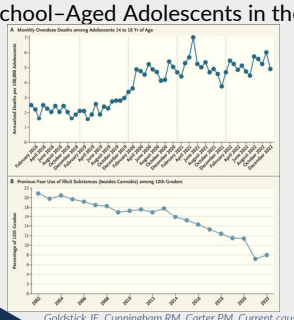
Drug-Overdose Mortality and Previous-Year Illicit-Drug Use among High-School–Aged Adolescents in the United States.



Goldstick JE, Cunningham RM, Carter PM. Current causes of death in children and adolescents in the United States. N Engl J Med 2022;386:1955-1956.

10

Recent Trends for High School Students

From 2019 to 2021, prevalence of current substance use:

- Decreased for alcohol (from 29.2% to 22.7%), marijuana (from 21.7% to 15.8%), and binge drinking (from 13.7% to 10.5%).
- No change was observed in prevalence of current prescription opioid misuse.
- Lifetime alcohol use, marijuana use, cocaine use, and prescription opioid misuse decreased from 2019 to 2021; lifetime inhalant use increased from 6.4% to 8.1%.

Hoots BE, Li J, Hertz MF, Esser MB, Rico A, Zavala EY, Jones CM. Alcohol and Other Substance Use Before and During the COVID-19 Pandemic Among High School Students - Youth Risk Behavior Survey, United States, 2021. MMWR Suppl. 2023 Apr 28;72(1):84-92. doi: 10.15585/mmwr.su7201a10. PMID: 37104552; PMCID: PMC10156154.

11

Prevalence of current and lifetime use of specific substances among high school students, by sexual identity — Youth Risk Behavior Survey, United States, 2021*

Behavior/Substance	Heterosexual %	Lesbian, gay, or bisexual %	Questioning or other %
Current use†			
Alcohol	21.6	29.3§	20.9¶
Marijuana	14.0	25.6§	16.5¶
Binge drinking	10.3	13.6§	7.6¶
Prescription opioid misuse	4.3	11.7§	10.3§
Lifetime use			
Alcohol	45.8	58.0§	46.2¶
Marijuana	25.8	41.2§	27.5¶
Inhalants	6.0	15.1§	13.4§
Ecstasy	2.1	6.0§	3.9¶
Cocaine	1.8	4.4§	3.1¶
Methamphetamine	1.1	3.4§	3.0§
Heroin	0.8	1.9§	2.4§
Injection drug use	1.0	1.9§	2.7§
Synthetic marijuana	5.9	9.7§	6.1¶
Prescription opioid misuse	9.4	21.5§	18.6§

Hoots BE, Li J, Hertz MF, Esser MB, Rico A, Zavala EY, Jones CM. Alcohol and Other Substance Use Before and During the COVID-19 Pandemic Among High School Students - Youth Risk Behavior Survey, United States, 2021. MMWR Suppl. 2023 Apr 28;72(1):84-92. doi: 10.15585/mmwr.su7201a10. PMID: 37104552; PMCID: PMC10156154.

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Random Tidbits

- Stimulant involved drug overdoses rising among youth; greatest rise in 11-14 year olds
- Inhalant use associated with violence, criminal activity, other substance use disorder, school dropout
- College students
  - depressive symptoms associated with non-medical prescription drug use
  - past year non-medical use of prescription medication prevalence 20%; higher among males and members of fraternities and sororities

13

CRAFFT: A Brief Screening Test for Adolescent Substance Use*

- C - Have you ever ridden in a CAR driven by someone (including yourself) who was "high" or had been using alcohol or drugs?
- R - Do you ever use alcohol or drugs to RELAX, feel better about yourself, or fit in?
- A - Do you ever use alcohol/drugs while you are by yourself, ALONE?
- F - Do your family or FRIENDS ever tell you that you should cut down on your drinking or drug use?
- F - Do you ever FORGET things you did while using alcohol or drugs?
- T - Have you gotten into TROUBLE while you were using alcohol or drugs?

*2 or more yes answers suggests a significant problem

14

CRAFFT 2.1 + N

Ask about use of vaping device containing nicotine and/or flavors, or any tobacco products.

1. Ever tried to QUIT
2. Use NOW because hard to quit
3. Felt ADDICTED
4. CRAVINGS
5. Felt like NEEDED to vape/use tobacco
6. Hard to keep from using in PLACES where you shouldn't
7. When you HAVEN'T used
   a. Hard to CONCENTRATE
   b. IRRITABLE
   c. NEED/urge
   d. NERVOUS, restless, anxious

15

Do We Care About Cannabis?

- Vulnerable populations: youth, psychiatric illness, other substance use disorders
- Consequences of intoxication, e.g. MVCs
- Impact on learning
- Psychiatric consequences of use
- Progression to cannabis use disorders and other substance use disorders

16

Vulnerability in Youth

- Conditional risk of use disorder in adolescents as high as 40%
- Daily use of cannabis <age 17 associated with substantially increased risk of:
  - Later cannabis use disorder (OR=18)
  - High school drop out (OR=3)
  - Use of other drugs (OR=8)
  - Suicide attempts (OR=7)

Pooled longitudinal studies. N =2537 to N=3765. Silens et al. Lancet Psychiatry, 1,: 286 – 293, 2014S

17

Messaging – Overcoming Societal Attitudes

- Cannabis is addictive (but not everyone gets addicted)
- Cannabis can be harmful (but not everyone gets harmed)
- Broader use leads to broader problem use through access and decreased perceived harm
- This is a huge problem for youth and other vulnerable populations

18

Features of Adolescent Treatment

- Developmental barriers to treatment engagement
  - Invincibility
  - Immaturity
  - Motivation and treatment appeal
  - Salience of burdens of treatment
- Variable effectiveness of family leverage (or not)
- Pushback against sense of parental dependence and restriction
- Prominence of co-morbidity

19

Developmentally Informed Treatment - 1

- Adolescents rely on the support of adults, but also strive for autonomy
- Emphasize rewards and praise
- Emphasize adolescent learning styles, using energetic and fun activities while preserving therapeutic content
- Emphasize social alternatives to drug use
- Acknowledge normative attraction of thrill-seeking, risk, deviance
- Weave a safety net of supports: families (or surrogates), but expect some disdain

20

Developmentally Informed Treatment - 2

- Encourage adolescents to formulate their own solutions
- Natural consequences: Give some rope (but not too much) and don't enable
- Emotion regulation training
- Address sleep deprivation
- Treatment = habilitation, not rehabilitation
- Not effective- "Just grow up!", "Just say no"

21

Motivational Approaches

- Do you know other kids who have been in trouble?
- What are the pro's and con's for you?
- How much do you think is too much?
- What do you know about health risks?
- If it did become a problem in the future, how would you know?
- Do you know why I or your parents might think it's a problem?
- If you can stop anytime, would you be willing to see what it's like…
- Let's schedule you to come back and see how it's going…

22

Vignette

- 17M began prescription opioids at 15, progressing to daily use with withdrawal within 8 months; nasal heroin age 16, injection heroin 6 months later
- 3 episodes residential tx, 2 AMA, 1 completed
- Presents in crisis seeking detox ("Can I be out of here by Friday?")
- How should you care for him?

23

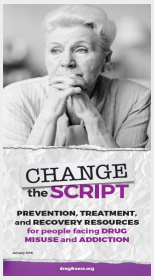
Adolescents and Treatment of OUD

- Medications feasible and effective (buprenorphine better than no buprenorphine)
- Availability of programs offering MOUD limited*
- Adolescents with non-fatal opioid overdose should be strongly considered for buprenorphine treatment
- Naltrexone requires acceptance with concern over retention
- Longer duration buprenorphine better
- XR buprenorphine should be considered

*Oldfield B, Chen K, Joudrey PJ et al. Availability of Specific Programs and Medications for Addiction Treatment to Vulnerable Populations: Results from the Addiction Treatment Locator, Assessment, and Standards (ATLAS) Survey. J Adddict Med 2023 Mar 17. doi: 10.1097/ADM.0000000000001158.

24

Older Adults



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Older Adults-"Hidden Problem"

- Lack of screening in primary care
- Lack of guidelines for assessing older adults
- Signs and symptoms of harmful use overlap with other conditions
- Ageist bias

26

Challenges in Detecting Problematic Use

- Relying on older patient's report of frequency and quantity of substance use can lead to underestimation of the problem
- Older adults and family members may not appreciate deleterious consequences of long-time patterns of drinking or drug use
- Harm can come from lower amounts of substances

27

Detecting Problematic Substance use

Lehmann & Fingerhood. NEJM 2018;379:2351-60

Table 2. Signs of Possible Problematic Substance Use in Older Adults.

Psychiatric symptoms: sleep disturbances, frequent mood swings, persistent irritability, anxiety, depression
Physical symptoms: nausea, vomiting, poor coordination, tremors
Physical signs: unexplained injuries, falls, or bruises; malnutrition; evidence of self-neglect, such as poor hygiene
Cognitive changes: confusion and disorientation, memory impairment, daytime drowsiness, impaired reaction time
Social and behavioral changes: withdrawal from usual social activities, family discord, premature requests for refills of prescription medications

28

Patient Vignette

- EB is a 72 F seen for initial visit. She has a history of chronic pain in hips and knees. Her previous provider will no longer prescribe oxycodone as for the past 2 months her 30-day script ran out after 2 weeks. Tearful and fearful that providers won't help her. Cannot take NSAIDs. She admits that she often takes oxycodone when she is upset.
- She lives alone in senior housing apartment; 2 daughters- both with difficulties (medical and social). Non-smoker; no alcohol.
- How should you care for her?

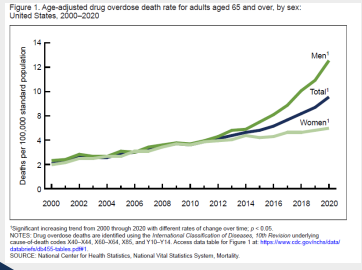
29

Themes in Older Adults with Opioid (substance) Use Disorder

- Living alone
- Sense of isolation (despite family)
- Opioid as a "friend"
- Shame
- Fear of how to live without opioid (substance)

30

Older adult overdose death rate based on gender



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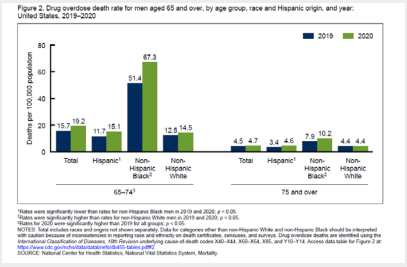
Older adult overdose death rate by race



32

American Geriatrics Society Beers Criteria

- Avoid chronic NSAIDs, muscle relaxants and use tramadol with caution (added 2019)
- Avoid opioids if history of falls or fracture

American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019 Apr;67(4):674-694. doi: 10.1111/jgs.15767. Epub 2019 Jan 29. PMID: 30693946.

33

Patient Vignette

- BR is a 82F brought to the ER by neighbor with "syncope", but it is noted that she has alcohol on her breath and her BAL is 228 mg/dl. When confronted she becomes tearful. Her son goes to her home and finds hidden miniatures throughout her apartment.
- How do you approach caring for her?

34

Short Michigan Alcoholism Screening Test-Geriatric Version (SMAST-G)

In the past year:

1. When talking with others, do you ever underestimate how much you actually drink?
2. After a few drinks, have you sometimes not eaten or been able to skip a meal because you didn't feel hungry?
3. Does having a few drinks help decrease your shakiness or tremors?
4. Does alcohol sometimes make it hard for you to remember parts of the day or night?
5. Do you usually take a drink to relax or calm your nerves?

35

Short Michigan Alcoholism Screening Test-Geriatric Version (SMAST-G)

6. Do you drink to take your mind off your problems?
7. Have you ever increased your drinking after experiencing a loss in your life?
8. Has a doctor or nurse ever said they were worried or concerned about your drinking?
9. Have you ever made rules to manage your drinking?
10. When you feel lonely, does having a drink help?

*2 or more "yes" responses indicative of alcohol problem.

36

Alcohol: the Most Commonly Used Substance

- Alcohol Use Disorder in Older Adults
  - Early Onset: 2/3 of older adults; Men>Women
  - Late Onset: more likely to be triggered by stressful life event (loss of spouse, retirement, medical disability, pain, sleep problem) ; Women>Men

37

Findings from NSDUH

- Prevalence of heavy drinking (5 or more drinks on one day on each of 5 or more days in past 30 days):
  - 5.6% of aged 50-54 year olds, 3.9% of aged 55-59
  - 4.7% of aged 60-64, 2.1% of 65+
- Prevalence of binge drinking (5 or more drinks on same occasion on at least 1 day in past 30 days):
  - 23.0% of aged 50-54, 15.9% of aged 55-59,
  - 14.1% of aged 60-64, 9.1% of aged 65+

www.niaaa.nih.gov/alcohols-effects-health/special-populations-co-occurring-disorders/older-adults

38

Increased Risks of Alcohol Even at "Low Consumption"

- Increased vulnerability to physiological effects
  - Decreased lean muscle mass
  - Decreased total body water
  - Less efficient liver enzymes that metabolize alcohol
  - Increased effective concentration of alcohol, higher and longer lasting blood alcohol levels
- Additional risks
  - Alcohol-medication interactions
  - Co-morbid chronic illnesses
  - Bariatric surgery

39

Patient Vignette

- CR is 82M with HTN and GERD and with recurrent depression which is being treated with 2 different antidepressants. His depression is much improved, but he continues to experience anxiety and stress, primarily related to worries about his wife's cancer and her poor health. He reports that he has decided to go to a marijuana dispensary and try cannabis to see if it can help his mood and his anxiety
- How do you respond?

40

Cannabis use and emergency visits among older adults in California

- Cannabis related ED visit rate for adults ≥ age 65, increased from 20.7/100,000 visits in 2005 to 395.0 per 100,000 ED visits in 2019, a 1804% increase.

Han BH, Brennan JJ, Orozoco, et al. Trends in emergency department visits associated with cannabis use among older adults in California, 2005-2019. J Am Geriatr Soc 2023Jan 9. doi: 10.1111/jgs.18180

41

Impact of Cannabis on Physical and Mental Health

- Older adults often see cannabis as "safer" alternative to alcohol, opioids, or pharmaceutical medications
- Short term use is associated with
  - Impaired short-term memory, impaired judgment/motor coordination, driving skills
  - Increased anxiety
  - Paranoia and psychosis have dose-response effect

42

Patient vignette

- LK is an 80F with long history of episodic anxiety and low mood and insomnia- prescribed temazepam for 30 years. She has 6 month history of low mood, panicky feelings, crying spells, anxiety, poor appetite; can't multitask or concentrate. Medications are- temazepam 30mg qhs, trazodone 50mg qhs, eszopiclone 3mg qhs, tramadol 50mg prn pain, gabapentin 2400mg daily

43

Benzodiazepine prescribing in older adults

- What are the reasons?
  - Anxiety symptoms, anxiety disorders, depression with anxiety, sleeplessness
- What are the problems?
  - Often prescribed for years, without good indication of continuing need
  - Often prescribed for symptoms, without recognition of the true underlying cause: e.g. depression, normal worry, cognitive impairment
  - Increased frequency of adverse effects with aging, polypharmacy and use of meds with long half-lives

44

Deprescribing

- Emphasize that you will not withdraw appropriate care: "I understand that I need to treat your symptoms but we need to do so without causing you other problems."
- Reassure that you will monitor closely for symptoms recurrence: "We'll reduce the medicine very slowly and will stay in close contact to watch for returning symptoms."

45

Benzodiazepine tapering

Initial Considerations
- Use scheduled rather than prn dosing
- Consider switching to a longer-acting benzodiazepine
- Schedule follow-ups every 2-4 weeks- can be telemedicine or phone call

Tapering Considerations
- Reduce total daily dose (TDD) by 10-25% to start
- Continue reducing TDD by 10-25% every 2-4 weeks
- For patients on supra-therapeutic doses consider initial reduction of 25-30%

46

Treatment Approach for Older Adults

- Don't minimize
- Confront with compassion
- Remove shame
- Build self-esteem
- Give encouragement/hope
- Undo isolation
- Work on coping skills
- Facilitate finding new ways to stay busy with use of peers

47

Some Conclusions:
Treatment for Youth and the Elderly is Effective, but …

- We need to learn to improve it
- There isn't enough of it
- Access and engagement is a problem

- Treatment works!

48

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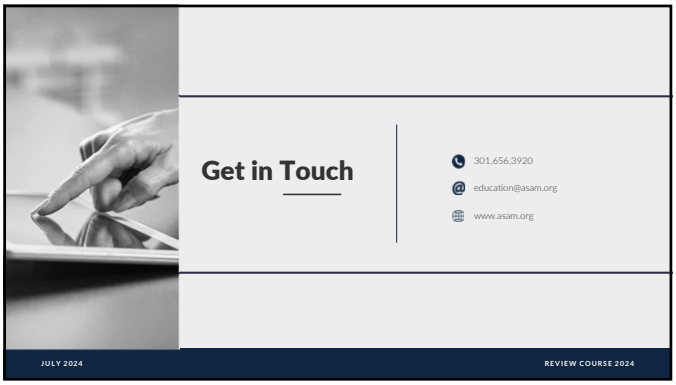

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ASAM REVIEW COURSE 2024

Evolution of addiction and treatment: History and Impact

Paul H. Earley, MD, DFASAM
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Past President, *Federation of State Physician Health Programs*
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1

Financial Disclosure

Paul H. Earley, MD, DFASAM

- No relevant disclosures

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2

Addiction Treatment History

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Benjamin Rush, M.D.

- Published: Inquiry into the Effects of Ardent Spirits on the Human Mind and Body in 1784
- Asserted that alcohol was the causal agent in alcoholism
- Asserted that loss of control over drinking is the characteristic symptom of inebriety
- Stated that total abstinence from alcohol was the only effective cure
- Called for creation of a "Sober House" for the care of the confirmed drunkard (1810)

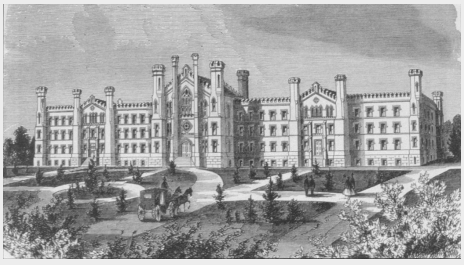
4

The 19th Century

- In the early 1800's, an increase in grain supply, rapid crop spoilage, and an emerging entrepreneurial spirit increased the supply of distilled alcohol.
- As a result, drinkers increased their consumption of distilled alcohol.
- Definitive data is missing, but alcoholism seemed to increase, especially in urban areas.
- In the 1840s, the temperance movement took on the alcohol problem.

5

New York State Inebriate Asylum



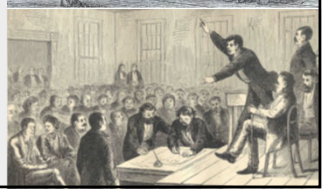
1864 - Containment

6

The Washingtonians

- Social network
- Public recitation of stories
- Faith-based change

1840 to 1855



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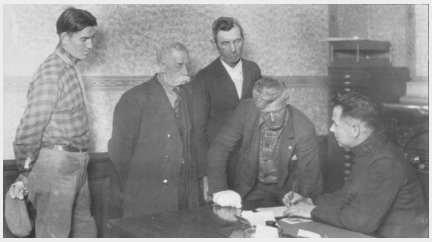
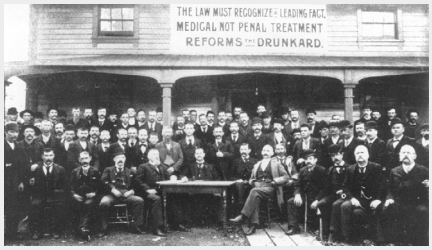
The Salvation Army



Founded in 1865, it continues to be the largest addiction treatment system in the world..

8

The Keeley League



- 1879 - First franchised, private, for-profit addiction treatment system
- 1891 – Keeley forms first patient mutual aid society

9

Keeley League

- Keeley used repeated "double chloride of gold" injections. Followed up with "take home bottles."
- This was part of the dangerous patent medicine industry that led to subsequent regulation and development of science-based medications.
- However, other elements became part of later addiction treatment programs:
  - Regular sleep, exercise, health recreation
  - Abstinence and careful selection of friends
  - Continued socializing by graduates
  - Viewed inebriety as a disease
  - "Recovered" alcoholics worked in his centers

10

Towns Hospital

CHARLES B. TOWNS HOSPITAL
293 Central Park West New York, New York
For ALCOHOLISM and DRUG ADDICTION

ANY PHYSICIAN having an addict patient is invited to write for Hospital literature.

This institution has specialized in addictions for over 20 years. Its method of treatment has been fully described in THE JOURNAL A. M. A.; in The Handbook of Therapy, from the A. M. A. Press; and in other scientific literature. The treatment is a regular hospital procedure, and provides a definite means for eliminating the toxic products of alcohol and drugs from the tissues. A complete Department of Physical Therapy, with gymnasium and other facilities for physical rebuilding, is maintained. Operated as an "open" institution. Physicians are not only invited but urged to accompany and stay with their patients.

Located Directly Across from Central Park

1901

- Focused on removing the craving and restoring physical health and diet
- Varied from NY Inebriate Asylum about issues of treatment coercion
- Physicians were not only invited but urged to accompany and stay with their patients

11

Prohibition

- Based upon the concept that alcohol itself is the cause of alcoholism (and what was described at the time as personal and social evil), thus no one should drink.
- In the U.S., lasted from
  - 1919 until 1933

12

Drugs and the Legal System

- At the turn of the century, the sale of drugs was not controlled in any manner.
- Starting in the late 1800's, home remedies containing alcohol, opium, morphine, cocaine, and cannabis professing "cures" for any number of illnesses.
- Sigmund Freud experiments with cocaine and winds up recommending it for the treatment of morphinism for his friend and colleague Ernst von Fleischl-Marxow.
- The Pure Food and Drug Act, and later the Harrison Act (1914), created a split between legal and illegal drugs consumed by U.S. citizens.

13

The Harrison Act

- Drugs deemed legal (and thus, taxed): alcohol and tobacco (Nicotine)
- Illegal drugs placed into a hierarchy
  - Heroin, cocaine, and many hallucinogens were placed as Schedule I. This includes peyote; however, Native Americans can apply for special dispensation as a religious sacrament.
  - Misplacements of certain drugs, notably marijuana. This increased the belief that the legal system does not understand addiction risk and is uninterested in medical or social safety.
- Paradoxically, the two legal drugs are the most medically toxic to the body.

14

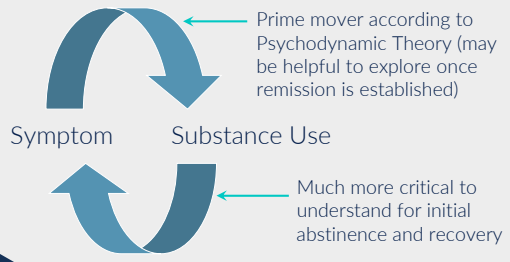
The Legal System

- The brain center that drives addiction was unaltered by the Harrison Act.
  - Once addicted, economics of supply and demand describes use of substances in such individuals as "inelastic demand."
  - As a result, many individuals who develop addiction violate laws and become criminals.
- Today, the prison industry flourishes, and the treatment industry is all but defunct.
  - 65% of prison inmates meet criteria for SUDs.
  - Recent evolution of state and local drug court programs promise innovative and effective solutions.

Shoveling Up II: The Impact of Substance Abuse on Federal, State and Local Budgets, CASA (2009)

15

Self-Medication Hypothesis of Addiction



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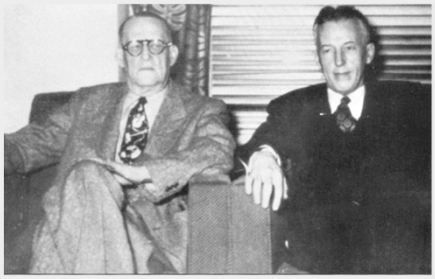
Bob Smith and Bill Wilson



Met in 1935

17

Innovations from A.A.

- Emancipated spirituality from its roots in religious institutions.
- Legitimized varieties of spiritual experiences in recovery.
- Found alternatives to religious antidotes for guilt including self-inventory, confession, acts of restitution, and acts of service.
- Encouraged service work and working with others.
- Established the first chronic care system for a chronic disease.
- A.A. was a peer-led social movement that used a spiritually-based program with explicit instructions.

18

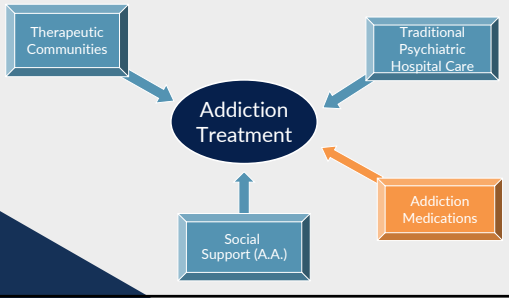
Hazelden and the Minnesota Model

A centralized treatment system that focused on detoxification and the principles of A.A.

Opened 1949

19

The Origins of Addiction Treatment



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Elements of the Minnesota Model

- Alcoholism is an involuntary, primary, chronic, progressive biopsychosocial spiritual disease.
- Recovery is the goal of treatment, not abstinence.
- Focus on treatment of a central disease process, abandoning the psychoanalytic and moral models of addiction.
- Addiction is best treated in a milieu of dignity and respect.
- A revised view of motivation: initial motivation (or lack thereof) is not a predictor of outcome. Also, motivation is as much the responsibility of the milieu as the patient.

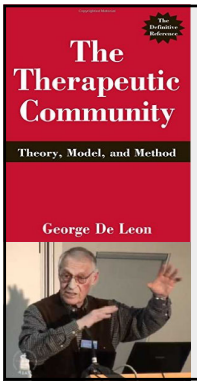
21

Federal Narcotics Farm Lexington, Kentucky

For a long period of time, this was the world's epicenter for addiction research and drug treatment . Convicts did time alongside individuals who volunteered to enter the center for treatment.

1935 to 1970

22



The Therapeutic Community

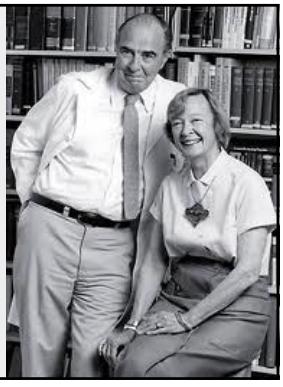
- Whole person focused, centered on lifestyle changes
- Goals are:
  - Becoming pro-social
  - Honesty
  - Taking responsibility for self
  - Willingness to learn from others
- Democratically run, everyone, including staff, are part of the community
- Drives individual change through "community as method"
- Introduced the concept of ongoing support, most often lifelong disease management

23

Medications for the Treatment of OUD

- Heroin dispensing in England and Switzerland.
- Methadone therapy in the U.S. (1964)
  - Humane treatment in an era of discrimination and legal interdiction
  - Biological disease model
  - Although A.A. took this stand earlier, this was the first medical treatment that took a firm stand that addiction is a chronic disease.
  - In The ASAM Criteria, it is referred to as Opioid Treatment Services (OTS)

Drs. Dole and Nyswander



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Addiction is a Brain Disease

- Alan Leshner, Ph.D. and former head of NIDA, began describing addiction as a brain disease in 1996
- He stated that addiction is a disease of the brain that has several important components:
  - A social context
  - Behavioral, psychological and spiritual aspects
- Recovery takes time, time measured in years

25

Lessons From History

- Addiction is an ever-present phenomenon, changing focus from time to time on different substances and behaviors. (Don't believe that the current drugs abused will be the primary drug of misuse!)
- Treatment has focused on religious conversion, psychotherapy, characterological manipulation, legal interdiction, and pharmaceutical intervention at various times—a single modality, universally applied, has, inevitably, failed.
- Short-term interventions do not work. Addiction is a chronic condition requiring long-term care.
- The illness is very complex and has multiple antecedents. The clinician must adapt his or her approach to each patient.

26

The ASAM Criteria

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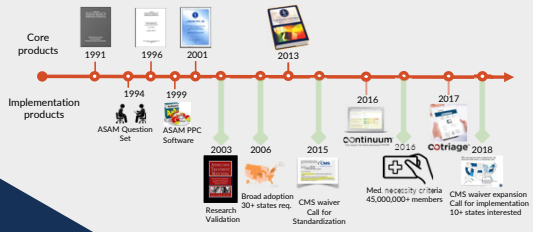
27

The Evolution of the ASAM Criteria

For the least intensive or restrictive care that meets the patient's multi-dimensional needs and to ensure ongoing care and the optimal treatment outcome.

28

The ASAM Criteria Widespread adoption & validation



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The ASAM Criteria – Treatment Axis

- Digits demarcate major types of treatment with decimal places defining intensity. The system is designed for increased granularity and refinement in the future.

- Level 0.5 Early Intervention ← Prevention Services
- Level 1 Outpatient Treatment ← Less than three times per week, commonly individual services
- Level 2.1 Intensive Outpatient
- Level 2.5 Partial Hospitalization ← Group-based treatment at a specialized center
- Level 3.1 Clinically Managed Low Intensity Residential Services
- Level 3.3 Clinically Managed Medium Intensity Residential Treatment
- Level 3.5 Clinically Managed High Intensity Residential Treatment
- Level 3.7 Medically Monitored Intensive Inpatient Treatment
- Level 4 Medically Managed Intensive Inpatient Treatment ← Medical Hospital

Residential Services

30

The ASAM Criteria – The Dimensional Axis

- Dimension 1: Acute Intoxication and/or Withdrawal Potential
- Dimension 2: Biomedical Conditions and Complications
- Dimension 3: Emotional, Behavioral or Cognitive Conditions and Complications
- Dimension 4: Readiness to Change
- Dimension 5: Relapse, Continued Use or Continued Problem Potential
- Dimension 6: Recovery/Living Environment

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Putting the ASAM Criteria Axes Together

		Levels of Care								
		0.5	1	2.1	2.5	3.1	3.3	3.5	3.7	4
Dimensions of Care	Dimension 1									
	Dimension 2									
	Dimension 3									
	Dimension 4									
	Dimension 5									
	Dimension 6									

32

The ASAM Criteria

- Provides a template for the type and intensity of addiction treatment.
- Reiterates the importance of long-term management.
- Ensures cost-effective care.
- Ensures adequate staffing for the different levels of care.
- Emphasizes the importance of patient evaluation and ongoing reevaluation.
- Is the emerging national standard that will reengineer our disorganized and chaotic addiction treatment system in the U.S.

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Components of the ASAM Criteria System

34

The ASAM Definition of Addiction

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The Definition of Addiction Recently Revised

- Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences.
- Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases.

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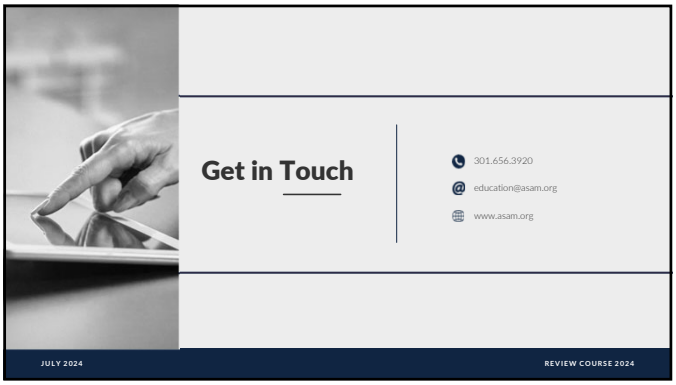
The Definition of Addiction

- Note that ASAM's definition of addiction is distinctly different that the criteria in the DSM-5.
  - DSM-5 uses characteristic signs and symptoms to make a diagnosis.
  - The ASAM definition used the word Addiction and outlines causation and characteristics of the disease.
- ASAM's definition emphasizes
  - Addiction is chronic
  - Addiction is treatable
  - The illness is complex, and its many etiologies are important in its genesis and treatment
  - The response to prevention and treatment is similar to other chronic conditions.

37



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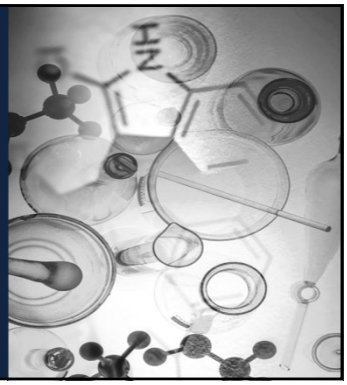
Pharmacology and Toxicology: Principles, Applications, and Limitations

Lewis S. Nelson, MD, MBA, FASAM
Professor and Chair of Emergency Medicine
Chief, Division of Medical Toxicology and Addiction Medicine
Rutgers New Jersey Medical School



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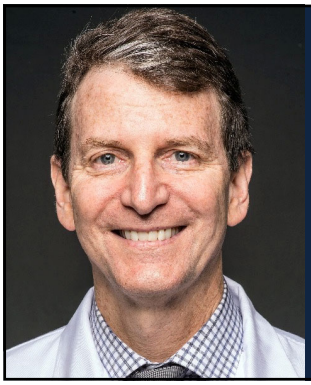

Financial Disclosure

Lewis S. Nelson, MD, MBA, FASAM

- No relevant disclosures

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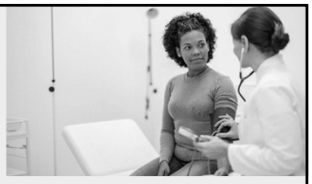
Learning Objectives



1. **Explain** the differences between and clinical relevance of tolerance, dependence, and hyperalgesia.
2. **Describe** the pharmacologic principles of pharmacokinetics and pharmacodynamics and how each impacts addiction risk and addiction treatment.
3. **Discuss** the interpretation pitfalls of screening and confirmatory urine drug tests in the management of patients with substance use.

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3

Addiction Medicine IS Pharmacology

- Drugs have to get to the brain to elicit a response.
  - Blood brain barrier is an effective barrier
- Euphoria – rate of rise
- Dependence – duration of exposure

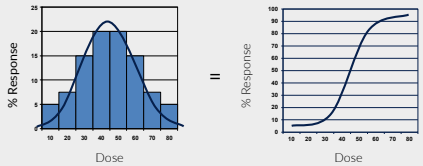
4

Pharmacokinetics and Pharmacodynamics

Absorption (Bioavailability)	Distribution	Elimination
Biotransformation	Dose Response (Clinical Effect)	Potency
Drug interaction	Tolerance	Dependence

5

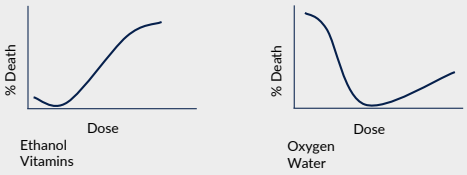
Dose-Response



Response = Anything (Blood pressure, Euphoria, Death)

6

Dose-Response



Response = Death

7

Potency

Rank order the potency at causing death:

Agent	LD50 (approx.)
Ethanol	5,000 (mg/kg)
Nicotine	2 (mg/kg)
Morphine	1 (mg/kg)
Fentanyl	0.01 (10 µg/kg)
Botulinum	0.000001 (2 ng/kg)

Don't confuse potency with clinical effect

8

Which has more potent THC?

1980's weed

Trick question:
The THC is the same potency
The higher concentration weed is more "potent"

Don't confuse potency of a drug with its concentration

2020 weed

9

Potency doesn't really matter

Agent	Potency (vs morphine)
Tramadol	0.2
Morphine	1
Oxycodone	1.3
Methadone	4
Heroin	4
Buprenorphine	30
Fentanyl	100
Carfentanil	10,000

Any of these drugs will kill you if you take enough

10

Dose Makes The Poison

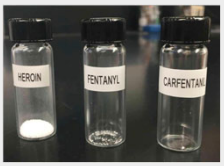
"What is there that is not poison? All things are poison and nothing [is] without poison. Solely the dose determines that a thing is not a poison"

Paracelsus (1493-1541)
in *Third Defense*

Philip Theophrastus Bombast von Hohenheim
aka PARACELSUS (1493-1541)

11

Potency doesn't really matter



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Absorption

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Routes of Administration

- Oral
  - Potentially extensive first-pass
- IV, IN, IM, SC, SL, buccal, inhalational, rectal
  - Bypass hepatic first-pass
- Intrathecal
  - Unique –bypass Blood Brain Barrier
- Transdermal
  - Bypass hepatic first-pass
  - Depot in skin/body fat can influence absorption
- Intranasal
  - May directly access CNS (nose-to-brain)

14

Bioavailability

- The amount of unchanged drug reaching systemic circulation after administration is the bioavailability (F).
- F depends upon:
  - Route (IV is 100%)
  - Site specific membrane permeability
  - Drug transporter activity (p-glycoprotein)
  - First-pass metabolism (hepatic)

	Route		
	Oral	**Sublingual**	**Buccal**
Buprenorphine	10%	50%	30%
	Oral	**Sublingual**	**Intranasal**
Naloxone	1%	20%	50%
	Oral		
Morphine	33%		
Oxycodone	75%		

Kuhlman JJ, et al. J Anal Toxicol 1996;20(6):369–78.

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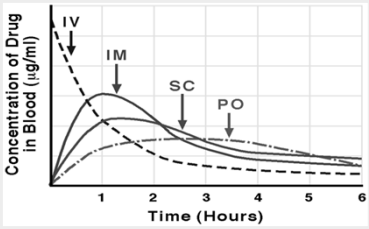
Area Under the Curve (AUC)



Wolff K, et al. The SAGE Handbook of Drug & Alcohol Studies

16

17

Distribution

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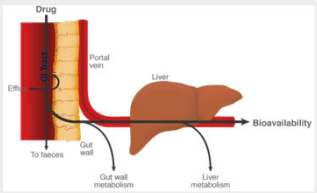
First Pass Hepatic Metabolism

Bypass first pass



www.doctoralerts.com

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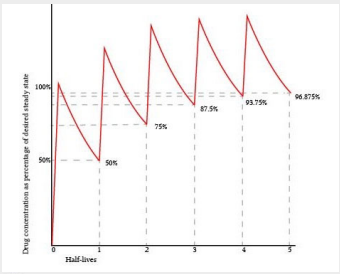
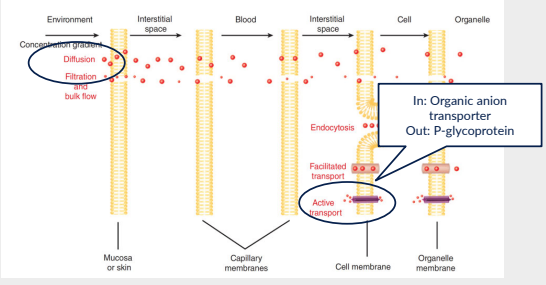
Steady State



- Requires approximately 5 half-lives
  - Regardless of the compound's half-life
- Explains (in part) the risk and difficulty of methadone induction
  - T½ ~24 hr (12-36 hr)

www.derangedphysiology.com/

20



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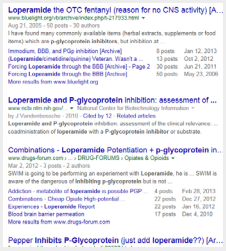
P-Glycoprotein



"Street pharmacologists" understand these principles

Loperamide and p-glycoprotein inhibitors

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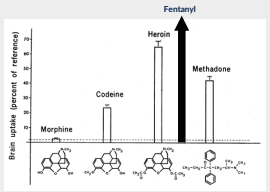
Lipophilicity

Lipophilicity = Reward = Abuse liability

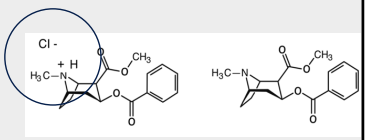
Drug	LogP
Buprenorphine	4.98
Fentanyl	4.05
Methadone	3.93
Naloxone	2.09
Hydromorphone	1.6
Heroin	1.58
Morphine	0.89



Oldendorf WH. Science. 1972

23

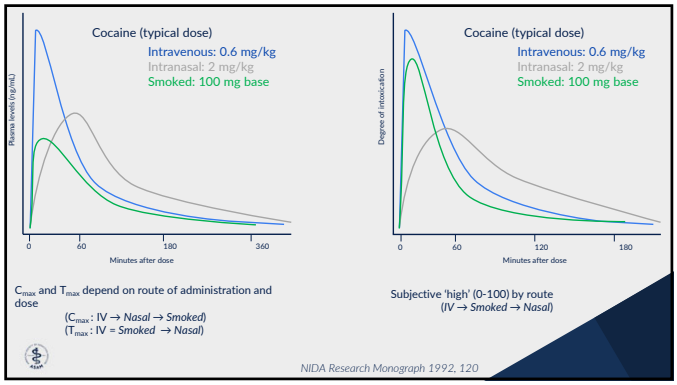
Addiction Medicine IS Pharmacology



Cocaine hydrochloride (salt)

Cocaine base (alkaloidal)

24



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Elimination

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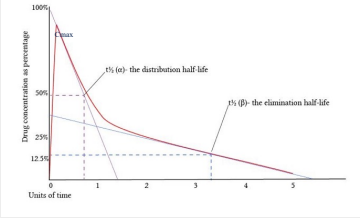
T1/2 (Half-life) is The Time For Cmax to Fall by Half



- Distribution t½
  - Redistribution t½
- Terminal elimination t½
  - Context sensitive t½
  - Apparent t½

Drug	Half life (distrib)	Half life (redistrib)	Half life (term)	LogP
Fentanyl	2 min	12 min	480 min	4.05
Methadone	120 min	---	1440 min	3.93

Note: all half-lives have ranges, not shown

www.derangedphysiology.com/

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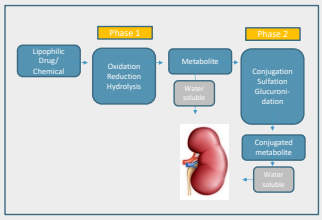
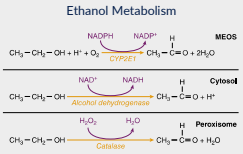
Biotransformation





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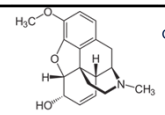
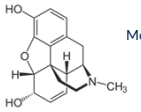
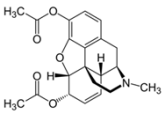
Activation through Biotransformation

- Codeine is demethylated in the liver to morphine
  - Occurs via CYP2D6
  - Codeine is a "pro-drug" (drug undergoes hepatic biotransformation or 'metabolism' to its active component
  - Lisdexamfetamine (Vyvanse™) is another example of a pro-drug

Fun pharm fact: *heroin does not bind to the mu receptor. Metabolism occurs in the CSF. Heroin is a pro-drug for morphine.*







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Biotransformation

TABLE 11–1 Characteristics of Different Cytochrome P450 Enzymes[20,21,22]

CYP Enzyme	1A2	2B6	2C9	2C19	2D6	2E1	3A4
Percent of liver CYPs	4%–16%	2%–5%	5%–29%	1%–4%	1%–4%	6%–17%	15%–37%
Contribution to enterocyte CYPs	None	None	Minor	Minor	Minor	Minor	70%
Organs other than liver with enzyme	Lung	Kidney	Small intestine, nasal mucosa, heart	Small intestine, nasal mucosa, heart	Small intestine, kidney, lung, heart	Lung, small intestine, kidney	Much in small intestine; some in kidney, nasal mucosa, lung, stomach
Percent of metabolism of typically used pharmaceuticals	9%	7%	13%	7%	20%	3%	30 %
Polymorphisms*	No	Yes	Yes	Yes	Yes	No	No
Allelic Frequency							
Decreased Activity							
African American		38%–62%	0%–1%	10%–17%	14%–30%		
Asian	—	14%–25%	2%–8%	25%–39%	47%–94%	—	—
Caucasian		23%–39%	16%–23%	6%–16%	31%–45%		
Increased Activity							
African American		0%–25%		15%–27%			
Asian	—	5%–15%	—	0%–2%	1%	—	—
Caucasian		6%		21%–25%	1%–9%		
Ethiopian					30%		

* Polymorphism is a genetic change that exists in at least 1% of the human population. Interpersonal allelic variations exist even in those listed as "No" for polymorphism.

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Receptor Pharmacology

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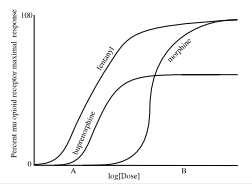
Efficacy

Ligand	% Efficacy
Full agonist	E = 100
Partial agonist	0 < E < 100
Antagonist	E = 0
Inverse agonist	E < 0



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Affinity

Ligand	Ki (Affinity) (nmol)
Hydrocodone	41.58
Oxycodone	25.87
Heroin	9.6
Methadone	3.38
Fentanyl	1.35
Morphine	1.14
Naloxone	1.1
Hydromorphone	0.6
Buprenorphine	0.21

Volpe DA. Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. Reg Toxicol Pharmacol 2011

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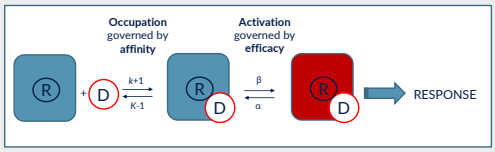
Receptor kinetics
On-off



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Pharmacodynamics

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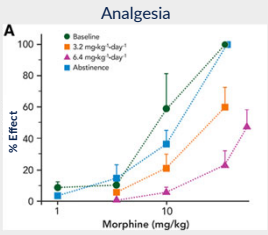
Tolerance

- Tolerance is the reduction in response to a drug after its repeated administration
- Tolerance shifts the dose-response curve to the right
  - Higher doses than initial doses to achieve the same effect



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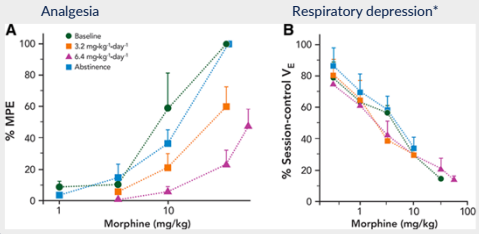
Differential Tolerance



*limited development of tolerance

Hayhurst. Anesthesiology 2016;124:483-8

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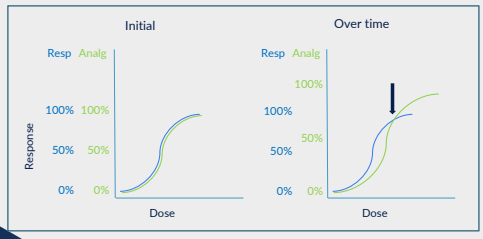
The Paradox of Differential Tolerance



Tolerance to analgesia is rapid
Tolerance to respiratory depression is slow

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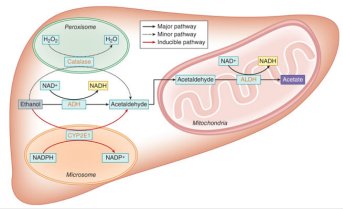
Pharmacokinetic Tolerance

- A consequence of increased metabolism after a drug is repeatedly administered
- Results in less drug being available at the receptor for drug activity.
- Ethanol
  - Although ADH is not inducible, CYP2E1 is
  - Accounts for more rapid elimination of alcohol in heavy, chronic users



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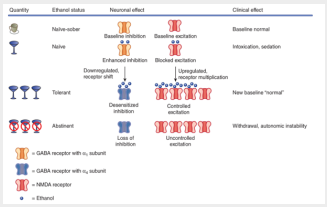
Pharmacodynamic Tolerance

- Down-regulation of receptors (higher drug concentration needed)
  - Desensitization of GABA (ethanol)
    - Receptor conformation
  - Desensitization of MOR (opioid)
    - Signal transduction
    - Decreased density (internalization)
- Up-regulation of receptors
  - Increased number of NMDA



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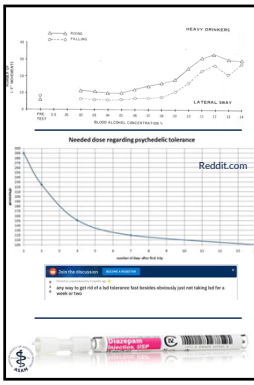

Other Clinical Examples of Tolerance

- Mellanby effect
  - Less "intoxicated" on descending limb of BAC curve
- MDMA, psilocybin, and LSD
  - Serotonin receptor
- BZD resistant alcohol withdrawal from IV (less with PO) diazepam
  - Tachyphylaxis

Mellanby E. Medical Research Committee. Special Report Series No 31. 1919.

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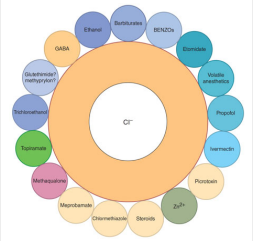
Conditioned Tolerance

42

Cross-Tolerance

- Tolerance to the repeated use of a specific drug in a given category is generalized to other drugs with the same structural or mechanistic category.



Goldfrank's Toxicologic Emergencies, 11th

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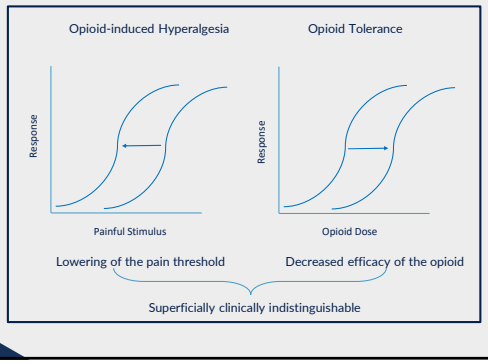


44

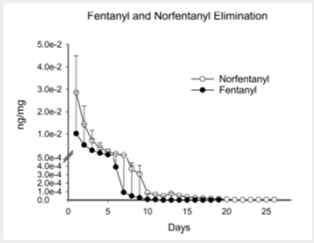
Physical Dependence

- A state that develops as a result of adaptation and the resetting of homeostatic mechanisms
- Withdrawal syndrome can occur in physically dependent person when the drug is abruptly stopped or dose reduced
  - Typically improves on restarting the drug
  - There can be a "point of no-return"
- Can occur with both addictive and non-addictive use of drugs
  - Caffeine, nicotine
- And with therapeutic use
  - Clonidine

45

Physical Dependence
Withdrawal Severity

- Depth of dependence is related to extent and duration of exposure
  - Receptor adaptation

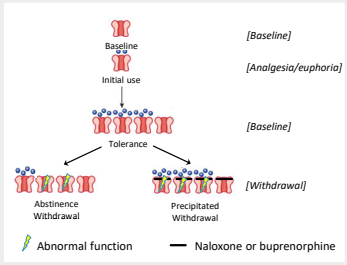


Huhn AS, et al. Drug Alcohol Depend 2020;108:147

46

Physical Dependence
Withdrawal Severity

- Related to rapidity of development of withdrawal



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Drug Interactions

REVIEW COURSE 2024

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Physiological Drug Interactions (Pharmacodynamic)

Heroin and cocaine

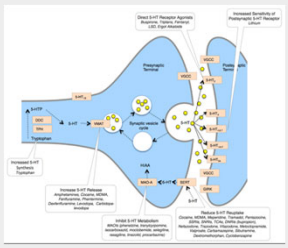
Alcohol and benzodiazepines

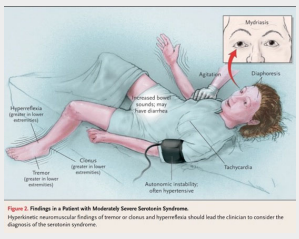
49

Physiological Drug Interactions (Pharmacodynamic)

50

PK/PD Drug Interactions

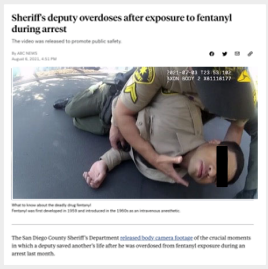


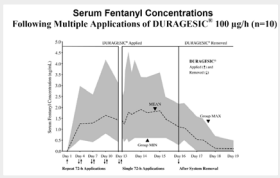


www.real-psychiatry.blogspot.com
Boyer E. NEJM 2005

51

Exposure Pathway





Duragesic prescribing information

52

Consensus Statement

Appropriate Use of Drug Testing in Clinical Addiction Medicine

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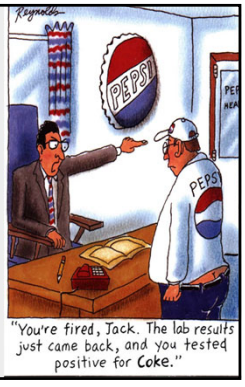
Philosophical Considerations (for substance use)

- Testing is not meant to "catch" the patient
  - Testing identifies recent use it does NOT identify addiction or impairment
  - A positive finding suggests need to review treatment plan
    - Not to prevent, limit, or punitively change treatment
- Tests must be interpreted in the context of patient self-report and other information from observed behaviors or reliable sources
- Language is important
  - e.g., clean vs dirty, pass/fail



54

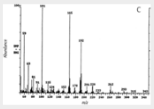
Screening and Confirmatory Tests

Screening (Presumptive) Assays – indicate the presumptive presence of drugs

Highly sensitive

Rapid, inexpensive

Cutoff - Yes/No



Confirmatory (Definitive) Assays – specifically identify the drug detected in the screening assay

Highly specific

Quantitative

Complicated, expensive

55

Screening Tests for "Drugs of Abuse"

- Enzyme immunoassay
  - Based on a substance's structure.
  - Relatively inexpensive, easily automated
- Analytical false positives are possible (e.g., amphetamine assay identifies pseudoephedrine)
  - Confirm "unconfirmed" positive screens in some clinical situations
- Analytical false negatives are uncommon (i.e., assay completely misses an expected analyte)
  - Clinical false negatives occur (e.g., opiate assay doesn't detect a non-morphinan opioid)

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"Drugs of Abuse" Screening

NIDA/SAMHSA 5

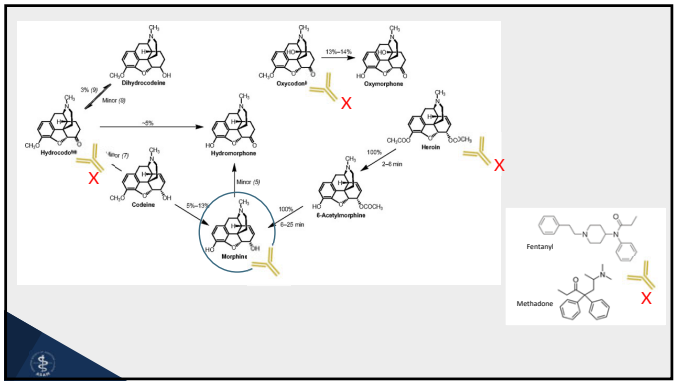
- Opiates
- Amphetamines
- Cocaine
- Marijuana
- Phencyclidine

Analyte	Screen, ng/mL	Confirmatory, ng/mL
Opiates	2,000	2,000
Cannabinoid	50	15
Amphetamine	500	250
Cocaine	300	150
Phencyclidine	25	25

NIDA-9 (Extended)

- Opiates
- Amphetamines
- Cocaine
- Marijuana
- Phencyclidine
- Barbiturates
- Benzodiazepines
- Methadone
- Propoxyphene

57



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The "Opiate" Assay: Not So Good for "Opioids"

	Online DAT opiates IA[1] assay	EMIT II+ opiates assay[2]	TDx/TDx-flex opiate opiate assay[3]	Architect/ Aeroset	Acsym opiate[3]	CEDIA opiate[4]	DRI opiate[4]	DRI oxycodone[4]
Morphine	100	100	100	100	100	100	100	<29
Codeine	133	99	>3.0	167	>3.0	125	167	<20
Ethyl morphine	101		<10		>100			
Diacetyl morphine (heroin)	82					53	86	<33
6-Acetylmorphine	78	69	>20	67	<30	81	79	<200
Dihydrocodeine	69	103	>3.6	106	>3.6	50	67	<100
Morphine-3-glucuronide	54	48	>57	47	>57	81	50	<11
Morphine-6-glucuronide			>5.7		<8.6	47	100	
Hydrocodone	28	121	>8.0	158	>12	48	18	<133
Hydromorphone	21	69	>4.9	54	>9.7	37	75	<333
Norcodeine	2							<10
Normorphine							0	<10
Oxycodone	0	12	>1.1	11	<1.7	3.1	1.9	100
Oxymorphone		1.5	<10	0	<15	1.9	0.7	103
Noroxycodone								<0.1
Noroxymorphone								<0.1
Meperidine	0	<0.6	<2.0	0	<3.0	0.2	0	
Levallorphan		<4	<6.0	13	<6.0			
Levorphanol		29	>6.0	27	>6.0		2.1	<50
Nalorphine		3	<20	2.3	<30			
Naloxone	0	0.04	<20	0	<30		0	<50
Imipramine	0					1.6		
Ranitidine						0	0	
Thebaine	25		<20		<30		<15	
Naltrexone	0						0	<20
Fentanyl			<60		<60			

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TABLE 7–4 Performance Characteristics of Common Urine Drug Screening Immunoassays*

Drug/Class	Detection Limits (ng/mL)†	Confirmation Limits (ng/mL)‡	Detection Interval§	Comments
Amphetamine/ methamphetamine	500	500	1–2 days (2–4 days)	Decongestants, ephedrine, l-methamphetamine, selegiline, and bupropion metabolites are reported to give false-positive test results with some assays; MDA, MDEA, and MDMA are variably detected.
Barbiturates	200		2–4 days	Phenobarbital detection interval is up to 4 weeks.
Benzodiazepines	100–300		1–10 days	Benzodiazepines vary in reactivity and potency. Hydrolysis of glucuronides increases sensitivity. False-positive test results are reported with oxaprozin.
Cannabinoids	50	15	1–3 days (1 month)	Screening assays detect inactive and active cannabinoids; confirmatory assay detects inactive metabolite THCA. Duration of positivity is highly dependent on screening assay detection limits.
Cocaine	150	100	2 days (1 wk)	Screening and confirmatory assays detect inactive metabolite BE. False-positive test results caused by cross-reactive compounds are unlikely.
Opiates			1–2 days (1 week)	Semisynthetic opioids derived from morphine show variable cross-reactivity. Fully synthetic opioids (eg, fentanyl, meperidine, methadone, tramadol) have minimal cross-reactivity. Quinolones are known to cross-react with some assays.
Codeine/morphine	2,000	2,000		
Hydrocodone/hydromorphone	300	100		
Oxycodone/oxymorphone	100	50		
6-Acetylmorphine	10	10		
Methadone	300		1–4 days	Doxylamine is reported to cross-react with some assays.
Phencyclidine	25	25	4–7 days (1 month)	Dextromethorphan, diphenhydramine, ketamine, and venlafaxine is reported to cross-react with some assays.

*Performance characteristics vary with manufacturer and may change over time. For the most accurate information, consult the package insert of the current kit or contact the manufacturer. †Substance Abuse and Mental Health Services Administration recommendations[17] are shown for amphetamines/methamphetamines, cannabinoids, cocaine, opiates, and phencyclidine immunoassays. Other commercial immunoassay cutoffs are also listed. Other cutoffs may be set by individual laboratories. ‡Values are after typical cross-values in parentheses are after heavy or prolonged use.

BE = benzoylecgonine; MDA = methylenedioxyamphetamine; MDEA = methylenedioxyethylamphetamine; MDMA = methylenedioxymethamphetamine; THCA = tetrahydrocannabinolic acid.

Goldfrank's Toxicologic Emergencies, 11th Edition

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Complicated situation

- You are evaluating your long-standing patient who tests positive for "opiates" on routine testing. The patient assures you they have not used any drugs.
- Analytical true positive
  - Clinical false positive (need 6-MAM)
- Note for all screens
  - Unclear which substance (e.g., which opioid)
  - Does not correlate with impairment
  - Cannot tell route, time of use, or amount used

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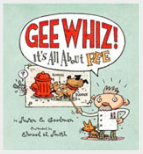
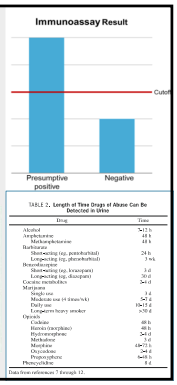
Interpretation of a Negative Opioid Screen

- Patient is not using (e.g., diversion)
- Clinical false negative
  - Collection/Lab error
  - Wrong assay used
    - e.g.: "Opiate" assay for oxycodone
  - Cutoffs are often used
  - Detection periods are short
  - Adulteration



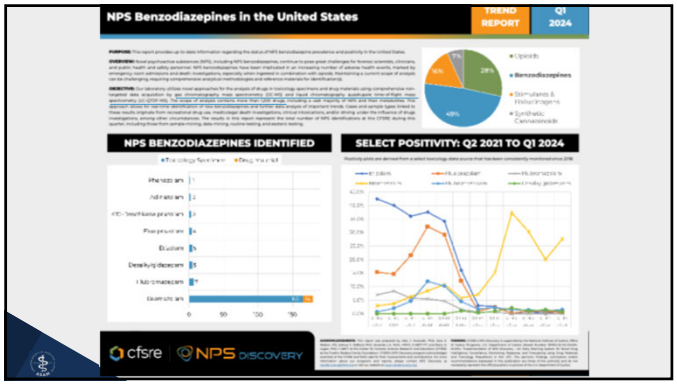


62

The Gold Standards for Confirmation

- Gas Chromatography/Mass Spectrometry
  - Gold standard for confirmation
  - Chemical "fingerprint" of drugs
  - Sensitive and specific
  - Legally defensible
- Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS)
  - Emerging Standard for Confirmation
  - Less sample preparation

63



64

Buprenorphine analysis

- Can only generalize about expected levels
  - No credible way to say "X" dose should give "Y" level
  - Patients tend to stay within a certain range over time unless dose change
    - Trending helpful and can detect aberrancy
- Adulterated specimen
  - Bup without metabolite (always)
  - Bup >1000 ng/mL, even with metabolite (suggestive)
- Higher Bup levels than Norbup levels due to:
  - Dosing shortly before urine test
  - CYP 3A4 inhibitor or substrate which slows conversion to metabolite

65

Matrix Considerations

- Window of detection
- Time to obtain results (availability of POCT)
- Ease of collection (need for trained personnel, collection facilities)
- Invasiveness/unpleasantness of collection
- Availability of the sample (e.g., renal health, shy bladder, baldness, dry mouth)
- Susceptibility of the sample to tampering

66

Drugs and metabolites are concentrated in urine
Can compare to creatinine

Drugs are found in much lower concentrations
Easy to observe

Drugs and metabolites incorporated into hair
Concentrations of drugs low with sporadic use

Prospective collection, 1-2 weeks
Inter and intraindividual variability

Invasive and expensive to test
More direct relationship to impairment

Easy to collect and observe
Essentially limited to ethanol

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TABLE 4. Comparing Testing Characteristics Across Matrices

	Blood	Breath	Oral Fluid	Urine	Sweat	Hair
General detection period	<24 hours [7] 1–8 hours [25] 1–48 hours [26]	~1 hr per standard drink	<24 hours [7] 12–24 hours [27] 1–36 hours [28] 5–48 hours [29] 12–48 hours [25]	1.5–4 days [29] 1–3 days [25,26,30]	Continuous, usually 1–4 weeks [2,26]	7–90 days [7] 7–100 days [26]
POCT/On-site immunoassay available	Yes, primarily used for alcohol	For alcohol	Yes	Yes	No	No
Primarily detects	Parent drug compound; blood alcohol concentration	Parent drug compound; blood alcohol concentration	Parent drug compound	Drug metabolite	Parent drug compound	Parent drug compound
Best use in treatment setting	Determination of acute impairment or intoxication for alcohol	Determination of acute impairment or intoxication for alcohol	Short-term detection in ongoing treatment	Intermediate-term detection in ongoing treatment	Medium-term prospective monitoring	Long-term monitoring; 3-month drug use history
Ease of collection	Requires staff trained in phlebotomy	Easily collected	Easily collected	Requires specialized collection facility (restroom)	Easily collected	Easily collected
Intrusiveness of collection	High for intravenous access	Low	Low	High	Low	Low
Resistance to tampering	High	High	High, but some uncertainty	Low	High, but some uncertainty	High when chemically untreated
Retesting same sample	Difficult	Generally not possible	Difficult	Possible	Possible depending on patch used	Easy

ASAM Appropriate Use of Drug Testing in Clinical Addiction Medicine, 2017

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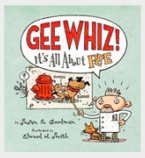
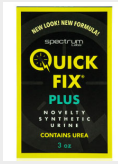
Specimen validity testing





69

Where Can I Get Help with Interpretation?

- Medical or forensic toxicologist
- Staff at the testing laboratory
- A physician with MRO certification

70

What property of fentanyl accounts for its enhanced psychoactive effects compared to morphine?

A. Charge
B. Lipophilicity
C. Molecular weight
D. Potency

71

A patient started on opioids requires increasing doses of medication to get adequate pain relief. At the same time, painful stimuli elicit more pain that they previously did. What does this represent?

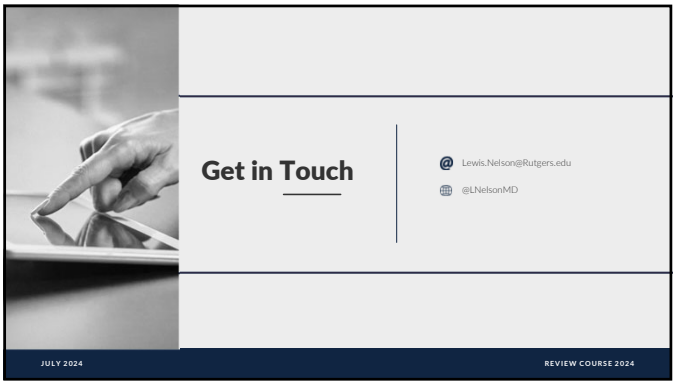
A. Hyperalgesia
B. Pharmacodynamic tolerance
C. Pharmacokinetic tolerance
D. Withdrawal

72

Which of the following drug screening tests is associated with the lowest rate of false positive results?

A. Amphetamine
B. Cocaine
C. Opioids
D. Phencyclidine

73



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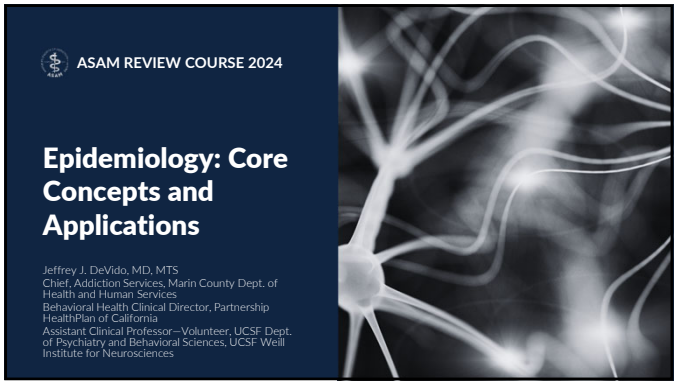
ASAM REVIEW COURSE 2024
Epidemiology: Core Concepts and Applications
Jeffrey J. DeVido, MD, MTS
Chief, Addiction Services, Marin County Dept. of Health and Human Services
Behavioral Health Clinical Director, Partnership HealthPlan of California
Assistant Clinical Professor—Volunteer, UCSF Dept. of Psychiatry and Behavioral Sciences, UCSF Weill Institute for Neurosciences

1


Financial Disclosure
Jeffrey J. DeVido, MD, MTS
• Equity shareholder: Altria/Philip Morris/Merck
The opinions expressed in this talk are mine and they do not represent the opinions of my employing institutions or those with whom I am professionally affiliated.
I will not be talking about off or on label medications for the treatment of any condition.
REVIEW COURSE 2024

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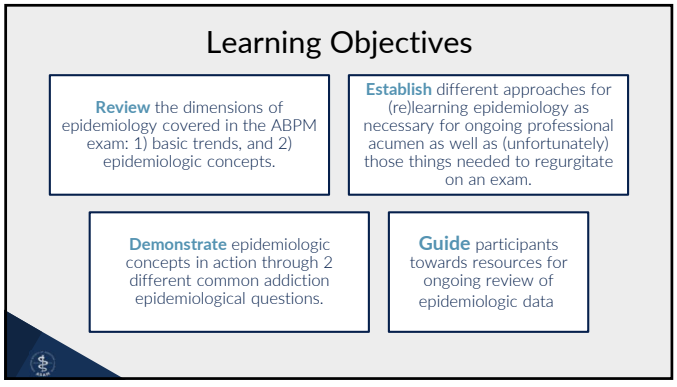

Learning Objectives
Review the dimensions of epidemiology covered in the ABPM exam: 1) basic trends, and 2) epidemiologic concepts.
Establish different approaches for (re)learning epidemiology as necessary for ongoing professional acumen as well as (unfortunately) those things needed to regurgitate on an exam.
Demonstrate epidemiologic concepts in action through 2 different common addiction epidemiological questions.
Guide participants towards resources for ongoing review of epidemiologic data

3

Presentation Outline

- Consider ways of thinking about and learning about epidemiology
- Cheat sheets vs. enduring learning patterns
- Highlight some important epidemiological trends AND how to find them yourselves…
- Follow two common questions in addiction medicine as a springboard for reviewing key concepts in epidemiology

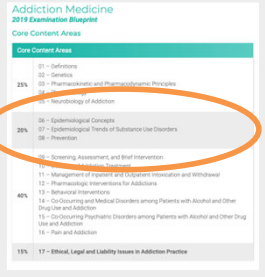
4

Two Ways to Think about Epidemiology

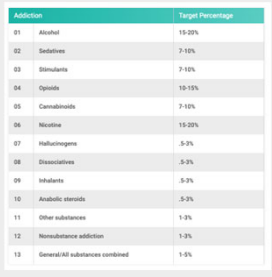
- What do I need to know for the test?
- What might I need to know professionally?

5

The ABPM Exam and Epi


Addiction Medicine
2019 Examination Blueprint
Core Content Areas

Core Content Areas		
25%	01 – Definitions 02 – Genetics 03 – Pharmacokinetic and Pharmacodynamic Principles 04 – Neurobiology of Addiction	
20%	06 – Epidemiological Concepts 07 – Epidemiological Trends of Substance Use Disorders 08 – Prevention	
40%	09 – Screening, Assessment, and Brief Intervention 10 – Medication-Assisted Treatment 11 – Management of Inpatient and Outpatient Intoxication and Withdrawal 12 – Pharmacologic Interventions for Addictions 13 – Behavioral Interventions 14 – Co-Occurring and Medical Disorders among Patients with Alcohol and Other Drug Use and Addiction 15 – Co-Occurring Psychiatric Disorders among Patients with Alcohol and Other Drug Use and Addiction 16 – Pain and Addiction	
15%	17 – Ethical, Legal and Liability Issues in Addiction Practice	



Addiction		Target Percentage
01	Alcohol	15-20%
02	Sedatives	7-10%
03	Stimulants	7-10%
04	Opioids	10-15%
05	Cannabinoids	7-10%
06	Nicotine	15-20%
07	Hallucinogens	.5-3%
08	Dissociatives	.5-3%
09	Inhalants	.5-3%
10	Anabolic steroids	.5-3%
11	Other substances	1-3%
12	Nonsubstance addiction	1-3%
13	General/All substances combined	1-5%

https://www.theabpm.org/become-certified/exam-content/addiction-medicine-content-outline/

6

For the Test Strategy:

Some assumptions:

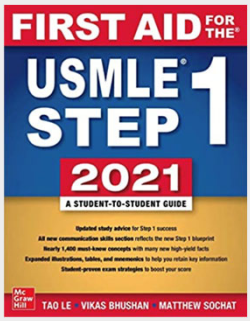
- All of you have had some rudimentary epidemiology/biostatistics
- Most of you have seen these concepts multiple times
- For the most part, you don't use these concepts as much as they come up on tests
- You scribble some notes on a cheat sheet to remind yourself as you're studying
- When you've been taught these concepts before, it has been shoveled to you in large amounts in short lectures

7

For the Test Strategy:

http://www.bishopmikelowry.com/wp-content/uploads/2013/03/drinking-from-the-firehose.jpg

8



https://www.amazon.com/First-USMLE-Step-2021-Thirty/dp/126046752X/ref=asc_df_126046752X/?tag=hyprod-20&linkCode=df0&hvadid=459537678676&hvpos=&hvnetw=g&hvrand=12792418851990343229&hvpone=&hvptwo=&hvqmt=&hvdev=c&hvdvcmdl=&hvlocint=&hvlocphy=9032089&hvtargid=pla-1113406220592&psc=1

9

So...

https://memegenerator.net/instance/26662134/med-student-meerkat-stay-on-your-toes

10

Let's Do A Quick Matching Exercise:

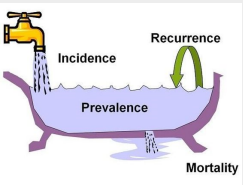
- Incidence
- Prevalence

- #of existing cases/Total #of people (at a point in time)
- Rate: #new cases/#people at risk (during a specified time period)

11

Incidence:

- Represents the RISK of a disease: new cases coming into a population in time
- Have to see people longitudinally (in time) so these data are harder to find for SUDs—PROSPECTIVE studies
  - Example: follow-ups on Epidemiologic Catchment Area study (1980s)
    - Highest incidence in youngest population (18-29 y/o)



http://image.slidesharecdn.com/measurementinepidemiology-141121024727-conversion-gate01/95/measurements-in-epidemiology-15-638.jpg?cb=1416559706

12

Let's Start with A Quick Matching Exercise:

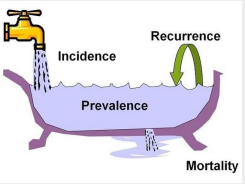
- Incidence
- Prevalence

- #of existing cases/Total #of people (at a point in time)
- Rate: #new cases/#people at risk (during a specified time period)

13

Prevalence:

- Represents the *public health burden* of a disease at a particular time
- CROSS SECTIONAL SURVEYS
  - Example: annual National Survey on Drug Use and Health (NSDUH)
    - Tobacco products, alcohol, illicit drugs



http://image.slidesharecdn.com/measurementinepidemiology-141121024727-conversion-gate01/95/measurements-in-epidemiology-15-638.jpg?cb=1416559706

14

Let's Start With Some Useful Basics:

Primary Prevention

Interventions designed to prevent the onset or future incidence of a specific problem

Secondary Prevention

An early intervention that decreases the prevalence of a specific problem

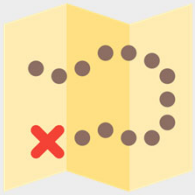
Tertiary Prevention

Treatment designed to improve quality of life and reduce the symptoms after a disease or disorder has developed
Does not reduce incidence or prevalence

https://press.rebus.community/introductiontocommunitypsychology/chapter/prevention-and-promotion/

15

Let's take a quick tour of some prevalence data and important trends to help us put the story together:

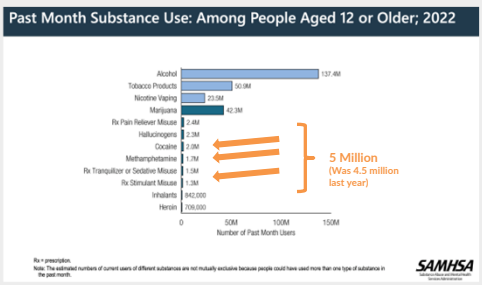


16

First: Big Picture

17

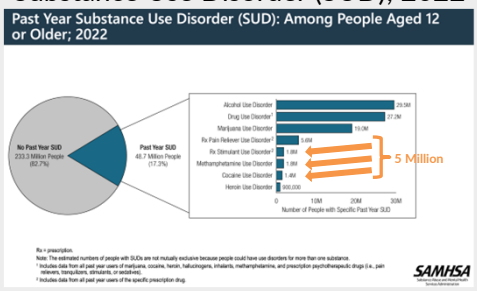
2022 NSDUH Prevalence: Past Month General Substance Use and Nicotine Vaping: Among People Aged 12 or Older; 2022



https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases#highlighted-pop-slides

18

People Aged 12 or Older with a Past Year Substance Use Disorder (SUD); 2022

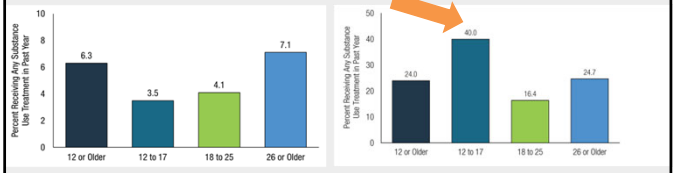


https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases#highlighted-pop-slides

19

But do people get treatment?

2021 ? 2022



https://www.samhsa.gov/data/sites/default/files/reports/rpt39443/2021_NNR_figure_slides.pdf

20

But do people get treatment?

2022

Substance use treatment = treatment received in the past year for the use of alcohol or drugs in an inpatient location; in an outpatient location; via telehealth; or in a prison, jail, or juvenile detention center; or the receipt of medication-assisted treatment (MAT) for alcohol use or opioid use.

A support group, a peer support specialist or recovery coach who works with a substance use treatment program or other treatment provider, services in an emergency room or emergency department, or detoxification or withdrawal support services from a healthcare professional. These other services were **NOT** classified as "substance use treatment."

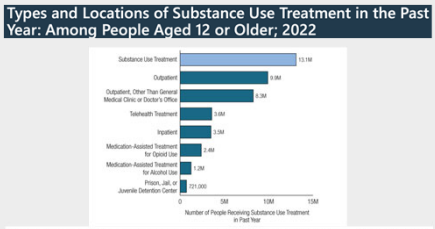
In 2022, the term "specialty facility" was dropped from 2022 NSDUH data products.

In 2022, respondents were classified as needing substance use treatment if they had a substance use disorder in the past year or received treatment for their alcohol or drug use through inpatient treatment or counseling, outpatient treatment or counseling, medication-assisted treatment, telehealth treatment, or treatment received in a prison, jail, or juvenile detention center.

https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases#new-changed

21

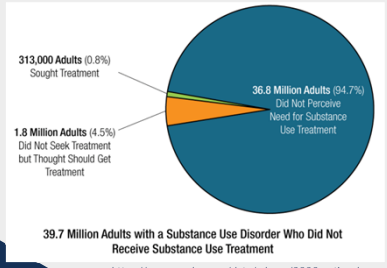
For the people who do get "treatment" where do people get it?



https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases#highlighted-pop-slides

22

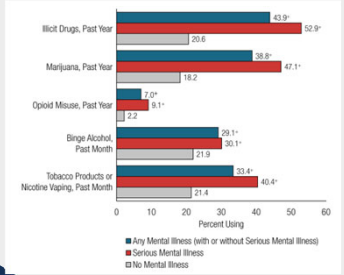
Perceived NEED for treatment (2022): 18 or older with past year SUD who did NOT receive SU treatment in past year



https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases#highlighted-pop-slides

23

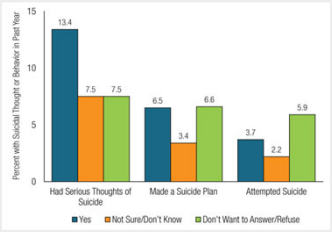
Past Year or Past Month Substance Use: Among Adults Aged 18 or Older; by Mental Illness Status, 2022



https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases#highlighted-pop-slides

24

Had Serious Thoughts of Suicide, Made a Suicide Plan, or Attempted Suicide in the Past Year: Among Youths Aged 12 to 17; 2022



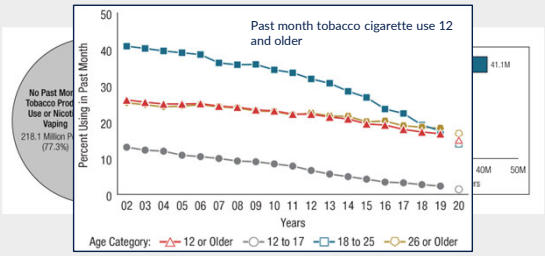
https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases#highlighted-pop-slides

25

Second: Looking a little closer by substance

26

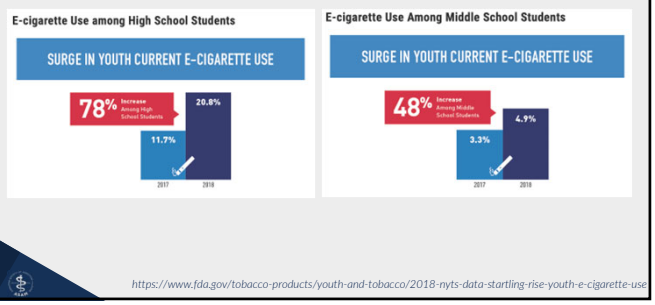
Tobacco/Nicotine



https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases#highlighted-pop-slides

27

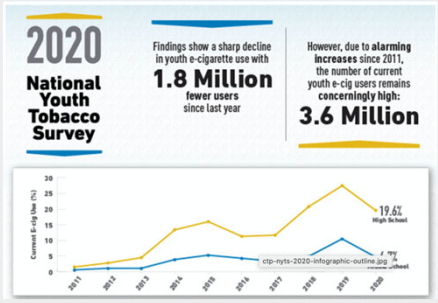
E-Cigarettes



https://www.fda.gov/tobacco-products/youth-and-tobacco/2018-nyts-data-startling-rise-youth-e-cigarette-use

28

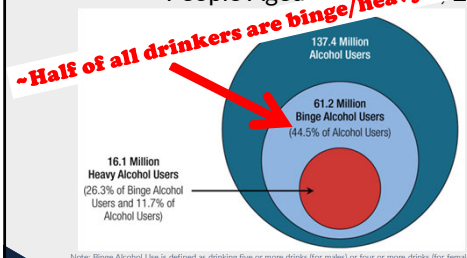
But(t):



https://www.fda.gov/tobacco-products/youth-and-tobacco/youth-tobacco-use-results-national-youth-tobacco-survey

29

Current, Binge, and Heavy Alcohol Use among People Aged 12 [illegible]



60.6% of all SUDs in US are Alcohol (may be overlap)

Note: Binge Alcohol Use is defined as drinking five or more drinks (for males) or four or more drinks (for females) on the same occasion on at least 1 day in the past 30 days. Heavy Alcohol Use is defined as binge drinking on the same occasion on 5 or more days in the past 30 days; all heavy alcohol users are also binge alcohol users.

https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases#highlighted-pop-slides

30

Alcohol deaths increase dramatically during pandemic, especially for younger adults: Research

Deaths were up 25% according to a recent study.

By Eli Cahan
May 10, 2022, 3:19 AM • 6 min read

BLOG

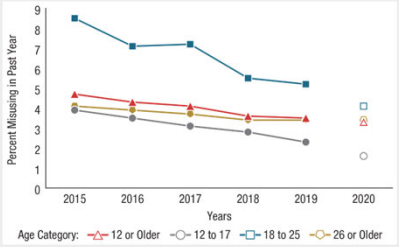
Behind the Numbers: Alcohol is Killing More People Than the Opioid Epidemic. Why Aren't We Talking About It?

https://abcnews.go.com/Health/alcohol-deaths-increase-dramatically-pandemic-younger-adults-research/story?id=84496498

https://www.caron.org/blog/alcohol-is-killing-more-people-than-the-opioid-epidemic

31

Past Year Prescription Pain Reliever Misuse: Among People Aged 12 or Older; 2015-2020



https://www.samhsa.gov/data/data-we-collect/nsduh-national-survey-drug-use-and-health

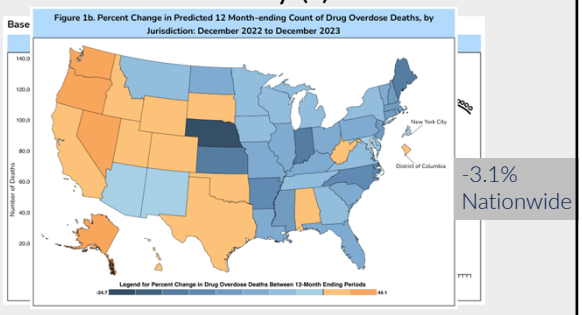
32

Yet…

https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates

33

Fortunately (?)…

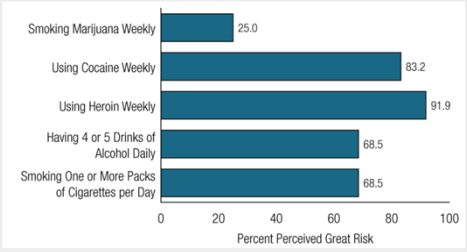


-3.1% Nationwide

https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

34

Perceived Great Risk from Substance Use: Among People Aged 12 or Older; 2022

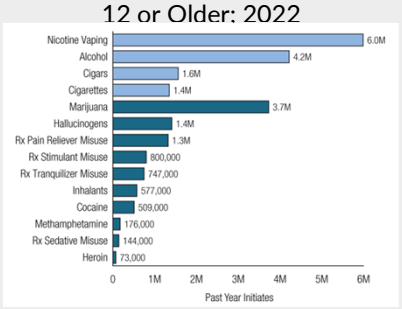


https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases#highlighted-pop-slides

35

36

Past Year Initiates of Substances: Among People Aged 12 or Older: 2022



https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases#highlighted-pop-slides

37

Past Year Hallucinogen Use: 2022

Kdoxflqrjhq#Kvh=

Dp rqj#dgxow#ljhg#1<#wr#53/#;(#uhsruwhg#sdvw0|hdu#kvh#ri#kdoxflqrjhqv/#vljqlilfdqw|#kljkhu#wkdq#1yh#|hdv#ljr#8(#q#534:,#lqg#13#|hdv#ljr#6(#q#5345,1#W|shv#ri#kdoxflqrjhqv#uhsruwhg#e|#sduwflsdqw#qfoxghg#DVG/#P G P D/#p hvfddgh/#sh|rwh/#vkurrp v#ru#svbrf|elq/#dqg#SFS1#

Sdvw0|hdu#kdoxflqrjhq#kvh#uhdfkhg#klvwrulfdo|#kljk#suhyddqfh#dp rqj#dgxow#68#wr#83#|hdv#roj/#uhsruwhg#e|#7(#q#5351#Wkh#suhyddqfh#uhsruwhg#q#5355#zdv#dovr#dl#xevwdqwldd#qfuhdvh#frp sduhg#wr#kh#|hdu#ehiruh#5(#q#5354,#lqg#ilyh#lqg#13#|hdv#ljr#qr#juhdwhu#wkdq#1(#q#erwk#534:#lqg#5345,1

https://nida.nih.gov/news-events/news-releases/2023/08/marijuana-and-hallucinogen-use-binge-drinking-reached-historic-highs-among-adults-35-to-50#:~:text=Past%2Dyear%20hallucinogen%20use%20reached,in%20both%202017%20and%202021.

38

https://www.townandcountrymag.com/leisure/arts-and-culture/a38687510/toad-venom-bufo-illegal-psychedelic-drug/
https://www.si.com/boxing/2021/11/17/mike-tyson-says-he-died-smoking-psychedelic-toad-venom

39

Third: Other Important Parts of the Story

40

Race/Ethnicity 2022

	National Average (%)	Black (%)	Asian (%)	American Indian/Alaska Native (%)	Hispanic (%)	Hawaiian/Pacific Islander (%)
Past Month Binge Alcohol Use (12+)	21.7	20.9	10.3	25.5	23.3	**
Past Month Heavy Alcohol Use (12+)	5.7	4.2	1.9	8.0	5.1	**
Past Year Illicit Drug Use (12+)	24.9	26.7	13.6	35.1	23.3	**
Past Year Marijuana Use (12+)	22.0	23.5	11.2	27.3	20.3	**
Past Year SUD (12+)	17.3	18.4	9.0	24.0	17.4	**
Suicidal Thinking Past Year (12+)	5.2	5.5	3.4	9.3	4.6	**

BLACK = national average
RED = ABOVE national average
BLUE = BELOW national average

https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases#highlighted-pop-slides

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Sexual Minority* 2022

	Straight (%)	Bisexual (%)	Gay (%)	Lesbian (%)
Binge Alcohol Use Past Month (18+)	22.8	32.6	29.9	29.2
Illicit Drug Use Past Month (18+)	15.2	42.2	34.9	34.3
Marijuana Use Past Month (18+)	13.9	39.1	29.8	32.5
Opioid Misuse Past Month (18+)	1.0	2.5	1.5	1.5
SUD Past Year (18+)	16.3	38.6	33.6	30.2
Suicidal Thoughts Past Year (18+)	4.0	19.9	10.8	12.8

RED = higher than national average
BLUE = Lower than national average
* Defined by SAMHSA as people who identify as lesbian, gay, or bisexual:
NSDUH began collecting data on this specific population in 2015

https://www.samhsa.gov/data/release/2022-national-survey-drug-use-and-health-nsduh-releases#highlighted-pop-slides

42

Gender…

- Women tend to initiate substance use later than men
- Women have accelerated course of disorder → "telescoping" (alcohol, marijuana, cocaine, prescription opioids)
- Women with SUDs → more severe impairment in employment, social/family, medical and psychiatric functioning
- Women have LOWER rates (2022) than men for binge drinking, illicit drug use, cannabis/opioid use, SUD
- Women have HIGHER rates (2022) than men for MDE, any mental illness, receipt of MH services

McHugh RK, et al. Sex and gender differences in substance use disorder. Clin Psychol Rev. 2017 Nov 10.

https://www.samhsa.gov/data/report/nsduh-2022-highlighted-population-slides

43

Let's Look at a Study…

- Question: Does Marijuana use cause psychosis?

Schizophrenia Bulletin vol. 42 no. 5 pp. 1262–1269, 2016
doi:10.1093/schbul/sbw003
Advance Access publication February 15, 2016

Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis

Arianna Marconi[1], Marta Di Forti[2], Cathryn M. Lewis[2], Robin M. Murray[1], and Evangelos Vassos[*,2]

[1]Department of Psychosis Studies, King's College London, Institute of Psychiatry Psychology & Neuroscience, London, UK; [2]King's College London, Institute of Psychiatry Psychology & Neuroscience, MRC SGDP Centre, London, UK

*To whom correspondence should be addressed; King's College London, Institute of Psychiatry Psychology & Neuroscience, MRC SGDP Centre, Box P082, De Crespigny Park, London SE5 8AF, UK; tel: +44-20-7848-5433, fax: +44-20-7848-0866, e-mail: evangelos.vassos@kcl.ac.uk

44

What Is This Study?

- Performed a systematic review and a meta-analysis
- Included: provided data on cannabis consumption prior to the onset of psychosis
  - 18 for systematic review and 10 for meta-analysis (66,816 individuals)
  - Continuous variable → amount of exposure
  - Cohort and cross-sectional studies included
- Findings:
  - Odds ratio 3.90 (95% confidence interval 2.84 to 5.34) for risk of schizophrenia and other psychosis-related outcomes among the heaviest cannabis users compared to non-users

45

What can we say about this study?

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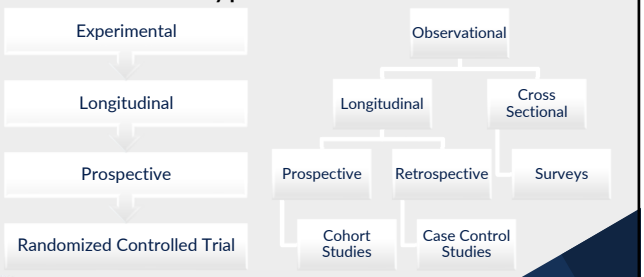
46

1) Quality of evidence, based on study design.

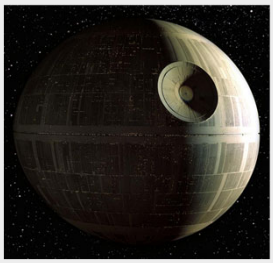
47

Types of Studies



48

Quantifying Risk…



49

Quantifying Risk…

Risk factor or intervention	Disease ⊕	Disease ⊖
⊕	a	b
⊖	c	d

$$AR = \frac{a}{a+b} - \frac{c}{c+d}$$

NNH = 1/AR

$$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

$$RR = \frac{a/(a+b)}{c/(c+d)}$$

$$ARR = \frac{c}{c+d} - \frac{a}{a+b}$$

NNT = 1/ARR

50

Odds Ratio--more

- What is an odds ratio? **Ratio of Odds**
- Higher the Odds Ratio, stronger the association between the exposure and the outcome appears to be
- If Odds Ratio is 1, then that means that the ratio of the odds shows NO ASSOCIATION between the exposure and the outcome
- (those with disease who were exposed/those with disease not exposed)/(those without disease exposed/those without disease not exposed)

51

Odds Ratio—An Example

- Imagine: relationship between getting breast cancer and driving an American car vs. not
  - If no correlation between these two, then the ratio of those with disease who drove American cars/those with disease who didn't would be likely close to 1, and ratio of those without disease who drove American cars/those without disease who did not drive American cars would also be close to 1, and the ratio of those two would be one = no relationship

52

Back To The Cannabis Paper… 2) An ASSOCIATION Was Found

- Odds ratio 3.90 (95% confidence interval 2.84 to 5.34) for risk of schizophrenia and other psychosis-related outcomes among the heaviest cannabis users compared to non-users
  - Dose-response effect seen such that increasing exposure to cannabis increases risk of psychosis-related outcomes

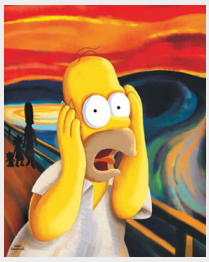
53

What about Confidence Interval?

- (95% confidence interval 2.84 to 5.34)
  - This is the range of values within which the true mean of the population is expected to fall, with a specified probability
  - Probability: 95% CI basically corresponds to p=0.05
  - If this includes 1, for odds ratio or relative risk, null hypothesis is NOT rejected (no significant difference)

54

Oh No, Not the "Null Hypothesis"!!!



55

Oh No, Not the "Null Hypothesis"!!!

Study results support:	Reality: H_1	Reality: H_0
H_1	Power $(1-\beta)$	α Type I error
H_0	β Type II error	Correct

56

Oh No, Not the "Null Hypothesis"!!!

Stating that there is not an effect when one does exists: False negative error

Study results support:	Reality: H_1	Reality: H_0
H_1	Power $(1-\beta)$	α Type I error
H_0	β Type II error	Correct

Stating that there is an effect when none exists: False positive error

57

2) An Association Was Found

- Does this mean that cannabis CAUSES psychosis, based on this paper?

58

Why the heck is his urine toxicology screen negative?

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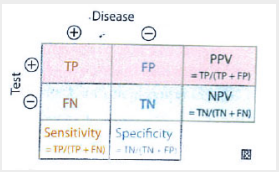
59

Question:

Patient's ED urine drug screen came back negative for opiates, so he must not have used the methadone he claims to be taking?

60

Sensitivity vs. Specificity



61

High sensitivity screen for opiates (those metabolized to morphine), but low sensitivity for synthetic opioids (methadone)

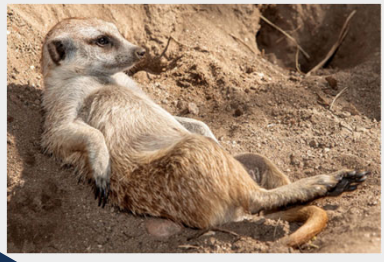
62

What We've Done

- Briefly reviewed scope of epidemiology covered on ABPM exam
- Examined trends in addictions and explored ways to find that data for future professional or personal use
- Followed two common questions in addiction medicine as a springboard for reviewing key concepts in epidemiology

63

Whew!....



https://animals.sandiegozoo.org/animals/meerkat

64

3 CME Questions

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65

A cross sectional survey is conducted to assess how many people at a given time in a particular population have moderate amphetamine use disorder. The survey has not been previously conducted. The total population is 50,000, and the survey reveals that 5,000 people report meeting criteria consistent with moderate amphetamine use disorder. What is the incidence of moderate amphetamine use disorder in this population?

A. 10,000
B. 45,000
C. 0.5
D. Incidence cannot be calculated from single cross-sectional surveys

66

Which of the following is TRUE regarding epidemiologic trends in addictive disorders?

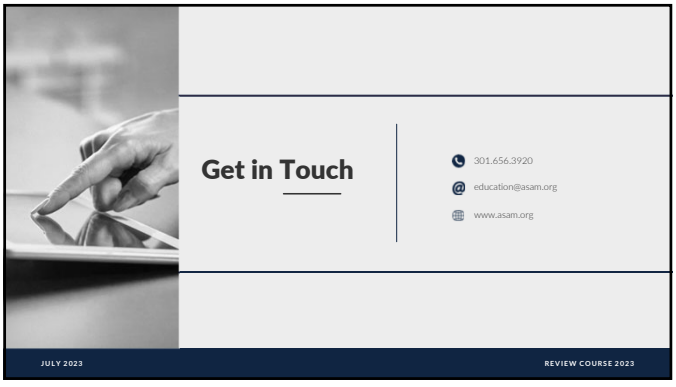
A. Tobacco use has had an overall incline from 2002 to 2019, in large part due to the spike in use of e-cigarettes (especially among younger Americans)
B. Prescription opioid use has modestly increased from 2018-2019 (heroin and prescription pain relievers)
C. Despite decreases in opioid use in recent years, substance related overdose deaths have INCREASED
D. Substance related overdose deaths have increased largely because of the increase in serious mental illness and alcohol use

67

A case control study finds an odds ratio of 5.5 (95% CI 0.5 to 7.5) regarding the association between an exposure and development of a condition. Which is true regarding the above comment?

A. The odds ratio of 5.5 reflects a strong association between the exposure and the development of the condition
B. The high odds ratio here conclusively means that the exposure causes the development of the condition
C. The 95% confidence interval crosses 1, meaning there is an intolerable risk that the perceived relationship (OR 5.5) is due to chance—a type 1 error (no effect/relationship exists)
D. Since case control studies generally "look forward" (i.e. are prospective), this study is likely to have a low chance of asserting a Type II (Beta) error.

68



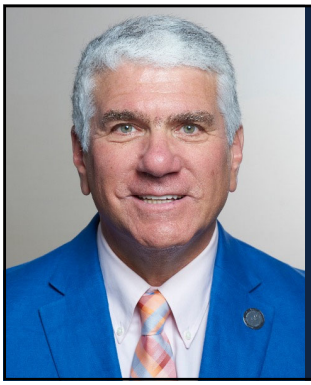
69

ASAM REVIEW COURSE 2024

Interesting Cases: Applying Concepts to Unexpected Real-Life Scenarios

Edwin A. Salsitz, MD, DFASAM
Associate Clinical Professor
Mount Sinai Beth Israel
New York, NY

1



Financial Disclosure

Edwin A. Salsitz, MD, DFASAM

- No relevant disclosures

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2

Name the Event

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3

Patient 1: 64-year-old Female

- Admitted to rehab for treatment of AUD following a "detox" protocol. MMTP 60mg for many years-OUD in Remission
- Married: Spouse no SUD
- F: +EtOH M: No EtOH 4S: No EtOH 2Children: No EtOH
- HS Graduate: Employed in Sales
- Social, Occasional EtOH until age 56
- ? Event → ↑↑ EtOH one year after event → AUD
- PE: unremarkable
- Labs: Normal CMP, CBC, Lipids
- UDT: + Methadone

4

What was the event?

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5

Bariatric Surgery

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6

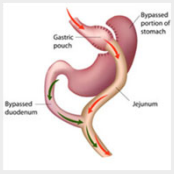
64-year-old Female with AUD

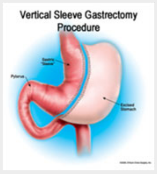
- Age 56: Bariatric Surgery: 5' 4" 240lbs. BMI= 41
- ? Type of Bariatric Surgery?
- ? RYBS, SG, LAGB
- SG
- Current BMI: 24
- 2 liters Vodka day

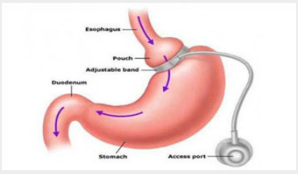
7

RYGB SG LAGB

Roux-en-Y







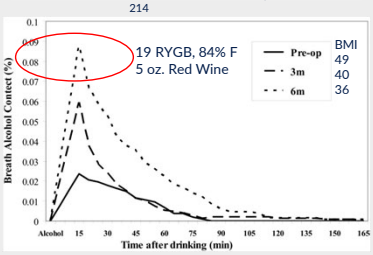
Roux-en-Y, is an end-to-side surgical anastomosis of bowel used to reconstruct the gastrointestinal tract. The name is derived from the surgeon who first described it César Roux and the stick-figure representation.

8

Impaired Alcohol Metabolism after Gastric Bypass Surgery: A Case-Crossover Trial

Gavit A Woodard, BS, John Downey, MD, Tina Hernandez-Boussard, PhD, MPH, John M Morton, MD, MPH, FACS

J Am Coll Surg 2011;212:209-214

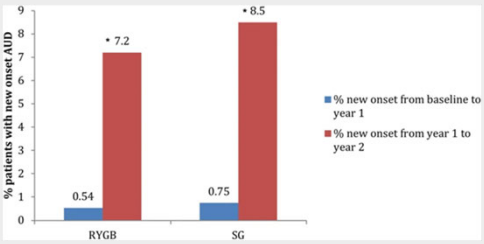


19 RYGB, 84% F
5 oz. Red Wine

BMI
49
40
36

9

Comparison of patients screening positive for AUD between baseline and year 1 and year 1 to year 2 following surgery

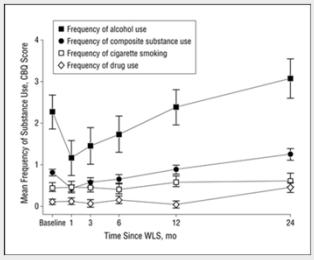


Ibrahim, N., Alameddine, M., Brennan, J. et al. New onset alcohol use disorder following bariatric surgery. Surg Endosc 33, 2521–2530 (2019)

10

Substance Use Following Bariatric Weight Loss Surgery

Alexis Conason, PsyD; Julio Teixeira, MD; Chia-Hao Hsu, PhD; Lauren Puma, MS; Danielle Knafo, PhD; Allan Geliebter, PhD



JAMA Surg. 2013;148(2):145-150

11

Addiction Transfer/Substitution

- Why the ~ 2-year delay?
- Why procedure-dependent?
- Occurs In Patients with Gastrectomy for peptic ulcer and CA with nl BMI
- Rodent Model: ↑EtOH after RYGB

12

Pharmacokinetics/Pharmacodynamics

- Explains Difference RYGB, SG, LAGB
- ↓ Gastric ADH (Cimetidine H2 Blocker)
- ↓Weight → ↑ Socialization
- ↑ Absorption, ↑ Cmax, earlier Tmax
- Feeling More Intoxicated
- AUD>> Other SUDs
- Cocaine Analogy: I.N. → Smoked (Crack Cocaine)

13

Predictors of AUD Post WLS

- Type of Weight Loss Surgery
- Male: Women More WLS
- Younger Age, FH
- EtOH use Pre-Op
- Tobacco, Illicit Drug Use
- ADHD
- Lower Sense of Belonging, Depression
- More Weight Loss → ↑ Socialization → ↑ EtOH

14

Key Takeaways

- New Onset EtOH related problems occur in ~ 10% of WLS Pts.
- More likely with RYGB & SG than with LAGB.
- Some WLS patients ↓ EtOH intake.
- EtOH problems increase over time. Usually begins ~2 years after WLS.
- Inform and Monitor all WLS patients about the risk of AUD/SUD over time.
- Special Thanks to Allan Geliebter PhD, for alerting me to the relationship between Bariatric Surgery and Alcohol

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Next Case

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16

"Rapid Sudden Death" After IV Drug Use

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17

Sudden Death IVDU

- 26 yo male
- 8 year hx of OUD
- Prescription Opioids→ IN Heroin→ IV Heroin last 12 months
- 3 non-fatal ODs last 8 months
- Non compliant with Bupe Rx and Psychosocial Tx
- Argued with his Mother: Went up to his Room: Mother heard a loud thud, found him on floor, unresponsive, with syringe and needle in his arm 5 minutes later.
- Naloxone Nasal Spray 4mg administered X2—No Response
- Patient could not be resuscitated by EMS

18

What Happened?

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19

Sudden Death IVDU

- ? Typical Opioid Induced Respiratory Depression Fatal Overdose
  - Time Frame: ≥ 1 hour: Naloxone Reversal Effectiveness Evidence
- Post Mortem Toxicology: +Fentanyl, -Norfentanyl, +Heroin, -6-MAM, +Morphine
- Fentanyl Induced Chest Wall Rigidity ("Wooden Chest")
  - Fentanyl Induced Respiratory Muscle Rigidity & Laryngospasm

20

Fentanyl Chest Wall Rigidity

- First Reported in 1953 in anesthesia literature
- Skeletal Muscle Rigidity: Chest Wall Most Common
- Most common with fentanyl and its congeners (lipid solubility)
- Most common with rapid IV administration
- ? Activation of the **coerulospinal noradrenergic pathway**, following mu receptor activation in LC
- ? dose related
- +/- Reversal with naloxone (IV route in literature): succinylcholine in OR
- Ventilatory Support
- Low or Absent Nor-fentanyl (appears in 2 minutes: CYP3A4)

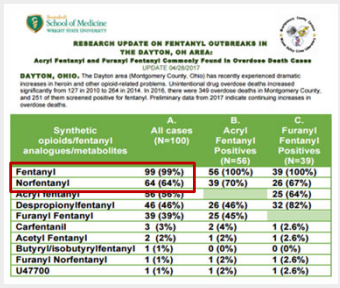
Burns, G et al. Clinical Toxicology, Vol 54, No 5, 420-23, 2016

21

100 Accidental OD deaths
2017:
99% + FENTANYL
Only 3 cases + HEROIN

64% + Nor-fentanyl

2 min: 3A4



Wright State University Boonshoft School of Medicine

RESEARCH UPDATE ON FENTANYL OUTBREAKS IN THE DAYTON, OH AREA:
Acryl Fentanyl and Furanyl Fentanyl Commonly Found In Overdose Death Cases
UPDATE 04/28/2017

DAYTON, OHIO. The Dayton area (Montgomery County, Ohio) has recently experienced dramatic increases in heroin and other opioid-related problems. Unintentional drug overdose deaths increased significantly from 127 in 2010 to 264 in 2014. In 2016, there were 348 overdose deaths in Montgomery County, and 251 of them screened positive for fentanyl. Preliminary data from 2017 indicate continuing increases in overdose deaths.

Synthetic opioids/fentanyl analogues/metabolites	A. All cases (N=100)	B. Acryl Fentanyl Positives (N=56)	C. Furanyl Fentanyl Positives (N=39)
Fentanyl	99 (99%)	56 (100%)	39 (100%)
Norfentanyl	64 (64%)	39 (70%)	26 (67%)
Acryl fentanyl	56 (56%)		25 (64%)
Despropionylfentanyl	46 (46%)	26 (46%)	32 (82%)
Furanyl Fentanyl	39 (39%)	25 (45%)	
Carfentanil	3 (3%)	2 (4%)	1 (2.6%)
Acetyl Fentanyl	2 (2%)	1 (2%)	1 (2.6%)
Butyryl/isobutyrylfentanyl	1 (1%)	0 (0%)	0 (0%)
Furanyl Norfentanyl	1 (1%)	1 (2%)	1 (2.6%)
U47700	1 (1%)	1 (2%)	1 (2.6%)

22

Fentanyl-Induced Chest Wall Rigidity

Başak Çoruh, MD; Mark B. Tonelli, MD; and David B. Park, MD

Fentanyl and other opiates used in procedural sedation and analgesia are associated with several well-known complications. We report the case of a man who developed the uncommon complication of chest wall rigidity and ineffective spontaneous ventilation following the administration of fentanyl during an elective bronchoscopy. His ventilation was assisted and the condition was reversed with naloxone. Although this complication is better described in pediatric patients and with anesthetic doses, chest wall rigidity can occur with analgesic doses of fentanyl and related compounds. Management includes ventilatory support and reversal with either naloxone or a short-acting neuromuscular blocking agent. This reaction does not appear to be a contraindication to future use of fentanyl or related compounds. Chest wall rigidity causing respiratory compromise should be readily recognized and treated by bronchoscopists.

CHEST 2013; 143(4):1145–1146

Taylor & Francis

CLINICAL RESEARCH

Could chest wall rigidity be a factor in rapid death from illicit fentanyl abuse?

Glenn Burns[a], Rebecca T. DeRienz[b], Daniel D. Baker[b], Marcel Casavant[c] and Henry A. Spiller[c]

[a]Central Ohio Poison Center, Ohio State University Medical Toxicology, Columbus, OH, USA; [b]Office of the Franklin County Coroner, Division of Forensic Toxicology, Columbus, OH, USA; [c]Department of Pediatrics, Central Ohio Poison Center, College of Medicine, Ohio State University, Columbus, OH, USA

ABSTRACT

Background: There has been a significant spike in fentanyl-related deaths from illicit fentanyl supplied via the heroin trade. Fast fentanyl access was primarily oral or dermal via prescription fentanyl patch diversion. One factor potentially driving this increase in fatalities is the change in route of administra-

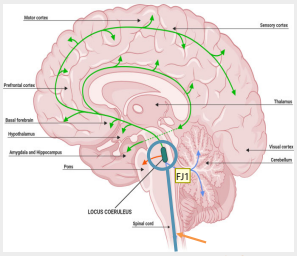
ARTICLE HISTORY
Received 2 December 2015
Revised 12 February 2016
Accepted 17 February 2016
Published online 17 March 2016

KEYWORDS
Chest wall rigidity; fentanyl; heroin; norfentanyl; opioids; overdose

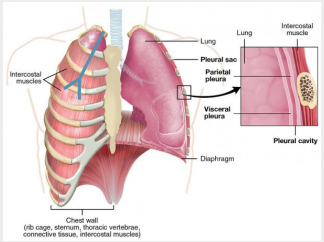
High levels of fentanyl but not norfentanyl = rapid death onset, and is associated with acute chest rigidity
42% No Nor-Fentanyl 20/48 cases

23

Cerulospinal Pathway



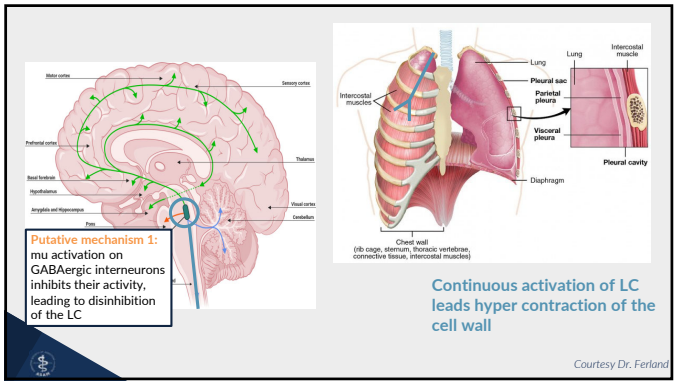
Spinal Motor Neuron



Activation of NE via GABA inhibition increases muscle tone

Courtesy Dr. Ferland

24



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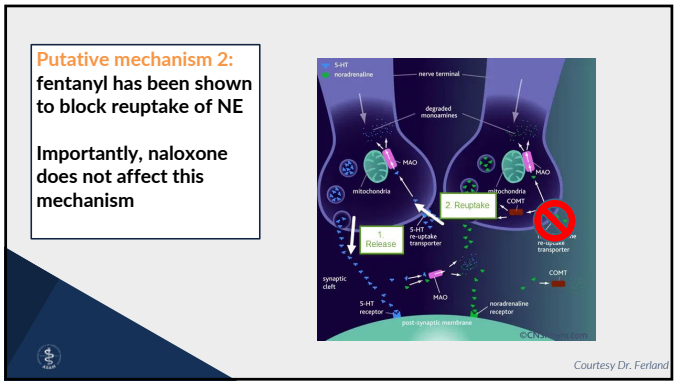

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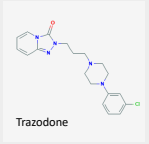
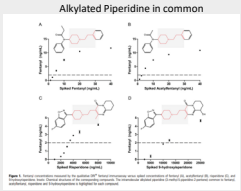
False Positive Fentanyl Immunoassay

- Trazodone
- Risperidone, Paliperodone, Iloperidone
- Some of the Fentanyl Analogues
- Not Norfentanyl
  - Diphenhydramine, Sertraline,
  - Labetalol, Fluoxetine, MDMA,
  - Methamphetamine, Amitriptyline





Lockwood et al. Harm Reduct J (2021) 18:30
J Addict Med 2021;15: 150–154
Journal of Analytical Toxicology 2014;38:672 –675

27

Next Case

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28

38 yo Female with AUD

- Admitted to inpatient rehab following alcohol "detox" with chlordiazepoxide Sept 2016
- Never felt happy—anxious, low self esteem
- Father physically abused patient: mother ignored
- Raped on street by stranger while intoxicated with EtOH: age 20
- EtOH, THC in H.S.: IN cocaine D/C'd 10 yrs ago: heroin IN X4 did not like: never IV. EtOH preferred: Benzos last few years

29

38 yo Female with AUD

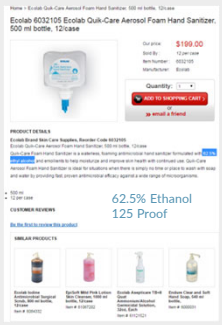
- Rehab is a locked unit, with visitors 1xweek--Sunday. Pt. had visitor on 3rd day of rehab
- Started on Gabapentin 300mg tid on admission for MAT for AUD
- On 4th day of rehab, 9AM, patient had altered mental status, and rapid response called. Patient was somnolent: O2 Sat=91%, Glu=64, BP=125/70, P=60, Pupils=nl. After DW50 and IV hydration MS improves. Remains on Rehab unit.
- UDT: Negative –opiate, cocaine, THC, benzo, PCP, MTD, Bupe
- Blood Alcohol Level: 312mg/dl

- What Happened??
- Where did the Alcohol come from?

30

Hand Sanitizer Ingestion

31



32

5% 10 Proof

13% 25 Proof

40% 80 Proof

50% 100 Proof

33

~ 25% Alcohol
50Proof

35% Alcohol
70Proof

10% Alcohol
20Proof

34

38 yo female with AUD

- 5 year hx of drinking hand sanitizer in health care facilities; like Vodka—but stronger
- Would drink Sanitizer to alleviate withdrawal
- No hangovers
- Also drank Listerine
- Required ICU and intubation in the past

35

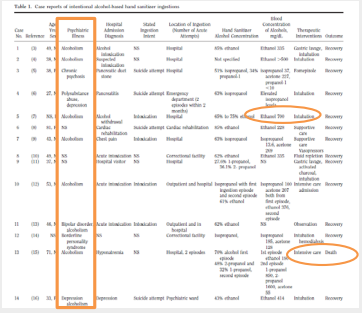


Table 1. Case reports of intentional alcohol-based hand sanitizer ingestions

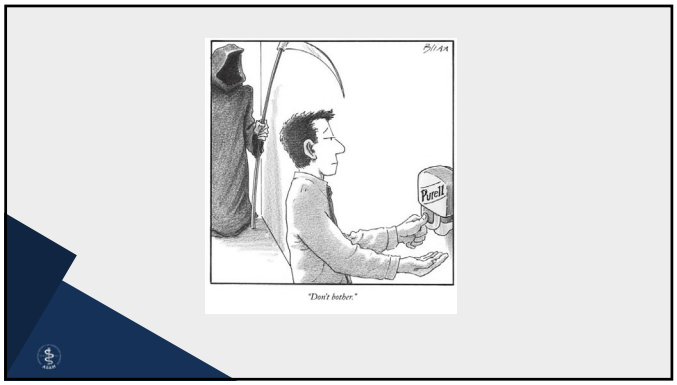
Case No.	Reference	Age	Sex	Psychiatric Illness	Hospital Admission Diagnosis	Stated Ingestion Intent	Location of Ingestion (Number of Acute Attempts)	Hand Sanitizer Alcohol Concentration	Blood Concentration of Alcohols, mg/dL	Therapeutic Interventions	Outcome
1	(3)	49, M	Alcoholism	Alcohol intoxication	NS	Hospital	65% ethanol	Ethanol 335	Gastric lavage, intubation	Recovery
2	(4)	56, M	Alcoholism	Suspected intoxication	NS	Hospital	Not specified	Ethanol >500	Intubation	Recovery
3	(5)	38, F	Chronic psychosis	Pancreatic duct stone	Suicide attempt	Hospital	51% isopropanol, 36% propanol-1	Isopropanol 57, acetone 227, propanol-1 1	Pramipexole	Recovery
4	(6)	27, M	Polysubstance abuse, depression	Pancreatitis	Suicide attempt	Emergency department (2 episodes within 2 months)	63% isopropanol	Elevated isopropanol levels	Intubation	Recovery
5	(7)	NR, M	Alcoholism	Alcohol withdrawal	Intoxication	Hospital	63% to 70% ethanol	Ethanol 700	Intubation	Recovery
6	(8)	40, F	NR	Cardiac rehabilitation	Suicide attempt	Cardiac rehabilitation	61% ethanol	Ethanol 269	Supportive care	Recovery
7	(9)	63, M	Alcoholism	Chest pain	Intoxication	Hospital	63% isopropanol	Isopropanol 12.6, acetone 1	Supportive care	Recovery
8	(10)	49, M	NS	Acute intoxication	NS	Correctional facility	62% ethanol	Ethanol 335	Intubation, fluid repletion	Recovery
9	(11)	37, M	NS	Hospital visitor	NS	Hospital	27.6% 1-propanol, 36.1% 2- propanol	NS	Gastric lavage, activated charcoal, intubation	Recovery
10	(12)	52, M	Alcoholism	Acute intoxication	Intoxication	Outpatient and hospital	Isopropanol with first ingestion episode and second episode 41% ethanol	Isopropanol 166 acetone 207 both from first episode, ethanol 35% second episode	Intubation	Recovery
11	(13)	68, M	Bipolar disorder, alcoholism, borderline personality disorder	Acute intoxication	Intoxication	Outpatient and in hospital	62% ethanol	NS	Observation	Recovery
12	(14)	NR	NS	NS	NS	Correctional facility	Isopropanol,	Isopropanol 190, acetone 1	Intubation, hemodialysis	Recovery
13	(15)	71, M	Alcoholism	Hyponatremia	NR	Hospital, 2 episodes	75% alcohol first episode 68% 1-propanol and 32% 1-propanol, second episode	1st episode ethanol 160, 2nd episode 1-propanol 1200, 2-propanol 1400, acetone 50	Intensive care	Death
14	(16)	33, F	Depression, alcoholism	Depression	Suicide attempt	Psychiatric ward	43% ethanol	Ethanol 414	Intubation	Recovery

Critical Care Medicine. 40(1):290-294, January 2012

36


Subway Riders Scrub Anti-Semitic Graffiti, as 'Decent Human Beings'
With Ample Purell, Riders Scrub Graffiti
than 354,000 times. "I've never seen so many people simultaneously reach into their bags and pockets looking for tissues and Purell," Mr. Locke wrote. "Within about two minutes, all the Nazi symbolism was gone." Mr. Nied
February 05, 2017 - By JONAH ENGEL BROMWICH - N.Y. / Region - Print Headline: "With Ample Purell, Riders Scrub Graffiti"

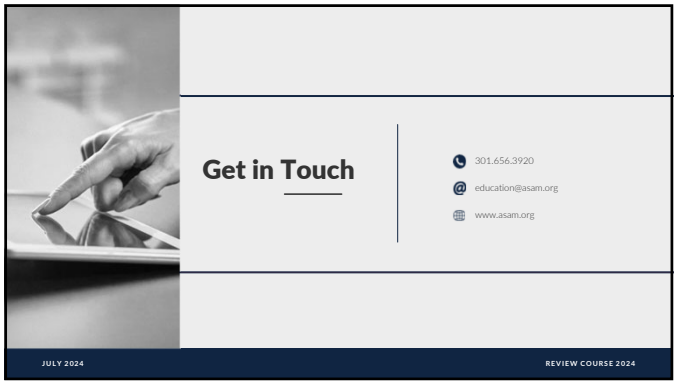
37


Purell
"Don't bother."

38


KEEP CALM AND CARRY ON

39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CO-OCCURRING MENTAL HEALTH AND SUBSTANCE USE DISORDERS

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Financial Disclosure

I, Mason Turner, MD, DFASAM, have nothing to disclose, and in this presentation, I have indicated where proposed use of "off label" drugs is mentioned.

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Educational Objectives

After attending this presentation, participants will be able to:

- Formulate a diagnostic assessment approach for differentiating substance-induced and primary mental health conditions.
- Describe the epidemiology of major mental health conditions relative to substance use disorders
- Apply treatment approaches for co-occurring disorders in their practice environment
- Describe inequities in healthcare delivery for those with co-occurring disorders and understand one method by which they can address those inequities.

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IMPORTANCE OF CO-OCCURRING DISORDERS

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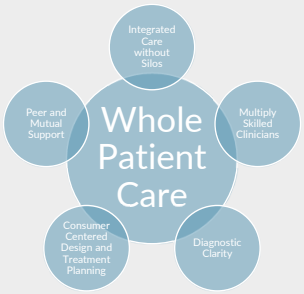
IMPORTANCE OF CO-OCCURRING DISORDERS



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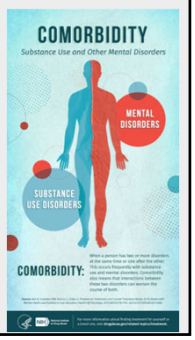
IMPORTANCE OF CO-OCCURRING DISORDERS

Co-occurring: The co-existence of both a mental illness and a substance use disorder. May also apply to other illness states as well (i.e., pain, medical illness, etc.).

Co-morbidity: The existence of two or more disorders at the same time or one after the other. Interactions worsen the course of both.



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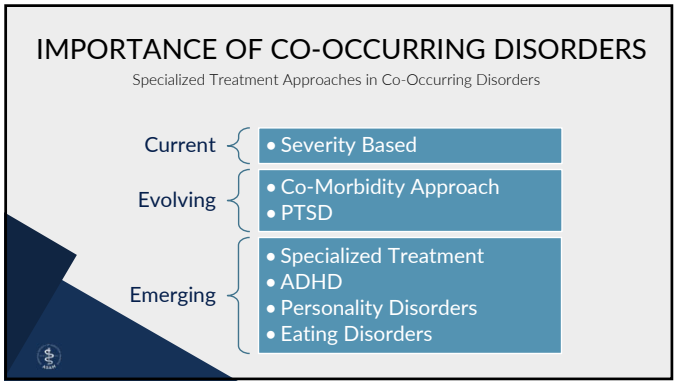
IMPORTANCE OF CO-OCCURRING DISORDERS
Specialized Treatment Approaches in Co-Occurring Disorders
Current
• Severity Based
Evolving
• Co-Morbidity Approach
• PTSD
Emerging
• Specialized Treatment
• ADHD
• Personality Disorders
• Eating Disorders

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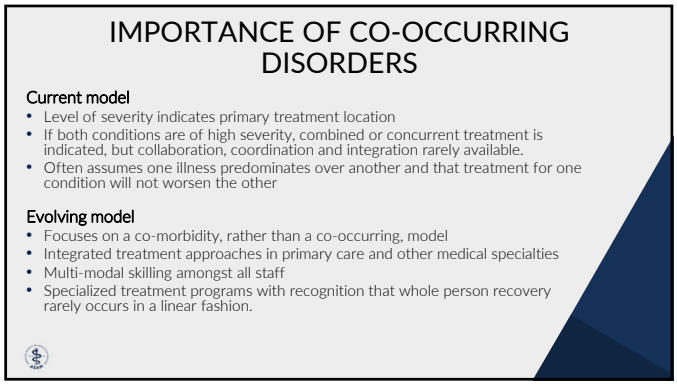
IMPORTANCE OF CO-OCCURRING DISORDERS
Current model
• Level of severity indicates primary treatment location
• If both conditions are of high severity, combined or concurrent treatment is indicated, but collaboration, coordination and integration rarely available.
• Often assumes one illness predominates over another and that treatment for one condition will not worsen the other
Evolving model
• Focuses on a co-morbidity, rather than a co-occurring, model
• Integrated treatment approaches in primary care and other medical specialties
• Multi-modal skilling amongst all staff
• Specialized treatment programs with recognition that whole person recovery rarely occurs in a linear fashion.

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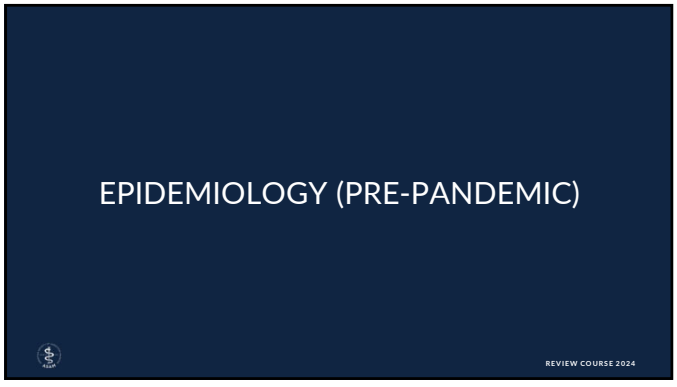
EPIDEMIOLOGY (PRE-PANDEMIC)
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EPIDEMIOLOGY

- 7.7 million adults have co-occurring mental health and substance use disorders.
- Of the 20.3 million adults with substance use disorders, 37.9% also had mental illnesses.
- Among the 42.1 million adults with mental illness, 18.2% also had substance use disorders.
- Rates of lifetime prevalence are much higher

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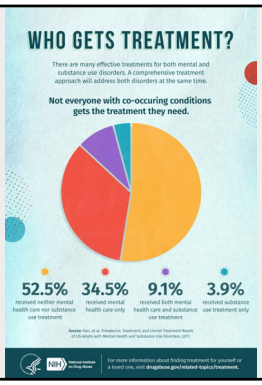
EPIDEMIOLOGY

Of those with co-occurring disorders…

- 52.5% received ***neither*** mental health care nor substance use treatment.
- 34.5% received ***mental health care only.***
- 9.1% received ***both*** mental health care and substance use treatment.
- 3.9% received ***substance use disorder treatment only.***



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EPIDEMIOLOGY

Among adults with co-occurring disorders who did not receive mental health care, their reasons for not receiving it were as follows:

- 52.2% could not afford the cost.
- 23.8% did not know where to go for treatment.
- 23.0% said they could handle the problem without treatment.
- 13.6% feared being committed.
- 12.4% said it might cause their neighbors to have a negative opinion of them.
- 11.1% did not think treatment would help.
- 10.6% did not have the time.
- 10.1% were concerned about confidentiality.

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EPIDEMIOLOGY

Among adults with co-occurring disorders who did not receive substance use care, their reasons for not receiving it were as follows:

- 38.4% were not ready to stop using.
- 35.1% could not afford the cost.
- 13.1% said it might cause their neighbors to have a negative opinion of them.
- 13.0% said it might have a negative effect on their job.
- 11.5% did not know where to go for treatment.
- 9.9% had insurance but could not afford the co-insurance/co-payments.
- 9.0% said no program had the treatment type.

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PRINCIPLES OF TRIAGE, ASSESSMENT AND TREATMENT

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TRIAGE AND ASSESSMENT

- Consumer- and patient-centric with no wrong door
- Presenting Problem: Most likely of greatest concern to patient and is the initial starting point
- Standard of care is no longer "let's wait and see how you feel after 30, 60 or 90 days of sobriety."
- Special considerations for severe mental illness
- Full risk assessment is essential
- Consider entire ecosystem of care and patient's environment
- Beware of screening in early abstinence

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TRIAGE AND ASSESSMENT

Mental Health History

- Symptoms during periods of abstinence or (preferred) prior to initiation of use
- Relationship between cessation or reduction of use and psychiatric symptoms
- Patient's subjective experience of substance use to self-medicate (use caution)

Substance Use History

- Early substance use can indicate a primary mental health condition
- Substance use prior to onset of psychiatric illness does not imply the addiction is primary
- Progression of use and functional consequences

- **Comprehensive treatment history**
- **The complex role of trauma and PTSD**
- **DSM5 diagnostic criteria**

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PRINCIPLES OF TREATMENT

- As severity increases, likelihood of engagement in treatment does as well.
- From Flynn 2008, monotherapy is typically in mental health (20.7%) not addiction (7.6%) treatment programs.
- Psychotherapy versus psychopharmacology.
- Access to evidence-based practices for psychotherapy, including motivational interviewing, and multi-modal treatment is extremely limited in many areas.

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PRINCIPLES OF TREATMENT

- Risk of Inaction or Delayed Treatment
  - Cycle of use, return to use and remission from co-occurring disorders
  - Escalating functional consequences
- Defining Success and Treating to Target
  - Engagement
  - Abstinence
  - Functional improvement
  - Symptom reduction
  - Individualized treatment outcomes
- Flexible treatment approaches
- Shared decision-making re: treatment planning and goals

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MENTAL HEALTH CONDITIONS: A LIGHTNING REVIEW

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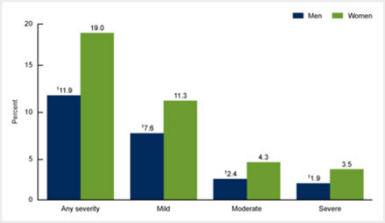
CO-OCCURRING ANXIETY DISORDERS

Percentage of adults aged 18 and over who experienced symptoms of anxiety in the past 2 weeks, by symptom severity and age group: United States, 2019



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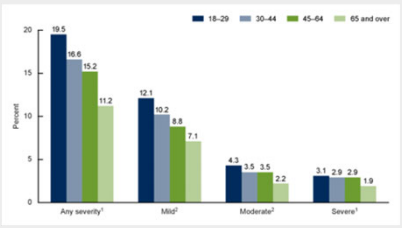
CO-OCCURRING ANXIETY DISORDERS

Percentage of adults aged 18 and over who experienced symptoms of anxiety in the past 2 weeks, by symptom severity and age group: United States, 2019



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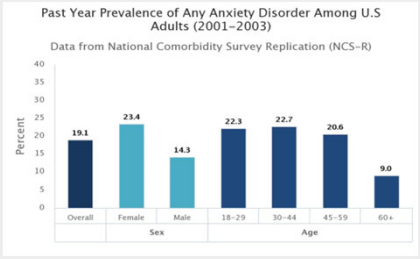
CO-OCCURRING ANXIETY DISORDERS



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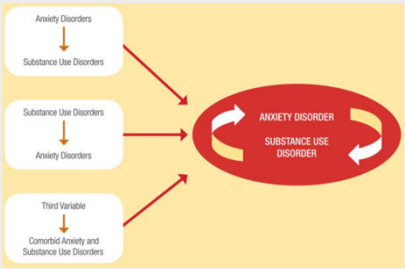
CO-OCCURRING ANXIETY DISORDERS



Smith JP and Book SW. Anxiety and Substance Use Disorders: A Review. Psychiatry Times. 2008 Oct; 25(10): 19–23.

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CO-OCCURRING ANXIETY DISORDERS

- Lifetime prevalence of anxiety disorders is over 30%. The pandemic story viz anxiety disorders has not been told yet.
- Mild substance use disorders likely not associated with anxiety disorders, but moderate and severe substance use disorders are highly related.
- Traditionally, alcohol use disorder is associated with anxiety disorders, but in fact, all substance use disorders are implicated.
- Substance-induced anxiety disorders are rare (<1%) with anxiety disorders usually preceding the substance use disorder.

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CO-OCCURRING ANXIETY DISORDERS

Diagnosis

Generalized anxiety and panic disorders: Most strongly associated with substance use disorders

- Generalized Anxiety Disorder: Significant worry and ruminations
- Panic Disorder: Panic attacks with or without agoraphobia
- Specific Phobias (i.e., fear of heights)
- Social Phobia: Spectrum from mild anxiety to full avoidance
- Obsessive-Compulsive Disorder: Not technically an anxiety disorder

Treatment

The presence of either generalized anxiety or panic disorder is likely to predict a higher degree of severity of the substance use disorder.

- Evidence-based psychotherapy, typically cognitive-behavioral therapy, is first-line
- Medications
  - SSRI's/SNRI's, typically only for generalized anxiety disorder or severe panic disorder
  - Benzodiazepines
    - Blunts psychotherapeutic effects
    - Risk of addiction is low, but misuse is common
    - Physiological dependence is a difficult issue
    - Long-term risk is equivocal

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CO-OCCURRING DEPRESSIVE DISORDERS

- Relationship between depression and substance use disorders is bidirectional: Odds ratio of 1.3 to 2.6.
- Adolescents: 2017 study found a doubling of the incidence of substance use disorders in adolescents with a major depressive episode in the last year (29.3% versus 14.3%).
- Substance-induced depression is also common
  - Direct physiological effects of substances
  - Psychosocial sequelae
  - Co-morbidities with SUDs (i.e., diabetes and chronic pain)

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CO-OCCURRING DEPRESSIVE DISORDERS

- Dysfunction in frontal-limbic reward pathways.
- Altered reward systems lead to compulsive use of substances and anhedonia.
- Repeated cycles of intoxication and withdrawal complicate any *de novo* diagnosis of major depressive disorder in the acute phase of addictions treatment.
- Symptoms of depressive disorders usually precede initiation of substance use or progression to a use disorder.

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CO-OCCURRING DEPRESSIVE DISORDERS

Diagnosis
- Major depressive disorder
- Persistent depressive disorder
- Substance-induced mood disorder
- Caution re: bipolar disorder

Major Depressive Episode versus Persistent Depression
- Major depressive episode (MDE): Usually intermittent with inter-episode recovery
- Persistent depressive disorder: Long term, chronic, mild depressed mood. May co-occur with an MDE

Substance-Induced Mood Disorders
- Over half of patients with alcohol and opioid use disorders.
- Usually, symptoms resolve quickly after cessation or reduction of use
- Persistent symptoms can occur and require medical treatment.

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CO-OCCURRING DEPRESSIVE DISORDERS

Treatment
- Mild depression: Self-care + psychotherapy first line
- Moderate depression: Psychotherapy ± pharmacotherapy
- Severe depression: Pharmacotherapy + Psychotherapy ± interventional treatments

Pharmacotherapy
- Standard algorithm
- SSRI's first line
- SNRI's and atypical anti-depressants
- Emerging role of psychedelics

Evidence-Based Psychotherapies
- Cognitive-Behavioral Therapy
- Interpersonal Therapy
- Supportive/Non-Directive Therapy not effective
- Access to EBP's is challenged

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CO-OCCURRING BIPOLAR DISORDERS

- Bipolar disorder affects 1%-4% of the US population with most studies/surveys consistent with a 4% lifetime prevalence rate for the combination of bipolar 1 and 2 disorders (2% for each).
- Eliciting symptom reports from patients can be challenging (see later patient education graphics)
- Bipolar 1 disorder
  - High correlation with SUD's with lifetime SUD prevalence rate of 50-60%. Some studies found rates as high as 90%.
  - Significant functional impairment, often with hospitalization.
- Bipolar 2 disorder
  - Likely under/mis-diagnosed (with major depressive disorder) with some key opinion leaders noting up to an 11% prevalence.
  - Correlation with substance use disorders is less well studied.

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CO-OCCURRING BIPOLAR DISORDERS

- Age of onset: Teens to early 20's with rare onset after age 40.
- Onset often, but not always, prior to substance initiation/progression.
- Substance intoxication can mimic mania. While ruling out substance-induced mania is important, treatment is largely the same for both conditions.
- Treat with a low suspicion given the bi-directionality of bipolar and substance use disorders and improved outcomes for both conditions with treatment of either.
- Use provisional diagnosis when unsure to avoid later confusion.

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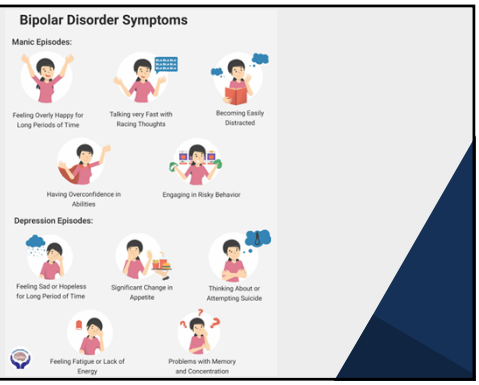

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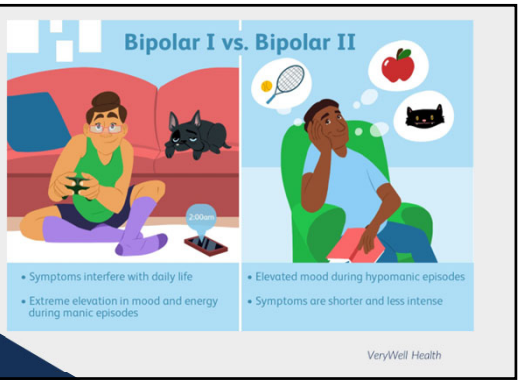

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CO-OCCURRING BIPOLAR DISORDERS

Diagnosis

- Bipolar 1: Manic episode ± Major depressive episode with or without psychosis
- Bipolar 2: Hypomania + Major depressive episode
- Cyclothymic disorder (rare in treatment-seeking populations): Hypomania + Dysthymia
- In general, any hospitalization during an elevated mood episode is likely mania, not hypomania

Treatment

- Pharmacotherapy
  - Mood stabilizers/Anti-manic agents
  - Anti-psychotics
  - Use caution with anti-depressants in bipolar 1, but acceptable with bipolar 2.
- Psychotherapy
  - Cognitive-behavioral therapy
  - Family-focused therapy
  - Interpersonal therapy
  - Social-rhythm therapy

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CO-OCCURRING PSYCHOTIC DISORDERS

- Initial presentation of psychotic illness: Usually mental health
- *However*, up to 50% co-occurrence of substance use disorders in those with psychotic disorders: Cross-skilling is essential when treating this population.
- Typical substances and use disorders with a primary psychotic disorder include cannabis and alcohol
- Substance-induced psychosis can be common and persistent with repeated use of certain substances, particularly methamphetamine.

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CO-OCCURRING PSYCHOTIC DISORDERS

- Continued use of substances is associated with increased symptoms, adjustment difficulties, treatment nonadherence, relapses, and hospitalizations, even with intensive treatment.
- Individualized treatment plans are essential
- May require treatment in specialized integrated programs.
- Role of family and caregivers is important to recognize.
- Aggressive medication management initially can help to reduce symptoms and increase engagement.

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CO-OCCURRING PSYCHOTIC DISORDERS

Diagnosis

- Schizophrenia
- Mood disorders with psychotic features
- Schizoaffective disorder
- Delusional disorder
- Substance-induced psychosis (particularly methamphetamine-induced psychosis/intoxication)
- Unspecified

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CO-OCCURRING PSYCHOTIC DISORDERS

- **Pharmacotherapy**
  - Anti-psychotics are first line but often poorly tolerated
  - Mood stabilizers and/or anti-depressants for mood symptoms
  - Consider clozapine early. Evidence indicates superior effects for both psychotic and substance use disorders with use of clozapine and superior reduction in suicide risk.
  - Long-acting injectables provide significant advantages but cost is a factor
- **Non-medical therapies**
  - Cognitive-behavioral therapy for psychosis
  - Family psychoeducational and interventional therapies
  - Mutual support groups (NAMI, Mental Health America)
- **Outcomes should focus on functional improvement, not necessarily symptom reduction or abstinence**

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CO-OCCURRING POST-TRAUMATIC STRESS DISORDER

- Patients with PTSD are 2-4 times more likely to have an SUD in general, but among treatment seeking populations, those who present with PTSD are 14 times more likely to have an SUD.
- Severity of trauma correlates with substance use in general and overall development of an SUD.
- Trauma cue-induced cravings and use are a major challenge.
- Trauma, independent of PTSD, is also correlated with substance use and progression to a use disorder. Less than 10% of those exposed to significant trauma will develop PTSD but may have addictions sequelae.

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CO-OCCURRING POST-TRAUMATIC STRESS DISORDER

Theories of etiology/correlation

- Self-medication hypothesis: Reduction of autonomic symptoms as well as psychological distress with ongoing substance use
- High-risk hypothesis: Substance use leads to presence in higher risk environments and situations that predispose to trauma and development of PTSD
- Susceptibility hypothesis: Chronic hyperarousal from substance use predisposes to PTSD rather than non-pathological reactions after traumatic events
- Shared risk model: Genetics, neurophysiological systems, recurrent trauma
- Possible direct effect of substance: Cannabis and suppression of negative memories, but unclear as to whether this leads to disordered use

Trauma without PTSD

- Minority stress
- Forced resilience
- Social determinants of health

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CO-OCCURRING POST-TRAUMATIC STRESS DISORDER

- Comprehensive diagnostic evaluation and treatment planning to include social determinants of health and safety/risk assessment
- Focus on safety and stabilization
- Treatment of single-episode versus recurrent PTSD requires differential approaches

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CO-OCCURRING POST-TRAUMATIC STRESS DISORDER

Specialized Evidence-Based Psychotherapies (First Line)

- Seeking Safety (SUD + PTSD)
- Prolonged exposure (Use in caution in early recovery)
- Eye movement desensitization and reprocessing
- Cognitive processing therapy

Pharmacotherapy

- Typically, less effective than for other co-occurring conditions.
- SSRI's and SNRI's are the best studied and most effective
- α-Adrenergic receptor antagonists important for symptom management.
- Anti-psychotics and benzodiazepines should generally be avoided due to risk and side effect profiles.

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CO-OCCURRING ADHD

- 15.2% of adults with attention-deficit hyperactivity disorder (ADHD) have a substance use disorder (SUD) compared with 5.6% of those without ADHD.
- Among adolescents, the rate of ADHD in those with an SUD is 24% versus 11.5% in the general adolescent population.
- Substance use begins earlier, and remission rates are lower or take longer to achieve, in those patients with ADHD.
- ADHD + SUD = Higher risk of attempted suicide
- Early *and* adequate treatment of ADHD in childhood is a primary prevention strategy for SUDs.
- Evidence supports use of psychostimulants in this population with appropriate monitoring and safe storage practices.

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CO-OCCURRING ADHD

Inattention/Poor Concentration
- Target symptom for most medications
- Can be independent of, or foundational to, other functional domains

Executive Dysfunction
- Poor impulse control
- Lack of long-term reward and consequence orientation
- Decreased academic and occupational functioning
- Improvement with medications is limited

Impaired Reward System
- Increased risk-taking behaviors
- Need for a higher degree of stimulation
- Does not improve with medications

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CO-OCCURRING ADHD

- Retrospective global study of 4.4 million people prescribed medications for ADHD versus 6.1 million prescribed asthma medications (low risk of diversion): Abuse, misuse and diversion of stimulants was 4 times more likely with stimulants
- In those patients who were dispensed stimulants rather than non-stimulants, those with ADHD were 8 times more likely to engage in "doctor shopping" behaviors.
- In a Swedish national registry study, 7.6% of those prescribed methylphenidate abused, misused or diverted the medication. The 46-65 age group was 17 times more likely to engage in these behaviors than the 6–12-year-old age group. Those with SUDs were twice as likely to misuse/divert.

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CO-OCCURRING ADHD

Diagnostic Challenges

- Contemporary lifestyle promotes short attention spans: Easy to confuse with ADHD
- Diagnosis of ADHD with active substance use/early recovery: Extraordinarily challenging without pre-morbid diagnostic verification in childhood.
- Inattentive symptoms are common across a range of behavioral health conditions.
- Malingering to obtain psychostimulants is common.
- Engaging in extensive history-gathering can be difficult and time-consuming.
- *De novo* ADHD diagnoses: Only with significant reduction or abstinence from substances and with objective verification.

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CO-OCCURRING ADHD

Treatment Considerations

- 2021 meta-analysis by Özgen and collaborators: Adolescents with concomitant ADHD + SUD did not respond as well to medications as those with only ADHD.
- Psychosocial treatments are poorly studied and open for innovation. Are these safer approaches?
- Dopamine dysregulation, particularly with stimulant use disorders, may mean that higher doses of stimulants are required to achieve similar effects. As such, safety considerations are important.

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CO-OCCURRING EATING DISORDERS

- Approximately 10% of patients with eating disorders will also have an active substance use disorder, but evidence is mixed:
  - **Anorexia Nervosa:** 16% comorbidity with the binge/purge subtype > restrictive subtype
  - **Bulimia Nervosa** : Less studied, with some evidence that 30% of those with an SUD have bulimia nervosa
  - **Binge Eating Disorder:** Up to 60% may have co-occurrence
- Alcohol, tobacco and caffeine are the most common substances used in those with eating disorders, but evidence also demonstrates increased use of sedative/hypnotics in those with anorexia and hallucinogens/MDMA in those with bulimia
- Evidence for best practice in diagnosis and treatment is lacking

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CO-OCCURRING EATING DISORDERS

Shared Etiologies

- Maladaptive activation of reward pathways
- Appetite suppression with certain substances can lead to increase in disordered eating
- Shared, but temporary, sense of well-being
- Management of chaotic inner experiences and response to one's environment
- Avoidance of negative feeling states

Treatment Challenges

- Motivation
- Retention
- Concurrent treatment is ideal, but sequential treatment is the norm
- No widely accepted standard of care for concurrent treatment
- Often, one condition worsens as the other improves

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CO-OCCURRING PERSONALITY DISORDERS

- Borderline and anti-social personality disorders carry the highest co-morbidity/co-occurrence with SUDs, and patients with borderline personality disorder have the highest treatment-seeking behavior. As such, most treatment efforts will focus on that disorder.
- Overall prevalence of personality disorders
  - General population: 10-14.8%
  - Substance use disorders: 34.8-73%.
- Personality pathology often precedes substance initiation/disordered use.
- Poor treatment response and outcomes relative to those without the co-morbidity.

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CO-OCCURRING PERSONALITY DISORDERS

- Psychotherapy is first-line treatment
  - Unlike for other co-occurring disorders, treatment may need to be sequential, especially for a first episode, in order to help patients learn skills to manage emotions in the treatment milieu and as abstinence progresses.
  - Dialectical behavioral therapy (DBT), dynamic deconstructive therapy and dual-focused schema therapy have the greatest evidence, but DBT is most prevalent.
- Disruptions in the milieu environment are common and lead to issues of discharge and lack of engagement.
- Pharmacotherapy should be limited to acute crises and treatment of co-morbidities only.

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CO-OCCURRING DISORDERS: EQUITY

- Between 2016 and 2020, 116,000 premature deaths occurred because of disparities in how mental health and addiction concerns were addressed among racial/ethnic minorities and indigenous groups.
- Secondary to minority stress, rates of problematic substance use and progression to use disorders are higher among minoritized groups across the spectrum.
- Engagement in addictions treatment, particularly with medications for opioid use disorder (MOUD), is far less for minoritized populations, particularly black men.

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CO-OCCURRING DISORDERS: EQUITY

- Among minoritized groups, the total excess cost burden (relative to non-minoritized groups) for mental illness, addiction and suicide was $278 billion from 2016-2020.
- Multiple explanations
  - Access to care
  - Discriminatory local, state and federal policies
  - Disparities in social determinants of health
  - Lack of culturally aware/sensitive therapeutic approaches
  - Lack of diversity in the workforce

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SUMMARY AND KEY TAKEAWAYS

- Co-occurring mental health and substance use disorders are common with a wide range of severity levels impacting clinical outcomes.
- Consider co-morbidity, not just co-occurrence.
- Diagnosis of co-occurring conditions is essential in order to create effective individualized treatment plans.
- Treatment of co-occurring disorders requires specialized approaches that integrate addictions and mental health treatment together rather than provide in silos or according to the severity of the presenting problem.
- Know key diagnostic criteria for the most common mental health conditions.

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56

ASAM REVIEW COURSE 2024

Medical Co-Morbidities: Diagnosis, Prevention and Complications

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1

Financial Disclosure

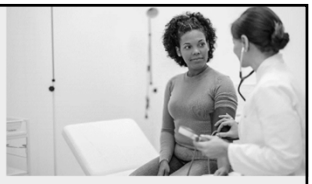
Carolyn Warner-Greer, MD, MSc, FASAM

- No relevant disclosures

REVIEW COURSE 2024

2

Learning Objectives



1

Conduct an appropriate history and physical exam for persons with substance use disorder.

2

Identify key medical co-morbidities that can occur with substance use disorder.

JULY 2024 REVIEW COURSE 2024

3

Presentation Outline

Routine and Preventive Care	Medical Consequences of Alcohol and Drug Use
• History • Physical examination • Labs • Preventative Care • Preconception Care	• Alcohol • Tobacco • Opioids • Stimulants • Injection Drug Use • Cannabis

4

SUD = Poor Medical Care

- Reasons
- Barriers
- Consequences

Chan Carusone, S., Guta, A., Robinson, S. et al. "Maybe if I stop the drugs, then maybe they'd care?"–hospital care experiences of people who use drugs. Harm Reduct J 16, 16 (2019).

5

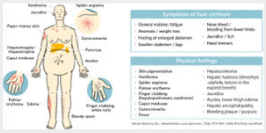
General Medical Evaluation

- Medical History
- Physical Examination
- Tests
- Preventative Counseling
- Preventative Screening
- Immunizations

6

Alcohol

- Affects every organ system
- Women>>Men
- Is any ETOH safe?
- Physical Exam Findings:

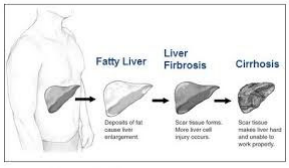


  - Spider angiomas
  - Palmar Erythema
  - Jaundice
  - Ascites

7

Alcohol

- GI-
  - Esophagitis/gastritis, Mallory-Weiss tears, esophageal varices
  - Pancreatitis (dose-related toxic effect)
  - Alcohol-related liver disease
    - AST/ALT >2
    - Fatty liver
    - Alcohol related hepatitis (ALH)
    - Cirrhosis-10-20%



UCSF, Department of Surgery

8

Alcohol

- Respiratory
  - Aspiration
  - OSA
- Infectious
  - Hepatitis
  - SBP
  - TB
- Nutrition-vitamin and mineral deficiencies
  - B1, B6, riboflavin, niacin, Vit D, Mg2+, Ca2+, folate, PO4, zinc

9

Alcohol

- CV
  - HTN-dose dependent
  - Cardiomyopathy-dilated
  - Atrial Fibrillation "Holiday Heart"
- Heme/Oncology
  - Anemia-macrocytic
  - Thrombocytopenia/pancytopenia
  - Coagulopathy
  - Increase CA: breast, oral, GI, hepatic (no safe threshold)

Zhao J, Stockwell T, Naimi T, Churchill S, Clay J, Sherk A. Association Between Daily Alcohol Intake and Risk of All-Cause Mortality: A Systematic Review and Meta-analyses. JAMA Netw Open. 2023;6(3)

10

Alcohol

- Neurological
  - Neuropathy-peripheral/autonomic
  - Sleep
  - Cognition
  - Cerebellar dysfunction
  - Trauma

Wernicke Encephalopathy	Korsakoff's Syndrome
C-Confusion	R-Retrograde amnesia
O-Ophthalmoplegia	A-Anterograde amnesia
A-Ataxia	C-Confabulation
T-Thiamine Deficiency	K-Korsakoff psychosis

Medical Maestro

11

Alcohol

- Endocrine
  - Hypogonadism
    - Direct testicular effect
    - Hepatic dysfunction → reduction in gonadal hormones
  - Decreased fertility
  - Hyperlipidemia

12

Tobacco

- Leading cause of preventable death
- CV
  - HTN
  - CAD (multifactorial)
  - Peripheral vascular disease
- GI
  - GERD/PUD
  - Pancreatitis
  - Inflammatory Bowel Disease
  - Malignancy

13

Tobacco

- Respiratory
  - COPD
  - Malignancy
  - Asthma
  - PTX
  - Pulmonary HTN
  - Pneumonia/bronchitis

14

Tobacco

- Heme/Onc
  - 49% of cancer deaths related to tobacco use
  - Oral, gastric, lung, breast, cervical, bladder, kidney
  - DVT/PE
- Neurological
- Infectious Disease
- Reproductive/Endocrinology
  - Grave's Disease/hypothyroidism
  - Erectile Dysfunction/infertility

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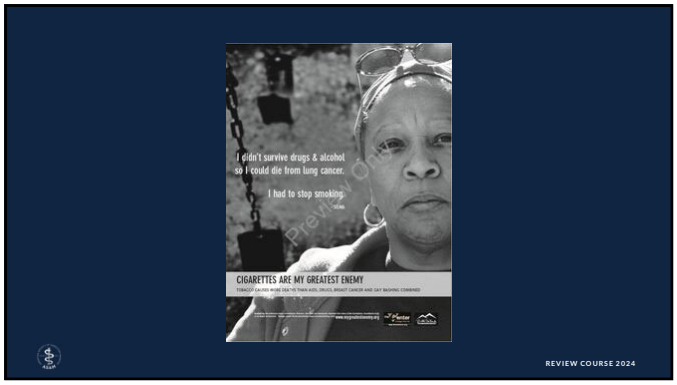


16

Tobacco Cessation and Recovery?

- Continued tobacco use predicted return to all substance use
- Should residential treatment programs allow nicotine use?
- Will patients leave prematurely?
- Philadelphia and NY experiences

Weinberger AH, Platt J, Esan H, Galea S, Erlich D, Goodwin RD. Cigarette Smoking Is Associated With Increased Risk of Substance Use Disorder Relapse: A Nationally Representative, Prospective Longitudinal Investigation. J Clin Psychiatry. 2017 Feb;78(2):e152-e160.

17

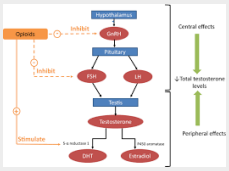
Opioids

- ID
  - IVDA-endocarditis, osteomyelitis, Hep C and HIV
  - STD
- Respiratory-overdose, chest wall rigidity with FENT, pulmonary edema
- Endocrine-reduction in steroid hormones
- Trauma-rhabdomyolysis, compartment syndrome
- Respiratory-OSA,
- GI-constipation

18

Opioid Induced Hypogonadism

- Low libido
- Muscle wasting
- Increased adiposity
- Depression
- Osteoporosis
- Treatment: Testosterone replacement



Mayo Clinic Proceedings: Innovations, Quality & Outcomes, ISSN: 2542-4548, Vol: 3, Issue: 3, Page: 276-284

19

QT Prolongation

- Normal: <430 ms-men, <450 ms-women
- Medications: methadone, quinolones, ondansetron, macrolides, hydroxyzine, citalopram
- ⬇ Mg2+, K+, Ca2+
- Screening:
  - Good family and medical history-look at all medicines
  - EKG at higher doses of methadone?
- Flockhart Table/APP-IUSOM

Treece JM, Al Madani M, El Khoury G, Khraisha O, Martin JE, Baumrucker SJ, et al. Comprehensive review on methadone induced QT prolongation and torsades. J Pharmacol Pharmacother 2018;9:66-7511-12-2017 R

20

Risk Factors for TdP

A CARLAT PSYCHIATRY REFERENCE TABLE

Risk Factors for Torsades de Pointes	
Nonmodifiable	Modifiable
Female sex	Multiple QT-prolonging medications
Older age	Drug toxicity
Structural or functional heart disease	Drug-drug interactions
Congenital long-QT syndrome	Severe acute illness
Personal history of drug-induced QT prolongation	Bradycardia
Family history of sudden (or aborted) cardiac death	Hypokalemia, hypomagnesemia, hypocalcemia
Poor metabolizer at CYP enzymes	Hepatic or renal impairment

Adapted from Funk MC et al, Am J Psychiatry 2020;177(3):273-274

From the Article
"Cardiovascular Psychiatry Part 1"
with Margo C. Funk, MD, MA, FACLP
The Carlat Psychiatry Report, Volume 21, Number 4&5, April/May 2023
www.thecarlatreport.com

21

LFT's and Naltrexone

- Indication OUD/AUD-baseline higher risk of hepatic disease
- No need to check LFT's prior to initiating treatment
- HCV, HBV not a contraindication
- Elevated LFT's no greater than placebo

Springer, Sandra A., "Monitoring of Liver Function Tests in Patients Receiving Naltrexone or Extended-Release Naltrexone," PCSS clinical guidelines, Update 2022

22

Stimulants

- CNS
  - CVA-5X increased risk hemorrhagic (METH), also ischemic (COC)
- CV
  - MI
  - HTN
  - Aortic dissection
  - Ventricular arrhythmia
  - Supportive treatment: β1blocker not associated with unopposed α activity
- GI
  - Ischemic bowel
  - Colitis

Arenas DJ, Beltran S, Zhou S, Goldberg LR. Cocaine, cardiomyopathy, and heart failure: a systematic review and meta-analysis. Sci Rep. 2020 Nov 13;10(1):19795

23

Do I get an EKG prior to starting a prescribed stimulant?

- Kids, young adults-no
  - Low pretest probability
  - Look at EKG if one is available
- Older Adults-poor data
  - Risk of RX stimulants is hypertension, tachycardia, vasospasm
  - BP and HR every 6 months
  - EKG annually? Look for QRS widening, ventricular conduction delay, arrhythmia

24

Stimulants

Toxicity	Emergency Presentation	Cause of Death
VASCULAR	Cardiac, stroke	Cardio/cerebrovascular
PSYCHIATRIC	Trauma, psychosis	Traumatic

25

Medical Complications of IVDU

- HIV
  - PWID=10% of new HIV cases since 2012
  - Reduction:
    - SSP-reduction in HIV by 50%
    - PrEP, overdose prevention sites
- Hepatitis
  - 65% PWID-->anti HCV +
  - SSP, MOUD-reduction in HCV
  - DAA regardless of stage of recovery
  - IVDU most common risk factor for new HBV

Levitt A, Mermin J, Jones CM, See I, Butler JC. Infectious Diseases and Injection Drug Use: Public Health Burden and Response. J Infect Dis. 2020 Sep 2;222(Suppl 5)

26

PrEP

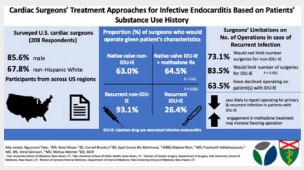
- Public Health Goal: reduce new HIV infections by 75% by 2025 and 90% by 2030
- CDC, FDA endorse PrEP as effective strategy to reduce new HIV infections among PWID
- Fewer than 1/500 PWID filled RX for PrEP
- LAI forms of PrEP-q 2 months

Streed CG, Morgan JR, Gai MJ, Larochelle MR, Paasche-Orlow MK, Taylor JL. Prevalence of HIV Preexposure Prophylaxis Prescribing Among Persons With Commercial Insurance and Likely Injection Drug Use. JAMA Netw Open. 2022;5(7):e2221346

27

Medical Complications of IVDU

- SBI
  - Osteomyelitis
  - Endocarditis
    - S. aureus (often methicillin resistant)
    - Osler nodes, Roth spots, splinter hemorrhages

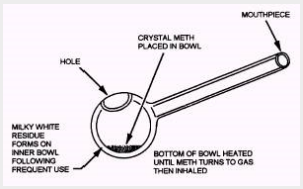


Seminars in Thoracic and Cardiovascular Surgery, ISSN: 1043-0679, Vol: 33, Issue: 3, Page: 703-709 2021

28

Medical Complications of Inhaling Drugs

- Inhalation and insufflation
- Shared equipment-->risks of ID
- Poor adherence to barriers during SI
- Trauma-burns, cuts
- Harm reduction



Best Practices Recommendations for Canadian Harm Reduction Programs-CATIE, 2020

29

Cannabis

- Hyperemesis Syndrome
  - Downregulation of CNS CBD R and upregulation of gut CBD R
  - Chronic cannabis use
  - Relieved with hot showers
  - Resolved with cessation
- Medical Cannabis
  - Medical condition with RCT suggests response to THC
  - Symptoms refractory to pharmacotherapy
  - No SUD/psychological morbidity

Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. JAMA. 2015;313(24):2474–2483

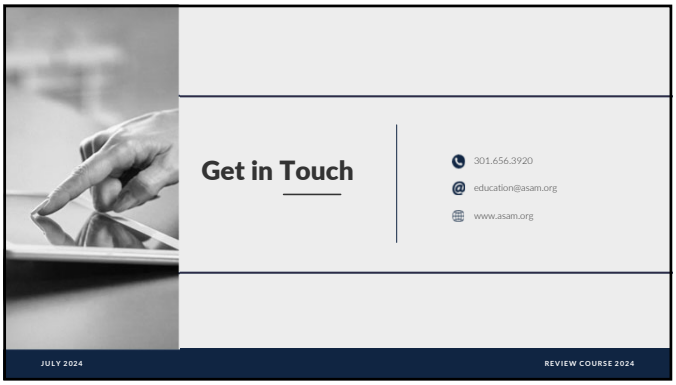
Gabriel P. A. et al. (2024) The impact of cannabis on non-medical opioid use among individuals receiving pharmacotherapies for opioid use disorder: a systematic review and meta-analysis of longitudinal studies, The American Journal of Drug and Alcohol Abuse, 50:1, 12-26, DOI: 10.1080/00952990.2023.2287406

30

Conclusion

- Targeted history and physical exam
- Physical health
- Teach patients to advocate for themselves
- Tobacco and alcohol most toxic substances
- Partnership with primary care colleagues

31



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ASAM REVIEW COURSE 2024

Pregnancy and Newborns: Considerations from Science to Systems

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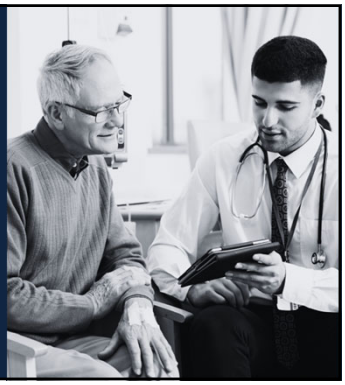

1

Financial Disclosure

Leslie Hayes, MD

- No relevant disclosures

REVIEW COURSE 2024

2

LEARNING OBJECTIVE

Describe the effect of substance use disorder on pregnancy and evidence-based treatment strategies for pregnant patients and newborns.

3

Presentation Outline

- Pregnancy and SUD
- The postpartum patient with SUD
- Effects of substance use during pregnancy on the newborn
- Neonatal opioid withdrawal syndrome

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4

Pregnancy and Substance Use Disorder

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5

Definition of terms for providers not regularly doing obstetric care

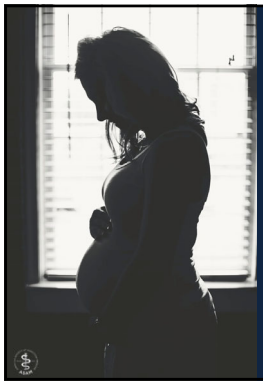
- G = Gravida = total number of pregnancies
- P = Para = total number of deliveries
- XX weeks = weeks since last menstrual period or weeks since conception + 2
- Full-term = 37-41 weeks gestation
- IUGR = Intrauterine growth restriction = fetal weight by ultrasound < 10th percentile
- SGA = small for gestational age = weight of newborn baby < 10th percentile for gestational age

6

Definition of terms for providers not regularly doing obstetric care

- Preterm labor = labor at < 37 weeks
- Preterm delivery = delivery at < 37 weeks
- Placental abruption = placenta pulls away from the wall of the uterus. Small abruptions can cause IUGR or preterm labor. Large abruptions can be fatal for mother and baby.

7



Case Study

33 yo G4P3 had been stable on buprenorphine-naloxone for 4 years. Presented to her buprenorphine provider for routine appointment and was discovered to be pregnant. Her buprenorphine provider did not give her a script because of this. She relapsed to heroin. She presented to our clinic at 25 weeks gestation, but because of transportation difficulties, she was unable to get restarted on buprenorphine and delivered a premature infant at 31 weeks. She restarted buprenorphine postpartum, and both she and baby did well.

8

Case Study

22yo G1P0 presents @ 9 weeks gestation. Actively using heroin. Desperately wanted to keep this pregnancy and this child. Started on buprenorphine maintenance, did well. Child with no signs of Neonatal Opioid Withdrawal Syndrome at birth. Currently 10 years old, doing well.

9

Substance use in pregnancy

- Use of alcohol, tobacco, and drugs during pregnancy is the leading preventable cause of mental, physical, and psychological impairments in children.
- Opioid-dependent pregnant women have an unintended pregnancy rate of 86%.[1]
  - Please provide or refer for contraception if you are treating patients with OUD who can get pregnant and don't want to do so.
  - Also, please start them on folate, 0.4 – 0.8 mg daily, even if they are not planning to get pregnant.[2]

1. *Weaver et al. Alcohol and Other Drug Use During Pregnancy: Management of the Mother and Child in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019 P. 1315*
2. *https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/folic-acid-for-the-prevention-of-neural-tube-defects-preventive-medication accessed 4/14/2024*

10

Rate of opioid use disorder in pregnancy is increasing

- Between 1998-2011, there was a 127% increase in opioid-dependent pregnant women presenting for delivery.[1]
- The estimated Maternal Opioid-related Diagnosis rate significantly increased from 2010 - 2017 from 3.5 per 1000 delivery hospitalizations (95% CI, 3.0-4.1) to 8.2 per 1000 delivery hospitalizations (95% CI, 7.7-8.7).[2]

1. *McCarthy et al. Opioid dependence and pregnancy: minimizing the stress on the fetal brain. American Journal of Obstetrics and Gynecology. 3 December 2016. pp 1-6*
2. *Hirai AH, Ko JY, Owens PL, Stocks C, Patrick SW. Neonatal Abstinence Syndrome and Maternal Opioid-Related Diagnoses in the US, 2010-2017. JAMA. 2021;325(2):146–155. doi:10.1001/jama.2020.24991*

11

Perinatal SBIRT: 4 Ps Plus

Parents	Did either of your parents ever have a problem with alcohol or drugs?
Partner	Does your partner have a problem with alcohol or drugs?
Past	Have you ever had a problem with alcohol or drugs in the past?
Past 30 days	In the past month, have you drunk any alcohol or used any substances?

[1]*ACOG committee opinion 711, 2017*
[2] *J Perinatol. 2005 Jun;25(6):368-74.*

12

PERINATAL SBIRT: 4P'S PLUS

- *A positive on the 4 P's does not mean that a patient has a substance use disorder, but it does mean that you need to ask more questions*

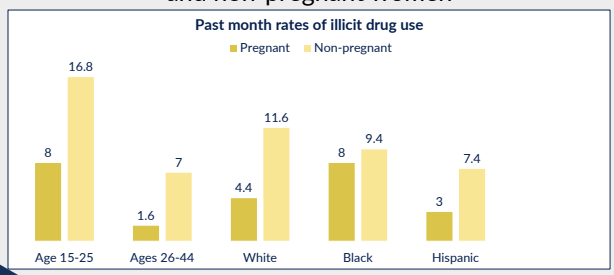
[1]ACOG committee opinion 711, 2017
[2] J Perinatol. 2005 Jun;25(6):368-74.

13

- What are medical implications of substance use disorder with pregnancy?
- What is the significance of pregnancy for any substance use disorder?

14

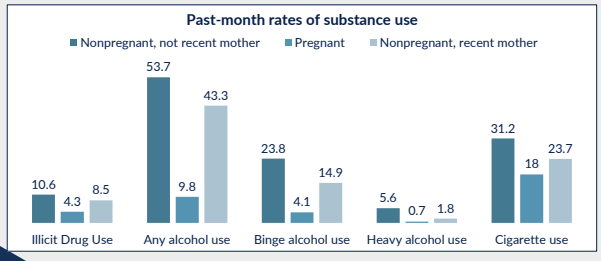
Percentages of past-month illicit drug use in pregnant and non-pregnant women



Helmbrecht et al. Management of Addiction Disorders in Pregnancy. J Addict Med; Vol 2, Number 1, March 2008, pp 1-16

15

Percentages among women aged 15-44 years who reported past-month substance use by pregnancy and recent motherhood status



Helmbrecht et al. Management of Addiction Disorders in Pregnancy. J Addict Med; Vol 2, Number 1, March 2008, pp 1-16

16

Birth defects with substances

- The drug with the most teratogenic potential is alcohol. [1]

[1]*Weaver et al. Alcohol and Other Drug Use During Pregnancy: Management of the Mother and Child in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019 P 1317*

17

Fetal alcohol syndrome

- Evidence of growth restriction (prenatal and/or postnatal)
  - Height and/or weight <= 10th percentile
- Evidence of deficient brain growth and/or abnormal morphogenesis
  - Structural brain anomalies or head circumference <=10th percentile
- Characteristic pattern of minor facial anomalies
  - Short palpebral fissures, thin vermillion border upper lip, smooth philtrum

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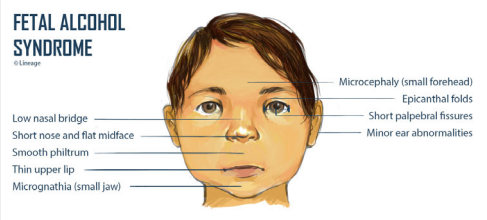
Fetal alcohol syndrome



19

Tobacco and pregnancy

- Neonates born to mothers who smoke weigh an average of 200 gm less than neonates born to mothers who don't smoke. [1]
- 22% of SUIDs (Sudden Unexpected infant deaths) can be directly attributed to maternal smoking during pregnancy. [2]

[1]Weaver et al. Alcohol and Other Drug Use During Pregnancy: Management of the Mother and Child in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019P 1318
[2]Anderson TM, Lavista Ferres JM, Ren SY, et al. Maternal Smoking Before and During Pregnancy and the Risk of Sudden Unexpected Infant Death. Pediatrics. 2019; 143(4):e20183325

20

Cannabis and pregnancy

- Difficult to get definitive answers on effects:
  - Women often using other substances, especially alcohol and tobacco
  - Psychosocial variables, such as income, age, and education, vary
  - Pre-existing conditions, such as ADHD or anxiety
  - Many studies done before level of THC was as high as now
- Cannabis use is common – the prevalence of self-reported marijuana use is 2-5%, and it increased from 2.37% in 2002 to 3.85% in the 2014 NSDUH.[1]

[1] Thompson R, DeJong K, Lo J. Marijuana Use in Pregnancy: A Review. Obstet Gynecol Surv. 2019 Jul;74(7):415-428

21

Cannabis and pregnancy

- Most common reasons to use cannabis in pregnancy are morning sickness and to manage anxiety/depression
  - Use of cannabis for morning sickness can lead to cannabinoid hyperemesis syndrome. [1]

[1] Badowski S, Smith G. Cannabis use during pregnancy and postpartum. Can Fam Physician. 2020;66(2):98-103.

22

Cannabis and pregnancy

- Data is mixed on effect of cannabis on pregnancy. [1]
  - Studies have given varied results on effect on birthweight [2,3], birth defects [4], and other outcomes.
  - There does seem to be a pattern of neurobehavioral effects on the fetus, with hyperactivity and sleep problems in toddlers, ADHD in pre-teens, and emotional dysregulation in adolescents. [5-7]

[1] Sheryl A. Ryan, Seth D. Ammerman, Mary E. O'Connor, COMMITTEE ON SUBSTANCE USE AND PREVENTION, SECTION ON BREASTFEEDING, Lucien Gonzalez, Stephen W. Patrick, Joanna Quigley, Leslie R. Walker, Joan Younger Meek, IBCLC, Margrete Johnston, Lisa Stellwagen, Jennifer Thomas, Julie Ware; Marijuana Use During Pregnancy and Breastfeeding: Implications for Neonatal and Childhood Outcomes. Pediatrics September 2018; 142 (3): e20181889. 10.1542/peds.2018-1889

[2] Badowski S, Smith G. Cannabis use during pregnancy and postpartum. Can Fam Physician. 2020;66(2):98-103.

[3] Gunn JK et al. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. BMJ Open. 2016 Apr 5;6(4):e009986. doi: 10.1136/bmjopen-2015-009986.

[4] Conner et al. Maternal Marijuana Use and Adverse Neonatal Outcomes: A Systematic Review and Meta-analysis. Obstet Gynecol. 2016 Oct;128(4):713-23. doi: 10.1097/AOG.0000000000001649.

[5] Weaver et al. Alcohol and Other Drug Use During Pregnancy: Management of the Mother and Child in Miller et al. The ASAM Principles of Addiction Medicine. Wolters Kluwer 2019P 1325

[6] Thompson R, DeJong K, Lo J. Marijuana Use in Pregnancy: A Review. Obstet Gynecol Surv. 2019 Jul;74(7):415-428

[7] Nashed et al. Cannabinoid Exposure: Emerging Evidence of Physiological and Neuropsychiatric Abnormalities Frontiers in Psychiatry. 11/2021

[8] Roncero et al. Cannabis use during pregnancy and its relationship with fetal developmental outcomes and psychiatric disorders. A systematic review. Reprod Health. 2020;17(1):25. 2020 Feb 17.

23

Cannabis and pregnancy –what we need to tell our patients

- Pregnant complain about hearing mixed messages from healthcare providers. They also state that want more research on the safety and effects of cannabis with pregnancy. [1]
- There is no recognized "safe" amount of marijuana with pregnancy.
  - Although marijuana hasn't been found definitively to be dangerous, it has also most definitely not been found to be safe.
  - It is also likely much more dangerous if combined with tobacco and alcohol.
- There is very likely a risk of long-term neurocognitive effects.
- While it may help with morning sickness, it can lead to cannabinoid hyperemesis syndrome, which is way worse, and there are better treatments.

Barbosa-Leiker et al. ***Daily Cannabis Use During Pregnancy and Postpartum in a State With Legalized Recreational Cannabis***. *Journal of Addiction Medicine*: November/December 2020 - Volume 14 - Issue 6 - p 467-474

24

Stimulant use and pregnancy

- Methamphetamine [1] and cocaine [2] use are associated with the following:
  - Preterm delivery
  - Low birth weight
  - Small for gestational age infants

1. Kalaitzopoulos et al. **Effect of Methamphetamine Hydrochloride on Pregnancy Outcome: A Systematic Review and Meta-analysis** Journal of Addiction Medicine: May/June 2018 - Volume 12 - Issue 3 - p 220-226
2. Smid MC et al. **Stimulant Use in Pregnancy: An Under-recognized Epidemic Among Pregnant Women** Clin Obstet Gynecol. 2019;62(1):168-184.

25

Implications of opioid use disorder with pregnancy – fetus

- Medication: Both use and withdrawal have fetal effects. **Withdrawal effects usually considered more serious.**
  - Withdrawal causes a hyperadrenergic state which causes constriction of blood vessels in placenta. Exacerbated by cocaine and methamphetamine use. Can cause preterm labor and placental abruption.
  - Biggest direct effect of opioid use is Neonatal Opioid Withdrawal Syndrome at birth.

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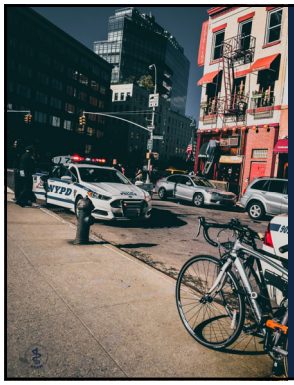
Maternal complications of opioid use with pregnancy

- A 2014 study found that opioid abuse or dependence increased the odds of major obstetrical morbidity and mortality:
  - In-house mortality aOR 4.6
  - Maternal cardiac arrest aOR 3.6
  - IUGR aOR 2.7
  - Placental abruption aOR 2.4
  - Preterm labor aOR 2.1
  - Oligohydramnios aOR 1.7
  - Transfusion aOR 1.7
  - Stillbirth aOR 1.5

Maeda, Ayumi et al. "Opioid abuse and dependence during pregnancy: temporal trends and obstetrical outcomes." Anesthesiology vol. 121,6 (2014): 1158-65. doi:10.1097/ALN.0000000000000472

27



Case Study
Pregnancy and Substance Use Disorder

28 yo G5P4, on methadone maintenance, disappeared from care at about 20 weeks, returned at 38 weeks in labor. Stated she had been at a methadone clinic in another community, but urine was negative for methadone, + for opiates. Baby went into horrible withdrawal at birth, child protective services involved and took child. Mother was arrested when she and her cousin, who was foster mother, got in fight on OB floor.

28

- What are psychosocial implications of substance use disorder with pregnancy?

29

Implications of substance use disorder with pregnancy

- Co-occurring disorders
  - Depression and other mental illness [1,2]
    - Both substance use disorder and depression cause poor self-care.
  - Domestic violence
    - Second-leading cause of trauma-related death in pregnancy.

1. *Metz et al. Maternal Deaths from Suicide and Overdose in Colorado, 2004-2012. Ob Gyn. Vol 128. No. 6. December 2016, pp 1233-1240*
2. *Schiff et al. Fatal and Nonfatal Overdose Among Pregnant and Postpartum Women in Massachusetts. Obstet Gynecol. 2018*

30

Implications of substance use disorder with pregnancy

- Psychosocial:
  - Most mothers/birthers have a high motivation to change.
  - Lot of guilt/shame for many individuals
  - Legal implications around custody of baby and older children
  - Most substance-using pregnant peopl have very poor self-care behaviors. If they continue to use drugs, they are unlikely to take good care of themselves during the pregnancy.

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Implications of substance use disorder with pregnancy

- Psychosocial:
  - Often have history of childhood sexual abuse or physical abuse (with implications for parenting)
  - High incidence of PTSD
  - Most women who use drugs start using because their partners use drugs. If they are still with that partner, it can be difficult for them to quit unless he quits as well.

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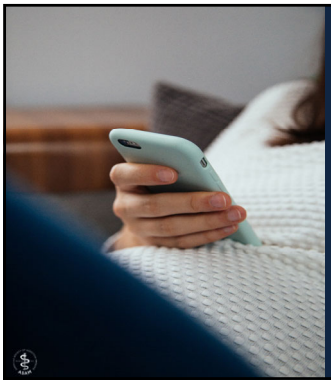

Comorbid Medical Conditions Case Study Pregnancy and Opioid Dependence

25 yo G2P1 presents at 26 weeks, stating, "I'm addicted to fentanyl." Scared that she will lose baby to child protective services or have medical complications. She wants to get into treatment.

33

- Is medication therapy an option for her?
- Which is better, buprenorphine or methadone?
- What about weaning off the fentanyl and using abstinence-based therapy?
- Does she need any special care for her pregnancy?

34

Prenatal Care

- In a study in the Journal of Perinatology, it was found that pregnant people with illicit drug use and no prenatal care had the highest risk for prematurity, low-birth weight and small for gestational age infants. As prenatal care increased, risk for prematurity, low birth weight and small for gestational age babies dropped. [1]
- Pregnant people will often delay or not get prenatal care because of stigma and fear of consequences, including being reported to child protective services. [2]

[1]*El-Mohandes et al. Prenatal Care reduces the Impact of Illicit Drug use on Perinatal Outcomes. Journal of Perinatology. 2003; 23:354-360*
[2]*Bishop et al. Pregnant Women and Substance Use. Overview of Research and Policy in the United States. Bridging the Divide: A Project of the Jacobs Institute of Women's Health. February 2017*

35

- Abstinence-based therapy is not recommended during pregnancy for anyone who is actively using opioids.[1]

[1]*Kampman and Jarvis. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. J Addict Med 2015;9 358-367*

36

Medication therapy and pregnancy

- Medication therapy for opioid use disorder (MOUD) is standard of care for pregnancy[1]

SAMHSA Advisory. Evidence-Based, Whole-Person Care for Pregnant People who have Opioid Use Disorder. March, 2024

37

Benefits of MOUD during pregnancy

- A recent study of 10,741 pregnant persons with OUD on Medicaid with 13,320 pregnancies showed the following benefits to Medication for Opioid Use Disorder:
  - Decreased rate of overdose
  - Decreased preterm birth
  - Decreased low birthweight
- All of the above outcomes improved with longer duration of MOUD during the pregnancy

Krans EE, Kim JY, Chen Q, Rothenberger SD, James AE 3rd, Kelley D, Jarlenski MP. Outcomes associated with the use of medications for opioid use disorder during pregnancy. Addiction. 2021 Dec;116(12):3504-3514. doi: 10.1111/add.15582. Epub 2021 Jun 9. PMID: 34033170; PMCID: PMC8578145.

38

Benefits of MOUD during pregnancy

- In addition to the medical benefits, infants with NOWS are significantly (odds ratio 3.9) more likely to be discharged to the parent, rather than foster or relative, care if the mother received prenatal MOUD

Singleton, Rosalyn et al. "Assessing the Impact of Prenatal Medication for Opioid Use Disorder on Discharge Home With Parents Among Infants With Neonatal Opioid Withdrawal Syndrome." Journal of addiction medicine vol. 16,6 (2022): e366-e373. doi:10.1097/ADM.0000000000000987

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Medication therapy and pregnancy

- 2010 NEJM study showed significantly less severe Neonatal Opioid Withdrawal Syndrome in buprenorphine group than the methadone group[1]
  - Babies exposed to buprenorphine required 89% less morphine, had a 43% shorter hospital stay, and shorter duration of treatment than babies exposed to methadone[1]
- 2022 study showed significantly lower rates of NOWS in babies exposed to buprenorphine than methadone.[2]

1. *Jones, H. et al. Neonatal Opioid Withdrawal Syndrome after Methadone or Buprenorphine Exposure. NEJM. Vol 363, 12/9/10 pp 2320-31.*
2. *Suarez et al. Buprenorphine versus Methadone for Opioid Use Disorder in Pregnancy NEJM Vol 387 12/1/2022 Pages: 2033-2044*

40

Medication therapy and pregnancy

- Most providers prefer to start with buprenorphine.
- However, if buprenorphine does not work for patient, it is essential to switch them to methadone quickly. Having the patient on a successful treatment for Opioid Use Disorder is the most essential part of treatment.
- "ANY OPIOID AGONIST THERAPY IS RECOMMENDED OVER UNTREATED OPIOID USE DISORDER IN PREGNANCY."[1]

Suarez et al. Buprenorphine versus Methadone for Opioid Use Disorder in Pregnancy NEJM Vol 387 12/1/2022 Pages: 2033-2044

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Neonatal Opioid Withdrawal Syndrome definition

- Neonatal Opioid Withdrawal Syndrome is highly treatable if diagnosed early, limited in duration, and, as far as we know, has limited long-term effects compared to the effects of untreated opioid use disorder.
- We should never use the possibility of NOWS to justify not properly treating opioid use disorder.
- We should also make sure that all pregnant women who are under treatment with medication facing the possibility of a baby with NOWS understand that they are doing the best possible thing for their baby.

42

Split dosing recommended for both buprenorphine and methadone during pregnancy

- A recent SAMHSA alert stressed the importance of split dosing of both methadone and buprenorphine during pregnancy to help manage the impact of metabolic changes.[1]

https://www.samhsa.gov/sites/default/files/split-dose-guidance-sotas-csat.pdf Accessed 4/24/2023

43

Starting buprenorphine in a pregnant person

- Very little data or consensus recommendation
- Most clinicians are doing micro-dosing as an outpatient or rapid micro-dosing in an inpatient setting
- Macrodosing may be considered if the patient presents in active withdrawal

44

Access to MOUD while pregnant

- A 2020 study of obstetricians showed that only a third of obstetricians always recommend MOUD and a fourth never recommend it. [1]
- MOUD providers are far less likely to accept pregnant patients than non-pregnant patients. [2]
  - Methadone 97% vs 91%
  - Buprenorphine 83% vs 51%
- Maternal mortality reviews have found MOUD rates ranging from 0-60% for pregnant patients with OUD who died of overdoses.[3,4,5,6,7]

1. *Ko, J.Y., Tong, V.T., Haight, S.C. et al. Obstetrician–gynecologists' practice patterns related to opioid use during pregnancy and postpartum—United States, 2017. J Perinatol 40, 412–421 (2020).*
2. *Stephen W. Patrick et al. (2018): Barriers to accessing treatment for pregnant women with opioid use disorder in Appalachian states, Substance Abuse*
3. *Metz et al. Maternal Deaths from Suicide and Overdose in Colorado, 2004-2012. Ob Gyn. Vol 128. No. 6. December 2016. pp 1233-1240*
4. *Schiff et al. Fatal and Nonfatal Overdose Among Pregnant and Postpartum Women in Massachusetts. Obstet Gynecol. 2018*
5. *Kountanis JA, Roberts M, Admon LK, et al. Maternal deaths due to suicide and overdose in the state of Michigan from 2008 to 2018. Am J Obstet Gynecol MFM 2023;5:100811.*
6. *Smid et al. Pregnancy-Associated Death in Utah: Contribution of Drug-Induced Deaths. Obstet Gynecol. 2019 Jun; 133(6): 1131-1140*
7. *Maryland Maternal Mortality Review. 2020 Annual Review. Health – General Article 13-1207 – 13-1208 and 13-1212.*

45

Morning sickness and methadone

- Both ondansetron and methadone cause QT prolongation, so use other treatments first.
- Lifestyle changes:
  - Small frequent meals
  - Avoid fluids with meals
  - Eat something before getting out of bed
  - Popsicles
- Ginger
- Pyridoxine, 10 mg + Doxylamine, 10mg tid

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What about medically monitored withdrawal?

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Medically monitored withdrawal

- THERE ARE NO GOOD STUDIES ON MEDICALLY MONITORED WITHDRAWAL. THE AVAILABLE STUDIES ARE OF POOR TO FAIR QUALITY AND HAVE CONFLICTING RESULTS.
- Recent meta-analysis reviewed 15 studies with 1,997 participants, of whom 1,126 went detoxification
  - Study quality was fair to poor with no randomized control trials
  - Mostly inpatient or residential setting with 3 incarceration studies
- Detoxification completion ranged from 9-100%.
- Relapse ranged from 0-100%
- 2 maternal deaths from postpartum overdose in one study

Terplan M, Laird HJ, Hand DJ, Wright TE, Premkumar A, Martin CE, Meyer MC, Jones HE, Krans EE. Opioid Detoxification During Pregnancy: A Systematic Review. Obstet Gynecol. 2018 May;131(5):803-814. doi: 10.1097/AOG.0000000000002562. PMID: 29630016; PMCID: PMC6034119.

48

Medically monitored withdrawal

- Rates of fetal demise and birthweights were similar between women who underwent detoxification and comparison group
- Rates of neonatal abstinence syndrome ranged from 0-100%

Terplan M, Laird HJ, Hand DJ, Wright TE, Premkumar A, Martin CE, Meyer MC, Jones HE, Krans EE. Opioid Detoxification During Pregnancy: A Systematic Review. Obstet Gynecol. 2018 May;131(5):803-814. doi: 10.1097/AOG.0000000000002562. PMID: 29630016; PMCID: PMC6034119.

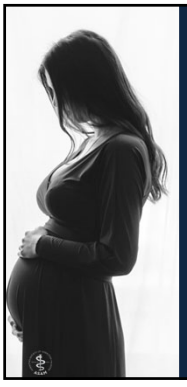
49

Medically Monitored withdrawal

- No study of medically monitored withdrawal has examined maternal outcomes postpartum[1]

1. Jones et al. Medically Assisted Withdrawal (Detoxification): Considering the Mother-Infant Dyad. J Addict Med 2017 DOI 10.1097

50



Comorbid Medical Conditions Case Study: Pregnancy and Opioid Dependence

34 yo G2P1 had been on buprenorphine-naloxone for heroin use disorder. She moved away and got pregnant and weaned herself off the buprenorphine. Moved back and declined to restart buprenorphine because "I am not going to ever go back to drugs." NSVD of healthy baby with negative urine drug screens throughout pregnancy. Died of an overdose about 1 year post-partum.

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MATERNAL MORTALITY AND OPIOID USE DISORDER

- Studies from Maryland[1], Tennessee[2], Colorado[3], Utah[4], Ohio[5], Massachusetts[6], California[7], Michigan[8], Virginia[9], Philadelphia[10], and New Mexico,[11] have found that postpartum overdose is one of the top causes of maternal mortality, causing 15-38% of deaths.

52

MATERNAL MORTALITY AND OPIOID USE DISORDER

1. Maryland Maternal Mortality Review. 2020 Annual Review. Health – General Article 13-1207 – 13-1208 and 13-1212.
2. Tennessee Maternal Mortality. Maternal Mortality in Tennessee 2021. 2023 Report to the Tennessee General Assembly Tennessee Department of Health | Family Health and Wellness | October 2023
3. Metz et al. Maternal Deaths from Suicide and Overdose in Colorado, 2004-2012. Ob Gyn. Vol 128. No. 6. December 2016. pp 1233-1240
4. Smid et al. Pregnancy-Associated Death in Utah: Contribution of Drug-Induced Deaths. Obstet Gynecol. 2019 Jun; 133(6): 1131-1140
5. Hall et al. Pregnancy-Associated Mortality Due to Accidental Drug Overdose and Suicide in Ohio, 2009-2018. Obstetrics and Gynecology. Vol 136, No 4 October 2020
6. Schiff et al. Fatal and Nonfatal Overdose Among Pregnant and Postpartum Women in Massachusetts. Obstet Gynecol. 2018
7. Goldman-Mellor S, Margerison CE. Maternal drug-related death and suicide are leading causes of postpartum death in California. Am J Obstet Gynecol 2019;221:489.e1-9
8. :Kountanis JA, Roberts M, Admon LK, et al. Maternal deaths due to suicide and overdose in the state of Michigan from 2008 to 2018. Am J Obstet Gynecol MFM 2023;5:100811.
9. Virginia Maternal Mortality Review Team Annual Report. Report To The Governor And The General Assembly 2023
10. Mehta PK, Bachhuber MA, Hoffman R, Srinivas SK. Deaths From Unintentional Injury, Homicide, and Suicide During or Within 1 Year of Pregnancy in Philadelphia. Am J Public Health. 2016 Dec;106(12):2208-2210. doi: 10.2105/AJPH.2016.303473. Epub 2016 Oct 13. PMID: 27736205; PMCID: PMC5105012
11. New Mexico Maternal Mortality Review Committee. Pregnancy-Associated Deaths 2015 – 2018. New Mexico Department of Health.

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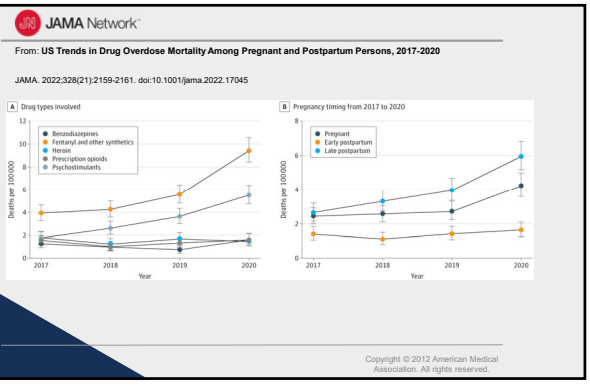

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Maternal mortality and opioid use disorder

- Studies in New Mexico, Philadelphia, and Maryland found that about half of maternal deaths were connected to substance use.[1,2,3]
  - Maryland[3] and Tennessee[4] found that about 3/4 of deaths where SUD contributed had a co-occurring mental health problem.
- Around 40% are associated with serious mental illness.[1,2]
- About 20% are associated with Intimate Partner Violence.[1,2]
  - 54.3% of suicides and 45.3% of homicides involved IPV.[5]

1. New Mexico Maternal Mortality Review Committee. Pregnancy-Associated Deaths 2015 – 2018. New Mexico Department of Health.
2. Mehta PK, Bachhuber MA, Hoffman R, Srinivas SK. Deaths From Unintentional Injury, Homicide, and Suicide During or Within 1 Year of Pregnancy in Philadelphia. Am J Public Health. 2016 Dec;106(12):2208-2210. doi: 10.2105/AJPH.2016.303473. Epub 2016 Oct 13. PMID: 27736205; PMCID: PMC5105012.
3. Maryland Maternal Mortality Review. 2020 Annual Review. Health – General Article 13-1207 – 13-1208 and 13-1212.
4. Tennessee Maternal Mortality. Maternal Mortality in Tennessee 2021. 2023 Report to the Tennessee General Assembly Tennessee Department of Health | Family Health and Wellness | October 2023
5. Glazer, Kimberly B, and Elizabeth A Howell. "A way forward in the maternal mortality crisis: addressing maternal health disparities and mental health." Archives of women's mental health vol. 24,5 (2021): 823-830. doi:10.1007/s00737-021-01161-0

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Maternal mortality and opioid use disorder

- Suicide and homicide are also a substantial contributors to postpartum mortality.[1]
- Risk factors for postpartum opioid overdose, postpartum suicide, and pregnancy-associated homicide have significant overlap.[2]
- Three of the most common include depression, intimate partner[3] violence, and substance use disorder.[2]

1. Campbell et al. Pregnancy- Associated Deaths from Homicide, Suicide, and Drug Overdose: Review of Research and the Intersection with Intimate Partner Violence. Journal of Women's Health. Volume 30, Number 2, 2021.
2. Mangla et al. Maternal self-harm deaths: an unrecognized and preventable outcome. American Journal of Obstetrics and Gynecology. October 2019.
3. Metz et al. Maternal Deaths from Suicide and Overdose in Colorado, 2004-2012. Ob Gyn. Vol 128. No. 6. December 2016. pp 1233-1240

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Maternal mortality and opioid use disorder

- Discontinuing psychiatric medications is associated with suicide.[2,3]
  - Roughly half of women on psychiatric medications discontinue them with pregnancy[1]
- Not taking or discontinuation of MOUD is a significant risk factor for overdose.[3,4]
  - Methadone discontinuation rate in the first six months postpartum was found to be 56% in one systematic review.[4]

1. Metz et al. Maternal Deaths from Suicide and Overdose in Colorado, 2004-2012. Ob Gyn. Vol 128. No. 6. December 2016. pp 1233-1240
2. Smid MC, Maeda J, Stone NM, Sylvester H, Baksh L, Debbink MP, Varner MW, Metz TD. Standardized Criteria for Review of Perinatal Suicides and Accidental Drug-Related Deaths. Obstet Gynecol. 2020 Oct;136(4):645-653. doi: 10.1097/AOG.0000000000003988. PMID: 32925616; PMCID: PMC8086704.
3. Trost et al. Preventing Pregnancy-Related Mental Health Deaths: Insights From 14 US Maternal Mortality Review Committees, 2008–17 Health Affairs 2021 40:10, 1551-1559
4. Wilder et al Medication assisted treatment discontinuation in pregnant and postpartum women with opioid use disorder. Drug and Alcohol Dependence 149 (2015) 225–231

57

Increased maternal mortality continued for many years after delivery in 2019 study

Mothers in Ontario and England with babies who had neonatal abstinence syndrome have a mortality rate that is over ten times as high as mothers who did not have an affected baby.

Roughly 1 in 20 mothers died over the next decade.

Top cause of death was unintentional injuries, but there were also high rates of murder and suicide, drug-related deaths, and unavoidable deaths.

Guttmann A et al. Long-term mortality in mothers of infants with neonatal abstinence syndrome: A population-based parallel-cohort study in England and Ontario, Canada. PLoS Med 16(11): e1002974. November 26, 2019.

58

What can be done

- Screen for depression postpartum. Use Edinburgh Postpartum Depression Screen or another tool.
- Screen for relapse.
- Talk about seatbelts.
- Distribute Narcan.
- Make sure every postpartum patient has a follow up appointment with primary care, postpartum care, and addiction medicine.
- Use home nursing liberally.

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Neonatal Opioid Withdrawal Syndrome

REVIEW COURSE 2024

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Neonatal Opioid Withdrawal Syndrome definition

- Neonatal Opioid Withdrawal Syndrome = physical withdrawal.
- Neonatal Opioid Withdrawal Syndrome baby is ≠ addicted to drugs.

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Clinical definition of opioid withdrawal in the neonate from the AAP

- Presence of clinical elements 1 and 2
- **(1)In utero exposure** to opioids with or without other psychotropic substances (recommended to be collected via confidential maternal self-report; toxicology testing also acceptable with maternal informed consent)
- **(2)Clinical signs** characteristic of substance withdrawal; any 2 of the following 5 signs qualify:
  - Excessive crying (easily irritable)
  - Fragmented sleep (<2-3 h after feeding)
  - Tremors (disturbed or undisturbed)
  - Increased muscle tone (stiff muscles)
  - Gastrointestinal dysfunction (hyperphagia, poor feeding, feeding intolerance, loose or watery stools)

Jilani et al. Standardizing the Clinical Definition of Opioid Withdrawal in the Neonate. The Journal of Pediatrics. September/October 2020 - Volume 14 - Issue 5

62

Neonatal Opioid Withdrawal Syndrome

- Neonatal Opioid Withdrawal Syndrome is highly treatable if diagnosed early, limited in duration, and, as far as we know, has limited long-term effects compared to the effects of untreated opioid use disorder.
- We should never use the possibility of NOWS to justify not properly treating opioid use disorder.
- We should also make sure that all pregnant women who are under treatment with medication facing the possibility of a baby with NOWS understand that they are doing the best possible thing for their baby.

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Non-pharmacologic treatment of Neonatal Opioid Withdrawal Syndrome

- Non-pharmacologic treatment includes the following:
  - Small, frequent feeds.
  - Quiet, dim light.
  - Swaddling or skin-to-skin.
  - Prenatal education for parents.
- Studies from Dartmouth [1] and Yale [2] showed substantial improvements in cost and length of stay using non-pharmacologic treatment.

1Holmes et al. Rooming-In to Treat Neonatal Opioid Withdrawal Syndrome: Improved Family-Centered Care at Lower Cost. Pediatrics 2016; pp 2015-2029
2Grossman et al. An Initiative to Improve the Quality of Care of Infants with Neonatal Opioid Withdrawal Syndrome. Pediatrics 2017;139(6)

64

Breastfeeding

- The Academy of Breastfeeding Medicine, the American Academy of Pediatrics, the American College of OB-GYN, the Substance Abuse and Mental Health Services Administration, and the American Society for Addiction Medicine recommend breastfeeding for women with substance use disorder.[1,2,3,4,5]
  - This includes women on MOUD.
- The recommendations from the Academy of Breastfeeding Medicine are the most recent. They recommend mothers breastfeed if they have discontinued use by the or during the delivery hospitalization.[2]
  - Women who were using at the time of delivery or who relapse should express and discard milk. There should be a multidisciplinary discussion about risks and benefits in this situation and when to start or restart breastfeeding.

1. *Jansson, L. et al, Methadone Maintenance and Breastfeeding in the Neonatal Period PEDIATRICS Vol. 121 No. 1 January 2008, pp. 106-114*
2. *Harris et al. Academy of Breastfeeding Medicine Clinical Protocol #21: Breastfeeding in the Setting of Substance Use and Substance Use Disorder (Revised 2023). BREASTFEEDING MEDICINE Volume 18, Number 10, 2023*
3. *Substance Use, Misuse, and Use Disorders During and Following Pregnancy, with an Emphasis on Opioids. ASAM Policy Statement. January 18, 2017*
4. *Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and Their Infants. SAMHSA, HHS Publication No. (SMA) 18-5054*
5. *ACOG Committee Opinion. Opioid Use and Opioid Use Disorder in Pregnancy. Number 711. August 2017*

65

Child protective services and mental health

Study in Manitoba showed that losing custody of a child-to-child protective services is associated with significantly worse maternal mental health outcomes than experiencing the death of a child

Risk of depression was 1.90 times greater for women who had lost a child to child protective services.

Risk of substance use was 8.54 times greater for women who had lost a child to child protective services.

Wall-Wieler, Elizabeth et al. Maternal Mental Health after Custody Loss and Death of a Child: A Retrospective Cohort Study Using Linkable Administrative Data. The Canadian Journal of Psychiatry. 2018, Vol. 63(5) 322-328.

66

To Call Child Protective Services or not

- Know your state laws and hospital policies
- Discuss child protective service involvement during pregnancy
  - What will trigger a referral
  - What will likely happen with a referral
- Discuss with your patient what to do if a referral is made:
  - Be honest with child protective services
  - Have a plan for SUD treatment
  - Have a plan to ensure the baby is safe

67

In Summary

1. Alcohol and tobacco are the most dangerous drugs for the fetus in pregnancy.
2. Medication treatment is recommended for opioid use disorder in pregnancy.
3. The postpartum period and after is a high-risk time for relapse and death in birthers with SUD.
4. Use non-medical treatments first for neonatal opioid withdrawal syndrome.

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Which of the following is correct about opioid use disorder and pregnancy?

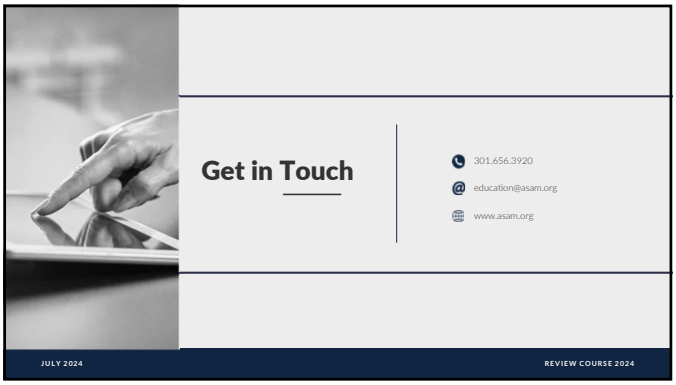
A. The highest risk time for relapse is postpartum
B. Medically-assisted withdrawal should be done during the second trimester to reduce the risk of neonatal opioid withdrawal syndrome
C. C-section is recommended for anyone actively using opioids
D. There is a high risk of congenital anomalies with opioid use

69

Which of the following is an example of an epigenetic phenomenon?

A. Children in a household with high levels of alcohol consumption are more likely to drink alcohol
B. Children in a high-stress environment are more likely to have certain genes expressed, some of which will predispose them to substance use disorder
C. Some alleles of the ADH2 gene will cause flushing and nausea with alcohol ingestion, and thus are protective against alcohol use disorder
D. People who are ultra rapid metabolizers of methadone don't do well on it.

70



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Cognitive Behavioral Therapy & Motivational Interviewing

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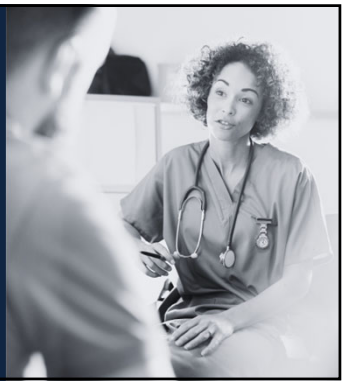

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Financial Disclosure

Carla Marienfeld, MD, FASAM, DFAPA

- Does disclose - CARI Therapeutics, Consultant and Stock.

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2

LEARNING OBJECTIVE

Identify the basic principles of common behavioral interventions and applications to addiction treatment.

3

Which of the following terms is used to describe the Spirit of MI?

A. Palliation
B. Acceptance
C. Comparison
D. Evolution

4

What is Motivational Interviewing About?

"MI is about arranging conversations so that people talk themselves into change based on their values and interests."

Miller and Rollnick, *Motivational Interviewing: Helping People Change, 3rd Edition*, 2013.

5

A Range of STYLES

DIRECTING ⟷ GUIDING ⟷ FOLLOWING

- Teach
- Assess
- Prescribe
- Lead

- Draw out
- Encourage
- Motivate

- Listen
- Understand
- Go along with

Miller and Rollnick, *Motivational Interviewing: Helping People Change, 3rd Edition*, 2013.

6

Spirit (PACE)

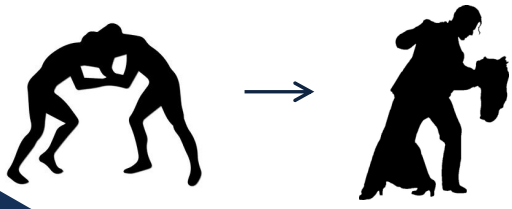
Emphasis on spirit rather than techniques.

- Partnership
- Acceptance
- Compassion
- Empowerment

Miller and Rollnick, Motivational Interviewing: Helping People Change and Grow , 4th Edition, 2023.

7

The Spirit of MI: Wrestling vs. Dancing



Source of metaphor: Jeff Allison

8

Which of the following four tasks are a part of motivational interviewing?

A. Engaging the patient in the change process
B. Fantasizing about a better future for yourself
C. Eliciting sustain talk from the patient
D. Perseverating on the change the patient wishes to make for themselves

9

Four Foundational Tasks of MI

- Planning (how will we get there?)
- Evoking (why are we going there?)
- Focusing (where shall we go?)
- Engaging (shall we walk together?)

10

Core Skills (OARS + I&A)

- Open Ended Questions
- Affirmations (simple and complex)
- Reflecting (simple and complex)
- Summarizing
- Informing & Advising (with permission, ask – offer - ask)

Miller and Rollnick, *Motivational Interviewing: Helping People Change, 3rd Edition*, 2013.

11

Reflective Listening

"Right now, drinking doesn't help me feel better the way it used to. In fact, I feel worse now."

- Echo: Drinking makes you feel worse now.
- Rephrase: So, you find that drinking is no longer helping you to feel better, the way it used to.
- Double-sided: In the past, drinking helped you to feel better. Now it makes matters worse.
- Continuation: … and you want to find some way to feel better instead of drinking.

12

Facilitating Change

- Change talk: as a person argues on behalf of one position, they becomes more committed to it; we talk ourselves into (or out of) things all the time.
- Sustain talk: the more of it is evoked during a counseling session, the more likely that the person will continue the status quo.

13

Encourage & Reinforce Change Talk

DARN CAT

- **D**: desire -- Want, wish, like
- **A**: ability -- Can, could, able
- **R**: reason -- Specific reason for change
- **N**: need -- Need to, have to, must, important

COMMITMENT LANGUAGE PREDICTS CHANGE

- **C**: commitment — Will, intend to, going to
- **A**: activation — Ready to, willing to (w/o specific commitment)
- **T**: taking steps — Report recent specific action toward change

14

Motivational Enhancement Therapy (MET)

- From the founders: "[MET] is a systematic intervention approach for evoking change... It is based on principles of motivational psychology and is designed to produce rapid, internally motivated change. This treatment strategy does not attempt to guide and train the client, step by step, through recovery, but instead employs motivational strategies to mobilize the client's own change resources."

– Miller et al., 1999

- Adapted from Motivational Interviewing
- 4 session protocol – great for short-term therapeutic relationships
- Used as a tailored approach for substance misusers
- Three phases
- Manual available here: https://casaa.unm.edu/download/MET.pdf

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Which of the following are part of Marlatt and Gordon's 1985 model of Relapse Prevention utilizing Cognitive Behavioral Therapy adapted for treatment of substance use disorders?

A. Eliciting change talk from the patient
B. Earning vouchers for negative urine drug screens
C. Targeting cognitive, affective, and situational triggers for substance use
D. Conducting a moral inventory

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Cognitive Behavioral Therapy (CBT) Efficacy

CBT models
- Among the most extensively evaluated interventions for SUDs

- Based primarily on Marlatt and Gordon's 1985 model of relapse prevention
  - Target cognitive, affective, and situational triggers for substance use
  - Provide skills training specific to coping alternatives

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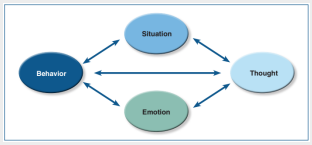
Cognitive Behavioral Therapy

- CBT says: Substance use is reinforcing; this interacts with psychological or behavioral coping deficits to produce increase in substance use
- SUD develops when this pattern is repeated
- Solution: more effective coping
- Also deals with expectancies (cognitions)
- Stages of treatment:
  - ✓ Building rapport and alliance
  - ✓ Preparing for change
  - ✓ CBT strategies
  - ✓ Maintaining change
  - ✓ Termination



https://www.treatmentworksforvets.org/wp-content/uploads/2018/04/CBT-SUD-Therapist-Manual.pdf

18

Core Elements of Cognitive Behavioral Therapy:

1. **Recognize:** triggers and cues, external and internal
2. **Anticipate/Avoid:** high risk situations, people, places
3. **Cope:** skills for relaxing, dealing with stress, tolerating dysphoria
4. **Connect:** options for support, socializing, fun, and meaning

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Cognitive Behavior Therapy: Basic Treatment Components (1):

Identification of high-risk situations
- "people, places, and things"

Development of coping skills
- To manage risks and triggers, as well as negative emotional states

Development of new lifestyle behaviors
- To decrease the need for and the role of substance use

Development of sense of self-efficacy
- Build on small successes in coping and positive choices

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Cognitive Behavior Therapy: Basic Treatment Components (2):

Communication skills
- Refusal skills
- Asking for help

Preparation for lapses
- Process to be learned from "lapses"
- Prevent lapse from becoming relapse
- Identify and manage patterns of thinking that increase risk

Dealing with relapse
- Relapse is not a catastrophe
- Minimize consequences

21

CRA vs CRAFT

Both are evidence supported behavioral treatments for SUD

Community Reinforcement Approach (CRA)

- Intended for the person
  - Based on the belief that a drinker's "community" (e.g., family, social and job environment) plays a critical role in supporting or discouraging use
  - Consequently, the environment needs to be restructured such that a sober lifestyle is more rewarding than a using lifestyle

Community Reinforcement and Family Therapy (CRAFT)

- An outgrowth of CRA
- Helps the family
  - Method for working with concerned family members in order to get a treatment-refusing person to enter treatment

22

Community Reinforcement Approach (CRA)

Based on operant conditioning: substance use as learned behavior

Naturalistic: uses contingencies already operating in the individual's natural environment to support change and abstinence (e.g., giving or withholding praise for behaviors)

Functional analysis of both healthy and substance use behaviors in terms of ability to reward or be aversive

Refining problem-solving and goal-setting efforts for individual and/or family (teaching positive communication, contracting skil

23

CRAFT

From the founder: "The Community Reinforcement Approach and Family Training (CRAFT) intervention is a scientifically based intervention designed to help concerned significant others (CSOs) to engage treatment-refusing substance abusers into treatment."

- Robert J. Meyers, 2019

- Goal: treatment engagement for the substance user
- "Positive approach" that avoids confrontation
- Culturally sensitive: works with cultural mores/beliefs to develop treatment plan
- Teaches CSOs to use positive reinforcers (rewards)
- Encourages CSOs to allow the substance user to suffer natural consequences of using behavior
- Includes: functional analysis, sobriety sampling, CRA treatment plan, behavioral skills training, job skills, social/rec counseling, relapse prevention, and relationship counseling

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Acceptance and Commitment Therapy (ACT)

Has some studies for use with SUDs

Six Core Processes

- Acceptance
- Cognitive Diffusion
- Being Present
- Self As Context
- Values
- Committed Action

Useful in helping pts consider how their substance use disconnects them from their values.

Comparing "sober values" to "using values" or reconnecting to values

25

Dialectical Behavior Therapy (DBT)

Manual driven behavioral treatment utilizing validation and motivational enhancement techniques

Often combination of group and individual elements

Addresses enhancement of four basic capabilities:

- Interpersonal effectiveness
- Emotional and self regulation capacities
- Ability to tolerate distress
- Mindfulness

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Dialectical Behavioral Therapy (DBT)

From the founder: "When DBT is successful, the patient learns to envision, articulate, pursue, and sustain goals that are independent of his or her history of out-of-control behavior, including substance abuse, and is better able to grapple with life's ordinary problems."

- Linehan, 2008

- Core processes: Change & acceptance
- Emphasis on abstinence
- Change: pushing for immediate and permanent cessation of drug abuse
- Acceptance: a relapse, should it occur, does not mean that the patient or the therapy cannot achieve the desired result
- Key skills: Cope ahead, Failing well
- Addict Mind → Clean Mind

27

Co-Occurring Psychiatric Disorders

General guidelines

- Concurrent treatment post-stabilization is best!

PTSD

- Cognitive Processing Therapy (CPT)
- Eye Movement Desensitization and Reprocessing (EMDR)
- Prolonged Exposure (PE)
- Concurrent Treatment of PTSD and SUDs using Prolonged Exposure

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In Summary

1. Many effective, evidence-based psychotherapy techniques
2. Can be done in many settings
3. Form the core of treatment for addictions

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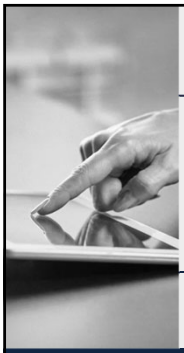

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Patient Interventions: Mutual Help, Psychotherapy, and Social Support

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1

Financial Disclosure

Paul H. Earley, MD, DFASAM

- No relevant disclosures

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2

A Very Brief Introduction

- Just covered by Dr. Marienfeld
  - CBT
  - DBT
  - ACT
  - Motivational Interviewing
- Recovery Support Services
- Relapse Prevention Training
- Twelve-step Support Systems
- Recovery Coaching
- Contingency Management
- Addressing Trauma - EMDR
- Recovery-based Partner Therapy

3

Behavioral Therapies: Individual

- Privacy
- Flexibility to address issues as they arise
- Focus on unique individually relevant issues
- More practical for some providers
- Avoidant patients (e.g., patients with schizophrenia, a trauma history, or are extremely socially anxious)

4

Behavioral Therapies: Groups

- Modal format for much SUD therapy:
  - Cost effective
  - Increase Access
  - Peers powerful agent of change
  - Better fidelity to model
  - Teaches healthy interdependence
- Advantages:
  - Define, watch and practice relapse prevention and other skills
  - Public affirmations moderate disease induced shame
  - Networks of support

5

Recovery Support Services

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6

Recovery Support Services[1]

- Translation and Transportation
- Housing & Family
- Parenting & Childcare
- Cultural and Gender Discrimination
- Employment
- Financial and Legal
- Schooling and Training

[1] Laudet, A. B. and K. Humphreys (2013). "Promoting recovery in an evolving policy context: what do we know and what do we need to know about recovery support services?" J Subst Abuse Treat **45(1): 126-133**

7

Relapse Prevention Training

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Principles of Relapse Prevention Training

- Relapse prevention provides definitive skills that can be taught and practiced.
- Research has validated two specific techniques
  - Cognitive Behavioral Approach[1]
  - Mindfulness-based Approach[2]
- Both arose from the University of Washington, G. Alan Marlatt's group.

[1] Marlatt, A., & Donovan, D. (2007). Relapse Prevention, Maintenance Strategies in the Treatment of Addictive Behaviors (Second ed.): Guilford Press.

[2] Bowen, S., Chawla, N., & Marlatt, G. A. (2011). Mindfulness-based relapse prevention for addictive behaviors : a clinician's guide. New York: Guilford Press.

9

Recognizing Cravings

- Cravings are a normal part of the human experience.
- Addiction disorders simply grab onto this process. In addiction recovery, they can be quite intense and/or persistent.
- The strength, frequency, and duration of cravings vary from person to person and from time to time and are not necessarily predictors of relapse.
- Cravings may never completely disappear.
- Learning to manage cravings, then, is a central part of successful remission.

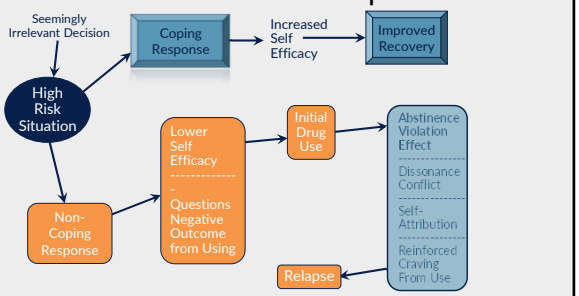
10

Types of Cravings

- Environmental cues (e.g., seeing a drug, smelling tobacco smoke, hearing addiction-related music).
- Visceral events (body sensations, taste, or smell)
- Emotional events (a feeling that the alcoholic "used to drink over")
- Memory tapes (scenes that play in the mind, especially those with strong visual "tapes").

11

Process Model of Relapse



1 Modified from Marlatt, A., & Donovan, D. (2007). Relapse Prevention, Maintenance Strategies in the Treatment of Addictive Behaviors (Second ed.): Guilford Press.

12

Essential Elements of the Process Model

- Collating a list of High-Risk Situations and clues for when they may occur is important for remission.
- Considering the best coping response for the most likely HRSs ahead of time is powerful medicine.
- Negative self talk (self-attribution) is counterproductive.
- Enacting coping responses decreases the probability of future relapse.

13

Mindfulness Model of Relapse Prevention

- Teaches Mindfulness - a mental state achieved by focusing one's awareness on the present moment, while calmly acknowledging and accepting one's feelings, thoughts, and bodily sensations.
- Meditation reduces impulsivity and teaches a calming self-awareness of one's current state.
- MBRP teaches patients to focus on increasing awareness, decreasing judgment, and shifting from "reacting" to "skillful responding."[1]

[1] Bowen, S., Chawla, N., Collins, S. E., Witkiewitz, K., Hsu, S., Grow, J. Marlatt, A. (2009). Mindfulness-Based Relapse Prevention for Substance Use Disorders: A Pilot Efficacy Trial. Substance Abuse, 30(4), 295-305.

14

Twelve Step Support Systems

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15

Mutual or Peer Support Groups

- Twelve-step programs:
  - Alcoholics Anonymous / Narcotics Anonymous / Cocaine Anonymous / Crystal Meth Anonymous / Nicotine Anonymous
  - Al Anon / Nar Anon
  - ACOA (Adult Children of Alcoholics)
- Other national support groups:
  - Smart Recovery
  - Women for Sobriety
  - Refuge Recovery
- Local, religiously affiliated and/or less formalized programs
  - Celebrate Recovery & Church groups
  - Continuing care groups at a treatment center

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Alcoholics Anonymous

- AA helps individuals recover through common process mechanisms associated with enhancing self-efficacy, coping skills, and motivation, and by facilitating adaptive social network changes.[1]
- Focuses individual on long-term goals and provides a holding place for that patience.
- Teaches relapse prevention skills.
- Normalizes the experience of loss of control, slippage of moral values, and substance-induced trauma.
- Sets discontinuation of abusable substances as the primary goal.
- Provides a path for reconciliation of the past.
- Provides a social network that is (relatively) free of substance use.

[1] *Kelly, J. F., Magill, M., & Stout, R. L. (2009). How do people recover from alcohol dependence? A systematic review of the research on mechanisms of behavior change in Alcoholics Anonymous. Addiction Research & Theory, 17(3), 236-259.*

17

Why Won't My Patients go to AA?

- A focus on spiritual principals and, by some, religious tenets.
- Spiritual references often turn off the agnostic or atheist if they do not mesh with spiritual beliefs of other members.
- Many patients with addiction disorders suffer from varying levels of social phobia.
- Newcomers find the format unusual, look for hierarchical structures where none exist.
- Most patients are not naturally drawn to AA, as its values and system is antithetical to the mindset and worldview that their illness has induced previously.

18

Why do Patients Dislike AA?

How patients approach their issues and situation:	What AA teaches:
Focus on short-term goals	Focus on long-term goals
Quick fix	Gradual change
I'm different	We are all the same
Pleasure (or relief from pain) is paramount	Pain helps you grow
I can do this	We can do this
Fight harder	The solution emerges when you admit defeat.
My problems will improve if external things get better.	Problems will only improve when you approach the world in a different manner.
Substances are the problem	I am the problem

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What do Patients Like in AA?

- Listening to stories of hope and transformation
- Not being forced to talk
- No obligatory dues or fees
- Ease of access: many cities have hundreds or even thousands of meetings throughout the day.
- A sense of warmth and belonging
- Acceptance and often unconditional love
- Coffee & cigarettes

20

Core Concepts of AA

- Proper implementation requires familiarity with the core concept and terms
  - Acceptance of the illness; working through "denial" and accepting "powerlessness"
  - Mentoring: Obtaining a sponsor who provides support and helps the individual understand the process.
  - Attendance at meetings must be frequent at first ("like old fashioned antibiotics, effective but has to be taken often for it to work")
  - Spirituality: Surrender to "higher power" of ones own choosing (often the group in its wisdom is that power)
- Explore what is helpful and what, at first, is not

21

Twelve-Step Facilitation

- Handoff can be cold, warm or with training.
  - Cold: "You should go to an AA meeting, look it up online."
  - Warm: " I know of a meeting at 8 pm on Pine St every weeknight. Would you consider going there twice between now and when we next meet?"
  - Manualized: "We are going to walk through a manual that teaches you how to use 12-Step programs to support your recovery. I will help you find a meeting locally. Then you can go to a meeting and report back next week and we will discuss what happened."
- Handoff with training is best implemented using a structured process and can be manual-driven.
  - Manual developed for project MATCH available through NIAAA[1]
  - MAAZE - Making Alcoholics Anonymous Easier[2]

1 Nowinski, J., et al. (1995). Twelve Step Facilitation Therapy Manual. Rockville, Maryland, U.S. Department of Health and Human Services
2 Kaskutas, L. A., et al. (2009). "Effectiveness of Making Alcoholics Anonymous Easier: a group format 12-step facilitation approach." J Subst Abuse Treat 37(3): 228-239

22

The 2020 Cochrane Review

- March 2020 Cochrane Review (authors Kelly, Humphreys & Ferri)
- 27 Studies, 10,566 participants, 21 RCT or quasi-RCT
- Compared MET & CBT with twelve step programs and twelve step facilitation.
- Concluded that AA/TSF:
  - Usually produced **higher** rates of continuous abstinence than the other established treatments investigated.
  - May be superior to other treatments for increasing the percentage of days of abstinence, particularly in the longer-term.

[1] Kelly, John F., Keith Humphreys, and Marica Ferri. "Alcoholics Anonymous and other 12-step programs for alcohol use disorder." Cochrane Database of Systematic Reviews (2020).

23

The 2020 Cochrane Review[1]

- Concluded that AA/TSF:
  - Performs as well as other treatments for reducing the intensity of alcohol consumption.
  - Four of the five economics studies found substantial cost-saving benefits for AA/TSF, these interventions reduce healthcare costs substantially.
- This is a clear evidence base for this modality for those with alcohol use disorder.
- Kelly stated, "It's the closest thing in public health we have to a free lunch."
- In addiction medicine, the term "Evidence-based medicine" has become conflated with MAT. Everyone should add AA to the category of Evidence-based medicine for AUD.

[1] Kelly, John F., Keith Humphreys, and Marica Ferri. "Alcoholics Anonymous and other 12-step programs for alcohol use disorder." Cochrane Database of Systematic Reviews 3 (2020).

24

Outcomes Using ROSC in OUD

- Benefits of active referral to twelve step programs in opioid use disorder less clear.
- One large recent review of ~21,000 patients provided three types of care[1]
  - Medication management (MM) only
  - Limited psychosocial (LP) therapy
  - Recovery-oriented, 12-step orientation (RO)
- Urine drug tests negative for opioids at the time of the second buprenorphine prescription were 34% for MM, 56% for LP, and 62% for RO (P < .001)

[1] Galanter, M., et al. (2020). "Buprenorphine Treatment for Opioid Use Disorder in Community-Based Settings: Outcome Related to Intensity of Services and Urine Drug Test Results." American Journal on Addictions

25

Recovery Coaching

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Recovery Coaching

- Recovery Coaching is provided by a paraprofessional and designed to sustain connection and help with day-to-day choices and actions.
- A Recovery Coach is a non-judgmental individual who encourages self-reflection and promotes actions that promote or endorse remission behaviors and recovery.
- RCs can work with individuals who are actively using and those in early remission.
- Recovery coaches do not offer primary treatment for addiction, do not diagnose, and are not associated with any particular method or means of recovery.
- Services provided include strengths-based support (as opposed to disease-focused assistance).

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Recovery Coaching

- Recovery coaching is ad hoc, often conducted via telephone or via electronic communication.
- May be linked with Contingency Management, urine drug screening and social services.
- Limited research[1] shows:
  - Improved relationships with providers and social supports
  - Increased satisfaction with the treatment overall
  - Reduced rates of relapse
  - Increased retention in treatment

[1] Reif, S., et al. (2014). "Peer recovery support for individuals with substance use disorders: Assessing the evidence." *Psychiatric Services* **65(7): 853-861.**

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Contingency Management

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Contingency Management

- Contingency Management (CM) is a treatment tool that is:
  - Among the most thoroughly researched behavioral approach to SUD treatment (>100 RCTs and multiple meta-analyses).
  - Among the most effective clinical approaches.
  - Cost-effective
  - Can be used with patients across the change spectrum (from decreasing use to attaining and maintaining remission.
  - Increases compliance with medications that treat addiction.

And yet, it is *rarely* utilized.

30

Contingency Management

- Is based upon operant conditioning or behavioral economics
- Breaks down the recovery process into a series of goals that are:
  - Concrete
  - Attainable
  - Realizable
- This sidesteps the hopelessness of many individuals with addiction diseases
- Subtly and subconsciously establishes priorities for recovery by:
  - Rewarding critical recovery behaviors
  - Prioritizes critical behaviors through reward intensity
- Important elements are:
  - Pro-remission or recovery behaviors are reinforced in close temporal proximity to the event.
  - Monetary reinforcers are the most simple and universal rewards, but other reinforcers (e.g., food vouchers) work in some situations.

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Contingency Management

- Rewards should be:
  - Immediate - immediate rewards are twice as effective as delayed rewards.[1]
  - Tangible - and matched to participant needs.
  - Intermittent - e.g., pulling a ticket from a punch bowl that may contain a prize of varying values are just as effective as constant reinforcement but is more cost effective.
  - Valuable - low value rewards are half as effective as high-value rewards.[1]
- Importantly, CM does not increase gambling.[2]

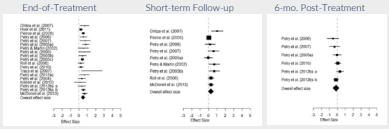
[1] Lussier, J. P., et al. (2006). "A meta-analysis of voucher-based reinforcement therapy for substance use disorders." Addiction **101(2): 192-203.**

[2] Petry, N. M., et al. (2006). "Prize-based contingency management does not increase gambling." Drug Alcohol Depend. **83(3): 269-273.**

32

Limitations of CM

- Research studies reported a cost of about $100 per month per patient in prizes (Petry, 2013)
- Studies were mostly 3-month trials
- Effects dissipate after 6 months (Benishek 2014).
  - Possibly CM shapes, but does not transform behavior



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Implementing Contingency Management

- Staff may have concerns about "paying patients to do the right thing."
  - This is overcome by pragmatic discussions. Motivation is a scarce commodity for many patients!
- The logistics are complex
  - Setting up measurable, concrete goals
  - Recording responses
  - Tracing and dispensing rewards
- The easiest method of implementation comes from technology.

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Affect Regulation and Recognition

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Affect Recognition and Regulation

- Many individuals have difficulties with either:
  - Recognizing and understanding feeling states
  - Responding in a productive manner to those feelings
- Addiction entraps and induces strong emotions and difficulties handling emotions trigger relapse and continued use.
- Therapy in emotions management is helpful in preventing relapse in such individuals.[1]
- Alexithymia (the inability to recognize and name feeling states) plays a role in a different population of those with substance use disorders.[2]

[1] Hsu, S. H., Collins, S. E., & Marlatt, G. A. (2013). Examining psychometric properties of distress tolerance and its moderation of mindfulness-based relapse prevention effects on alcohol and other drug use outcomes. Addict Behav, 38(3), 1852-1858.

[2] Morie, K. P., Yip, S. W., Nich, C., Hunkele, K., Carroll, K. M., & Potenza, M. N. (2016). Alexithymia and addiction: a review and preliminary data suggesting neurobiological links to reward/loss processing. Current addiction reports, 3(2), 239-248.

36

Partner Therapy

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Partner / Couples Therapy

- Several partner therapies have been studied and shown to be effective in increasing remission.[1]
- Important to explore the partner's relationship to substances as well as others in the home.
- Encourage reasonable accommodations by the partner to support remission. The partner's definition of "reasonable" is important!
- Remission is problematic when the identified patient is on the downside of a significant power differential.

[1] Powers, M. B., Vedel, E., & Emmelkamp, P. M. (2008). Behavioral couples therapy (BCT) for alcohol and drug use disorders: A meta-analysis. Clin Psychol Rev, 28(6), 952-962.

38

Trauma Symptom Abatement - EMDR

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Trauma & Addiction

- Physical, emotional, sexual, or religious trauma co-migrates with addiction disorders (incidence of addition higher in traumatized populations).[1]
- …with a suggestion that trauma especially childhood trauma contributes to the development of addiction disorders.
- Addiction often traumatizes its victim. Random flashbacks of intense addiction-related memories may trigger relapse.

[1] Khoury, L., Tang, Y. L., Bradley, B., Cubells, J. F., & Ressler, K. J. (2010). Substance use, childhood traumatic experience, and Posttraumatic Stress Disorder in an urban civilian population. Depress Anxiety, 27(12), 1077-1086.

40

Eye Movement Desensitization and Reprocessing (EMDR)

- Developed in 1987, the therapist gently guides the patient to briefly focus on the trauma memory.
- …while simultaneously engaging eye movements and/or other forms of rhythmic left-right stimulation.
- The process is highly structured and repeatable with multiple sessions that
  - Gather the history
  - Qualify the target memory
  - Process the memory to an adaptive resolution
  - Evaluate the outcome

41

Eye Movement Desensitization and Reprocessing (EMDR)

- Individuals with a trauma history often begin using substances to manage flashbacks and emotional unrest produced by their trauma.
- Trauma victims abuse alcohol, sedatives and dissociatives but, paradoxically use stimulants and cocaine.
- EMDR may be helpful in disengaging and disaffecting addiction-related memories.[1]
- EMDR and other interventions reduce trauma flashbacks and thus the substance use triggered by their recall.
- This in turn improves the prognosis of the addiction disorder.
- Other trauma-resolution techniques may also prove helpful.

[1] Hase, M., Schallmayer, S., & Sack, M. (2008). EMDR reprocessing of the addiction memory: Pretreatment, posttreatment, and 1-month follow-up. Journal of EMDR Practice and Research, 2(3), 170-179.

42

Conclusions

- A wide variety of psychosocial interventions are available to assist in recovery from substance use disorders.
- Careful assessment is the first and most important step in matching treatment to a particular individual's issues.
- Not addressing psychosocial issues leads to a worse prognosis and is bad medicine.
- Engaging patients with all psychosocial interventions requires an approach based upon compassion and concern.
- Physicians should have a basic understanding of the many types of therapeutic interventions in order to help patients engage in them when indicated.

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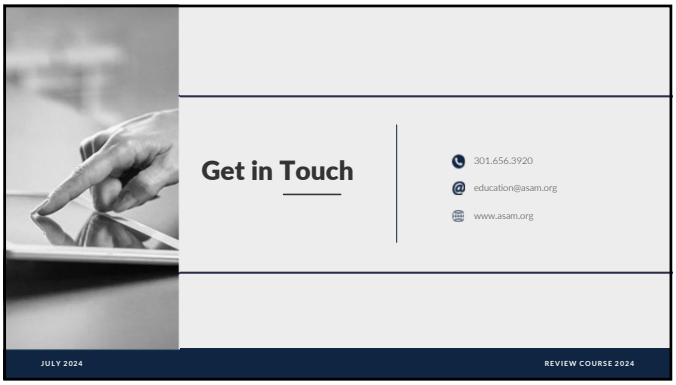

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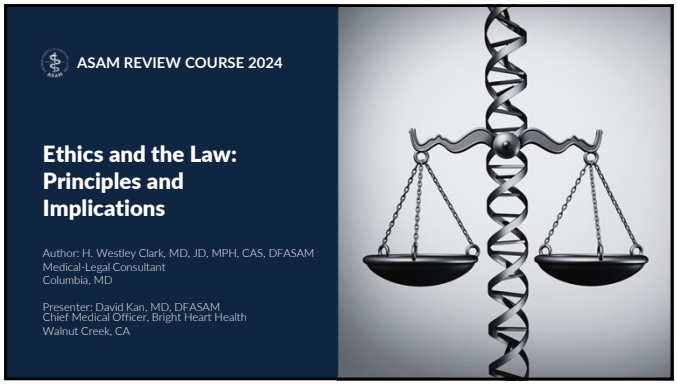
ASAM REVIEW COURSE 2024
Ethics and the Law: Principles and Implications
Author: H. Westley Clark, MD, JD, MPH, CAS, DFASAM
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Presenter: David Kan, MD, DFASAM
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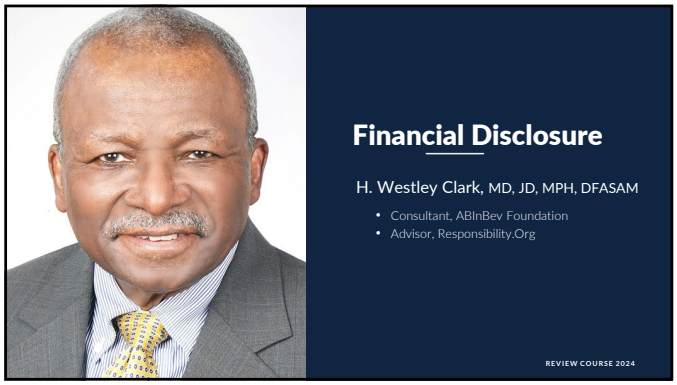
Financial Disclosure
H. Westley Clark, MD, JD, MPH, DFASAM
• Consultant, ABInBev Foundation
• Advisor, Responsibility.Org
REVIEW COURSE 2024

2


Financial Disclosure
David Kan, MD, DFASAM
• No relevant disclosures
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3

4

Presentation Outline

- Ethical Principles
- Informed Consent
- Privacy and Confidentiality
- Ethical Prescribing
- Special Topics

5

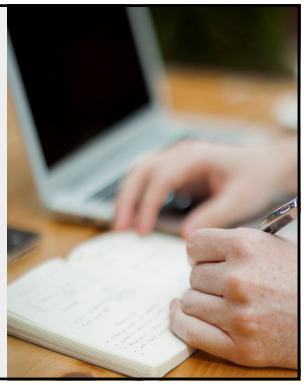
Ethical Principles

- Autonomy: self-determination, self-governance, moral independence
  - Example: Patient with alcohol use disorder, experiencing a recurrent upper GI bleed refusing voluntary inpatient addiction psychiatry admission

6

Ethical Principles

- Beneficence: actions should promote patient well-being
  - Example: A patient with a severe heroin use disorder sees PCP who offers him buprenorphine, referral to methadone treatment or inpatient withdrawal management and community recovery resources



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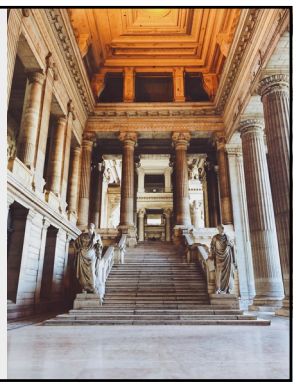
Ethical Principles

- Non-maleficence: do no harm (or as little as necessary)
  - Examples of harm: (1) Providing benzodiazepines for patients on high dose opioids or (2) prescribing buprenorphine without an exam for cash

8

Ethical Principles

- Justice:
  - Fairness in decisions
  - Equal distribution of resources and new treatments
  - Medical practitioners uphold laws
  - Examples: (1) Advocating for a patient rejected from inpatient substance use disorder treatment when the insurance provider deems it "not clinically indicated" or (2) Accepting cash only for the use of buprenorphine or naltrexone, limiting access to treatment .



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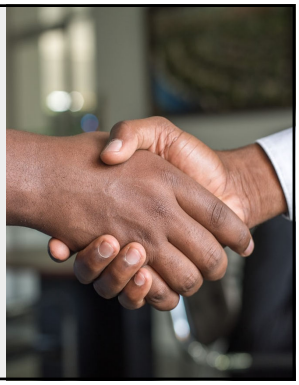
Ethical Principles

- Respect for people: treating people in a manner that acknowledges their intrinsic dignity
- Truth-telling: honesty, sharing information



10

Complex Ethical Scenario

- 40-year-old female anesthesiologist
- Taking opioid medications meant for patients, replacing with saline
- Has used oral opioids on the job but denies problems
- Asks you to notify nobody

11

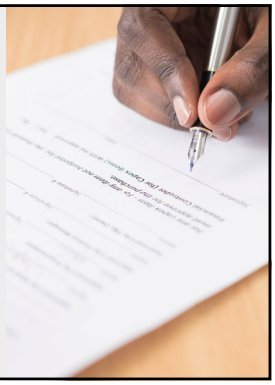
Which of the following is NOT true regarding informed consent?

A. It must be given voluntarily.
B. An individual must possess decisional capacity.
C. Patients with psychosis cannot give informed consent.
D. It involves the disclosure of information between the clinician and the patient.

12

Informed Consent

- Voluntariness
- Information disclosure
- Decisional capacity



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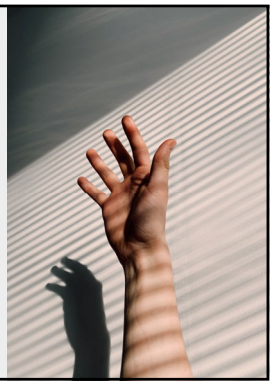
Voluntariness

- Freely given
- Coercion: punishment or excessive rewards
- Persuasion
- Influence
- Context-dependent
- Risk of infringing
  - SUDs treatment in custody
  - Drug court
  - Inpatient treatment



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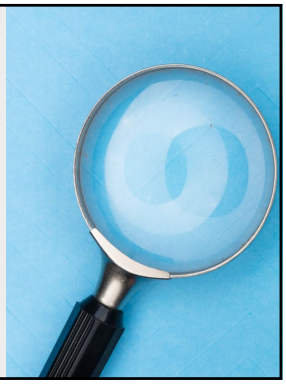
Information Disclosure

- Nature of illness and proposed treatment
- Risks/benefits
- Alternatives
- Consequences of foregoing treatment
- "Reasonable person" standard
- High standard of disclosure
  - Dependency producing medications (opioids)
  - Medications with known adverse events (disulfiram)
  - Medication combinations that should be avoided with MAOIs (methadone, bupropion, tramadol, etc.)



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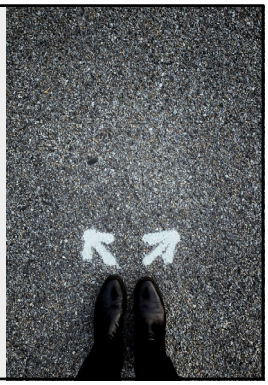
Decisional Capacity

- Communicate a choice
- Understand the relevant information
- Appreciate the situation and its consequences
- Reason about treatment options
- "Sliding scale" approach
- Potentially impaired
  - Intoxication
  - Substance-related neurocognitive problems
  - Dual diagnosis



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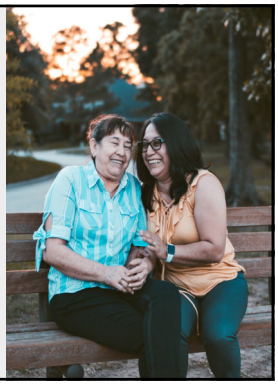
For Those Lacking Capacity

- Durable power of attorney for healthcare decisions (DPOAHC): form identifying surrogate decision-maker if one becomes incapacitated
- Advanced directive/living will: written statement expressing specific wishes, does not designate healthcare POA
- Guardian/conservator of the person: person appointed to make care decisions when patient is incapacitated



17

Pearls

- There are various ethical principles underlying medicine and addictions treatment that may come into conflict
- The process of informed consent requires voluntariness, information disclosure, and decisional capacity
- Certain treatment settings have the potential to infringe on voluntariness

18

Privacy and Confidentiality

- Privacy: patient's right to protection of sensitive information
- Confidentiality: clinician's obligation to protect sensitive information
- 42 CFR Part 2: Confidentiality of Alcohol and Drug Abuse Patient Records
- HIPAA

19

42 CFR Part 2 – Covered Programs

- Individual, entity, or identified unit within a general medical facility that provides SUDs diagnosis, treatment, or referral for treatment
- Medical personnel/staff in a general medical facility whose primary function is provision of SUDs diagnosis, treatment, or referral for treatment and who are identified as such providers.

20

42 CFR Part 2 – Federal Assistance

- Conducted in a federal department or agency
- Supported by federal funds
- Carried out under a license or registration from federal government
  - Medicare providers
  - Authorization to conduct maintenance treatment or withdrawal management
  - Registration under Controlled Substances Act to dispense a substance used in treatment of SUDs

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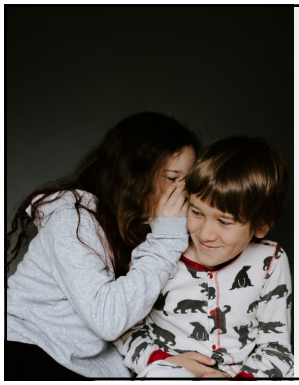


Disclosure

- Part 2 programs may only release patient information with the patient's consent
- Exceptions include:
  - Medical emergency
  - Error in manufacture, labeling, or sale of a product under FDA jurisdiction
  - Research
  - Valid court order with subpoena
  - Crimes committed on part 2 program premises
  - Reporting suspected child abuse or neglect
- Failure can result in criminal penalty (a fine)

22

HIPAA ('96), Privacy Rule ('00)

- All PHI protected
- Exceptions related to medical operations and public interest/benefit

23

Alignment 42 CFR Part 2/HIPAA/HITECH 2024 Amendments

- **Single Consent for Part 2**
  - One consent is enduring
- **Re-disclosure**
  - Permitted within HIPAA Privacy Rule
- **SUD Counseling Notes**
  - Additional protections – maintained separately from Part 2 record
- **Accounting of Disclosure/Restriction**
  - Must track disclosures for 3 years
  - Can limit disclosure
- **Prohibition on Use and Disclosure without consent or court order**
  - Legal proceedings
  - Law enforcement
  - Warrant
- **Penalties and breach reporting**
  - Civil penalties in addition to criminal
  - Breach reporting required within 60 days
- **HIPAA Privacy Practices**
  - Now aligned
- More changes in reference

https://www.hhs.gov/hipaa/for-professionals/special-topics/hipaa-part-2/index.html

24

Controlled Substance Act (1970)

- Classification and regulation
- Manufacturing
- Distribution
- Exportation and sale

25

CSA Regulation/Classification

- DEA licensure requirement
- Schedule I: illegal, no medical use (MDMA, methaqualone, gamma-hydroxybutyric acid (GHB), peyote)
- Schedules II-V: addictive potential
  - II: cocaine, methamphetamine, methadone, phencyclidine, oxycodone, fentanyl
  - III: ketamine, testosterone, buprenorphine, sodium oxybate
  - IV: benzos, zolpidem, tramadol,
  - V: diphenoxylate, pregabalin, *

** As of April 2023, gabapentin is not controlled under the CSA, but a number of states have made it a Schedule V drug. The DEA has been requested to reschedule gabapentin schedule V.*

26

Ethical Prescribing

- Patient risks
  - SUDs
  - Diversion
  - Exacerbation of comorbid medical or psychiatric illness
- Practices to address
  - Urine drug testing
  - Medication contract
  - PDMPs

27

Universal Precautions

1. Make a diagnosis with appropriate differential, including a physical exam
2. Psychological assessment (risk of substance use disorders)
3. Obtain informed consent
4. Treatment agreement
5. Pre- and post-intervention assessment of pain level and function
6. Appropriate trial of opioid therapy +/- adjunctive medication
7. Reassess pain score and level of functioning
8. Regularly assess 4 A's: analgesia, activity, adverse effects, aberrant behavior
9. Periodically review diagnosis and comorbid conditions
10. Documentation

28

Which of the following is NOT an example of misprescribing?

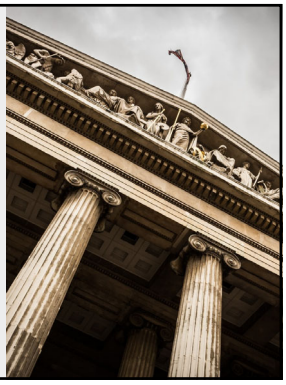
A. Providing a patient opioids at a dangerously high dose.
B. Providing a prescription for three months of opioids following an uncomplicated outpatient surgical procedure.
C. Providing a friend a prescription for Ativan for no medical purpose.
D. Providing a patient a prescription for Ativan for short-term treatment of anxiety after checking with the PDMP, without knowing she had multiple prescriptions from different providers.

29

Legal Consequences

- Misprescribe: inappropriate rationale, dose, quantity, lack of physical examination
- CSA: "unlawful for any person to knowingly or intentionally… manufacture, distribute, or dispense, or possess with intent… a controlled substance"
- Knowingly or Intentionally
- Without legitimate medical purpose
- Outside the usual course of professional practice

- State medical board sanctions
- Civil: malpractice
- Criminal: CSA, murder



30

Recent Case

- Oscar Lightner, MD.
- From March 2016 through August 2018
- Unlawfully prescribing over 600,000 pills of hydrocodone and prescriptions of carisoprodol and alprazolam
- People paid cash $250 to $500 for each visit to the clinic deemed by the DEA as a pill mill.
- Physician convicted by a jury

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Prescription Drug Monitoring Programs

- 50 states, D.C., Guam
- Mitigate abuse/diversion
- Models
  - Non-mandated use
  - Proactive reporting
  - Mandated use
- Criticisms
  - Inadequate information collection
  - Ineffective utilization in clinical settings
  - Limited interstate sharing
- Mixed data on effectiveness, differs by state

32

Pearls

- Confidentiality of substance abuse treatment is governed by 42 CFR Part 2, and HIPAA's Privacy Rule
- The Controlled Substances Act of 1970 established the DEA regulation and classification of addictive drugs and criminal penalties for distribution of drugs
- There are various models of ethical prescribing that generally involve informed consent, regular assessment and dose planning, and appropriate clinical documentation
- PDMPs, though potentially helpful, differ in their implementation and effectiveness

33

Addiction & the Law: Special Topics

- Adolescents
- Pregnant patients
- Justice-involved populations
- Civil commitment & substance use
- Americans with Disabilities Act (ADA)
- Impaired Clinician

34

Adolescents, Addiction, & the Law

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35

A 15-year-old patient comes to you requesting treatment for alcohol use disorder. Which of the following scenarios most likely requires guardian informed consent before initiating treatment?

A. She is a mature minor
B. She is married
C. She is serving in the military
D. She has run away from home
E. She is experiencing severe withdrawal

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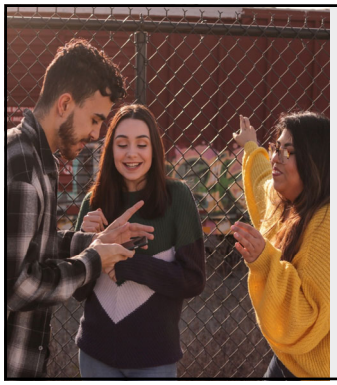


Legal Standards: Minor Informed Consent

- Age of majority
- Minor's ability to consent
- General medical care
- Mental health
- Substance use disorders
- Emancipation
- Legal
- Marriage, military
- Other forms
- Mature minors
- Have children
- High school graduate

37

Mature Minor Doctrine

- Definition
- Assessment of maturity:
- Age & maturity
- Emotional capacity
- Intelligence
- Risk of procedure/treatment
- Benefit to minor
- Informed consent assessment:
- Risks of forgoing treatment
- Long term consequences
- Brain development, impulsivity & "charged" environments

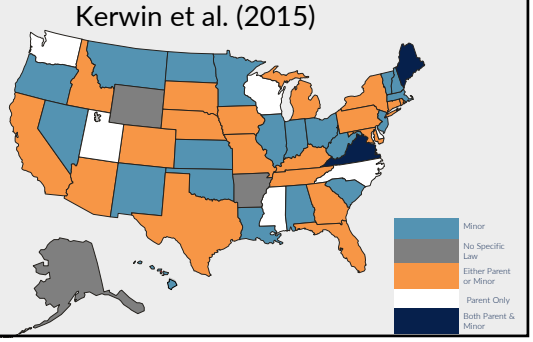
38

Minor Consent for SUD Treatment

- Laws vary by state
- Minimum age of consent can range from age 12-16
- May be able to consent to some services but not others
  - Withdrawal Management
  - Outpatient
    - Buprenorphine for those 16 -18
  - Inpatient
- Parental notification may still be required

39

Consent for Inpatient Substance Treatment Kerwin et al. (2015)



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Adolescent Autonomy, Privacy & Confidentiality

- Parental involvement
- Confidentiality can be preserved
- Insurance & privacy

41

Pearls

- State laws vary regarding minor consent requirements and may allow for a mature minor to consent
- Adolescents usually have the greatest autonomy to consent for substance use disorder treatment compared to other medical treatments
- When treating an adolescent patient, involve parents if possible while preserving the adolescent's confidentiality

42

Pregnancy, Substance Use, & the Law

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43

Legal Consequences Of Substance Use In Pregnancy

- Criminal
  - Feticide laws (38 states)
  - Chemical endangerment of a child (Amnesty)
  - Direct criminalization of use during pregnancy
- Civil
  - Substance Use = Child Abuse (24 States +DC)
  - Reporting to Child welfare (25 states + DC)
  - Civil commitment (3 states)

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Reporting Requirements to Child Welfare (Jarlenski, Guttmacher. Org)

- Mandated reporting of child abuse/neglect
  - Standard: Reasonable belief or suspicion for abuse
  - Prenatal drug use & Substance Exposed Newborns
- Clinical & ethical problems
- Guidelines
  - Inform of any mandated reporting requirements & limits of confidentiality
  - Obtain informed consent before drug testing (ACOG)

45

Pearls

- A person who uses substances during pregnancy can be subjected to civil or criminal penalties in many states
- Mandated reporting requirements of perinatal substance use vary across states
- Obtain informed consent before drug testing, including notification of reporting requirements

46

Justice-Involved Populations

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47

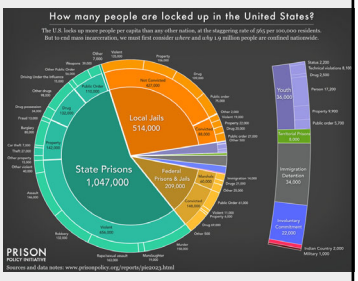
Approximately what percentage of women who are incarcerated in jail have a substance use disorder?

A. 25%
B. 33%
C. 50%
D. 75%
E. 90%

48

Statistics

- In 2020, 5.5 million people under correctional supervision in the U.S.
- History of incarceration in the U.S.
- SUDs & incarceration
  - Over 65% with active SUD
    - >75% of women have SUD
  - ~10- 15% receive treatment



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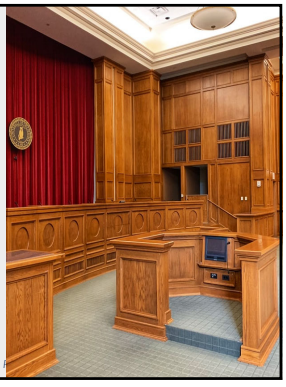
MAT in Corrections

- The Need
  - 75% will relapse within 3 months of release (SAMHSA)
  - 100x more likely to die of overdose within 2 weeks of release (BJS, Binswanger)
- Barriers
  - Lack of education
    - Substituting "one drug for another"/abstinence mentality
  - Diversion concerns
  - Cost
  - Lack of community providers to start or continue MAT
- BUT, more pilots across the US

50

Problem Solving (Treatment) Courts

- Drug, mental health, DUI, veteran's courts
- Therapeutic Jurisprudence
- Judge plays critical role
- Entry & Eligibility
- Structure & sanctions
- Efficacy (Logan)
  - Recidivism decreases
  - Future drug use reduced
- Treatment provider can be in dual role
- Some do not allow MAT (Matusow)



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FINAL TOPICS

- Civil commitment
- The Americans with Disabilities Act (ADA)
- Impaired Physicians

52

Civil Commitment

- **Standards**
  - Mentally ill (or substance disorder, below) AND
  - Dangerous to self/others OR
  - Gravely disabled
- **Substance use disorders**
  - 37 states + DC (NAMSDL)
- **Legal process**
  - Due process required
  - Hearing occurs in timely manner
  - Committed for specified time by the judge

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The Americans With Disabilities Act (ADA)

- **Disability: Physical or Mental impairment which:**
  - Limits in one or more major life activities
  - History of impairment
  - Regarded as having an impairment
- **Substance use**
  - Alcohol use disorder
  - Other substance use disorders
    - Protected: Not using now but is or has been in treatment for addiction or regarded by others as using drugs
    - Not protected: "Currently using drugs" or casual user
- **Exceptions**

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Physician Regulation & Impaired Physicians

- Medical practice acts & state medical boards
- Physician health programs & impaired physicians
  - Exist in nearly every state
  - Goals
  - Voluntary vs. mandated treatment
  - High success rates
- Duty to report impaired physicians:
  - Impairment: physical, mental or substance-related disorder that interferes with abilities to safely and competently perform professional duties
  - Legal standards (have knowledge of or reason to believe) & options
  - Ethical and professional duties

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Questions?

- Dkan@brightheartheath.com
- Complete bibliography available on request

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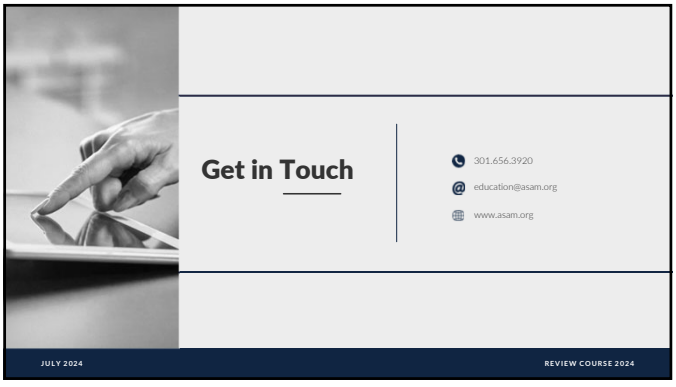

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Prevention and Public Health: From Theory to Practice

Amutha Rajagopal, MD, MPH
Assistant Professor
Addiction Medicine & Infectious Diseases
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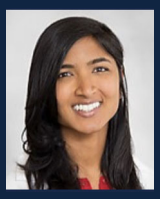

Financial Disclosure

Amutha Rajagopal, MD, MPH

- No relevant disclosures

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Learning Objectives

- Describe the importance of preventing unhealthy substance use
- Describe risks and protective factors for the development of substance use disorders
- Describe a public health approach to addressing unhealthy substance use
- Describe evidence-based prevention interventions

3

National Survey on Drug Use and Health (NSDUH)

- Provides nationally representative data on the use of tobacco, alcohol, and illicit drugs, SUD, and receipt of treatment among the non-institutionalized US population 12 years and older

2022 National Survey of Drug Use and Health (NSDUH) releases. SAMHSA.gov.

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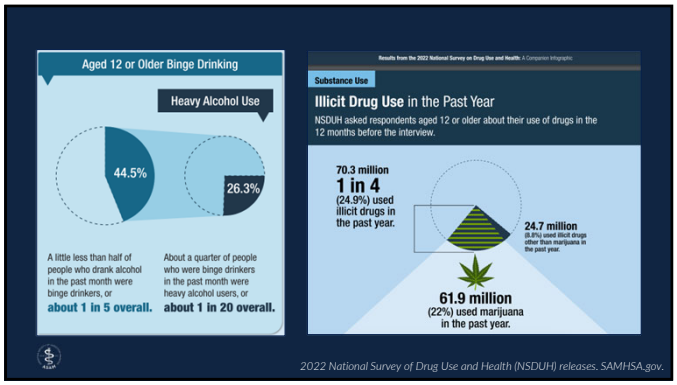

2022 National Survey of Drug Use and Health (NSDUH) releases. SAMHSA.gov.

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2022 National Survey of Drug Use and Health (NSDUH) releases. SAMHSA.gov.

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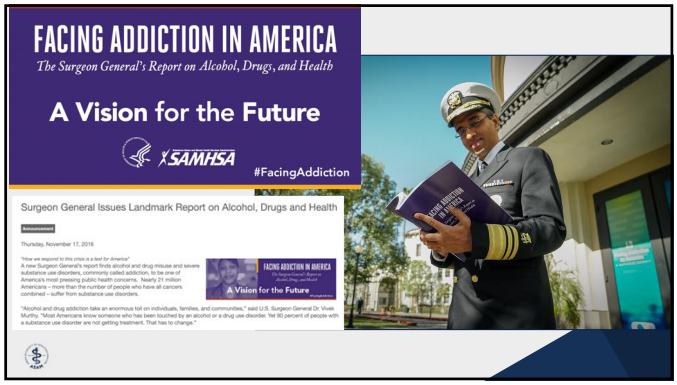

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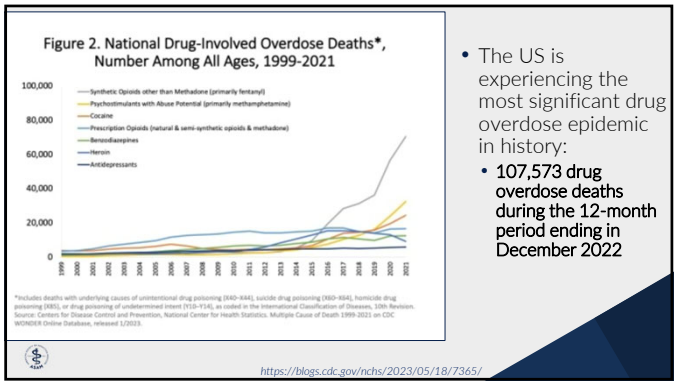


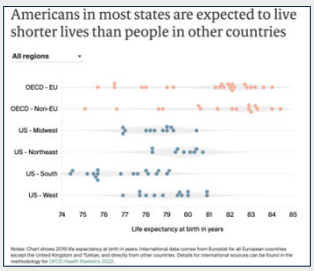
- The US is experiencing the most significant drug overdose epidemic in history:
  - 107,573 drug overdose deaths during the 12-month period ending in December 2022

https://blogs.cdc.gov/nchs/2023/05/18/7365/

8

Costs of Unhealthy Substance Use

- Data from CDC show that opioid use disorder and opioid overdose alone cost the United States $1.02 trillion in 2017



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9

Evidence-Based Prevention

- Evidence- based prevention interventions, carried out before the need for treatment, can delay early use and stop the progression from use to problematic use

SAMHSA. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. 2016

10

Risk Factors for Adolescent and Young Adult Substance Use

Risk Factors	Definition	Adolescent Substance Use	Young Adult Substance Use
Individual/Peer			
Early initiation of substance use[46,47]	Engaging in alcohol or drug use at a young age.	✔	✔
Early and persistent problem behavior[48,49]	Emotional distress, aggressiveness, and "difficult" temperaments in adolescents.	✔	
Rebelliousness[48,50]	High tolerance for deviance and rebellious activities.	✔	✔
Favorable attitudes toward substance use[51,52]	Positive feelings towards alcohol or drug use, low perception of risk.	✔	✔
Peer substance use[53-55]	Friends and peers who engage in alcohol or drug use.	✔	✔
Genetic predictors[56]	Genetic susceptibility to alcohol or drug use.	✔	✔

SAMHSA. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. 2016

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Risk Factors for Adolescent and Young Adult Substance Use

Risk Factors	Definition	Adolescent Substance Use	Young Adult Substance Use
Family			
Family management problems (monitoring, rewards, etc.)[57-60]	Poor management practices, including parents' failure to set clear expectations for children's behavior, failure to supervise and monitor children, and excessively severe, harsh, or inconsistent punishment.	✔	✔
Family conflict[61-63]	Conflict between parents or between parents and children, including abuse or neglect.	✔	✔
Favorable parental attitudes[64,65]	Parental attitudes that are favorable to drug use and parental approval of drinking and drug use.	✔	✔
Family history of substance misuse[66,67]	Persistent, progressive, and generalized substance use, misuse, and use disorders by family members.	✔	✔

SAMHSA. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. 2016

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Risk Factors for Adolescent and Young Adult Substance Use

Risk Factors	Definition	Adolescent Substance Use	Young Adult Substance Use
School			
Academic failure beginning in late elementary school[68,69]	Poor grades in school.	✔	✔
Lack of commitment to school[70,71]	When a young person no longer considers the role of the student as meaningful and rewarding, or lacks investment or commitment to school.	✔	✔

SAMHSA. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. 2016

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Risk Factors for Adolescent and Young Adult Substance Use

Risk Factors	Definition	Adolescent Substance Use	Young Adult Substance Use
Community			
Low cost of alcohol[80,72]	Low alcohol sales tax, happy hour specials, and other price discounting.	✔	✔
High availability of substances[73,74]	High number of alcohol outlets in a defined geographical area or per a sector of the population.	✔	✔
Community laws and norms favorable to substance use[75,76]	Community reinforcement of norms suggesting alcohol and drug use is acceptable for youth, including low tax rates on alcohol or tobacco or community beer tasting events.	✔	✔
Media portrayal of alcohol use[77-79]	Exposure to actors using alcohol in movies or television.	✔	
Low neighborhood attachment[81,81]	Low level of bonding to the neighborhood.	✔	
Community disorganization[82,83]	Living in neighborhoods with high population density, lack of natural surveillance of public places, physical deterioration, and high rates of adult crime.	✔	
Low socioeconomic status[84,85]	A parent's low socioeconomic status, as measured through a combination of education, income, and occupation.	✔	
Transitions and mobility[85,86]	Communities with high rates of mobility within or between communities.	✔	

SAMHSA. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. 2016

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Table 3.2: Protective Factors for Adolescent and Young Adult Substance Use

Protective Factors	Definition	Adolescent Substance Use	Young Adult Substance Use
Individual			
Social, emotional, behavioral, cognitive, and moral competence[87,88]	Interpersonal skills that help youth integrate feelings, thinking, and actions to achieve specific social and interpersonal goals.	✔	✔
Self-efficacy[89,90]	An individual's belief that they can modify, control, or abstain from substance use.	✔	✔
Spirituality[91,92]	Belief in a higher being, or involvement in spiritual practices or religious activities.	✔	✔
Resiliency[88]	An individual's capacity for adapting to change and stressful events in healthy and flexible ways.	✔	✔
Family, School, and Community			
Opportunities for positive social involvement[93,94]	Developmentally appropriate opportunities to be meaningfully involved with the family, school, or community.	✔	✔
Recognition for positive behavior[95]	Parents, teachers, peers and community members providing recognition for effort and accomplishments to motivate individuals to engage in positive behaviors in the future.	✔	✔
Bonding[95-97]	Attachment and commitment to, and positive communication with, family, schools, and communities.	✔	✔
Marriage or committed relationship[98]	Married or living with a partner in a committed relationship who does not misuse alcohol or drugs.		✔
Healthy beliefs and standards for behavior[97,99]	Family, school, and community norms that communicate clear and consistent expectations about not misusing alcohol and drugs.	✔	✔

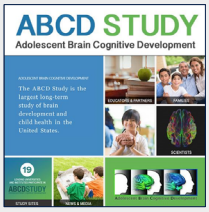
Note: These tables present some of the key risk and protective factors related to adolescent and young adult substance initiation and misuse.

SAMHSA. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. 2016

15

Evidence-Based Prevention

- Most risk factors and protective factors are modifiable through preventive programs and policies that reduce vulnerability at multiple levels: federal, state, community, family, school, and individual levels



SAMHSA. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. 2016

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The Public Health Systems Approach

SAMHSA. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. 2016

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Priorities of Research on Prevention of Substance Use Problems

- Identifying and targeting biological factors
- Identifying risk and protective factors for substance use and misuse, substance use disorders, and related health and safety problems
- Enhancing people's resilience and buffering against stressors to help prevent substance use and promote healthy behaviors across the lifespan.
- Developing strategies to prevent substance use and the progression of substance use to harmful use
- Understanding why and how effective prevention approaches work and improving their uptake and reach.
- Developing tailored prevention strategies to help underserved or low-resource populations with risk factors for substance use and related health problems.
- Supporting research to evaluate effective harm reduction approaches
- Addressing stigma towards people who use drugs.
- Including local partners, end users, and potential funders in the research process, including the development and testing of potential strategies, and ways to communicate findings.

https://nida.nih.gov/research-topics/prevention#nida-advancing-science

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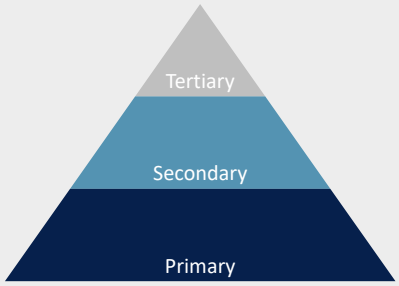
Public Health Frameworks: Tiers of Prevention



https://www.iwh.on.ca/what-researchers-mean-by/primary-secondary-and-tertiary-prevention

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Levels of Prevention

- Primary prevention aims to prevent disease or injury before it ever occurs
- Secondary prevention aims to reduce the impact of a disease or injury that has already occurred
- Tertiary prevention aims to soften the impact of an ongoing illness or injury that has lasting effects

https://www.iwh.on.ca/what-researchers-mean-by/primary-secondary-and-tertiary-prevention

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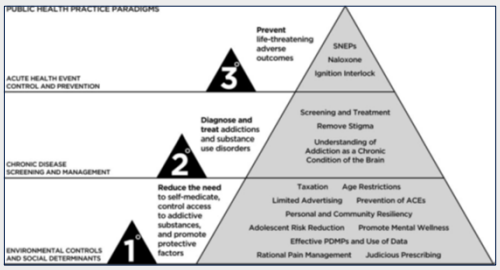
Public Health Approaches to Preventing Substance Use Problems



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21

Institute of Medicine Intervention Classifications

- Universal: broad approaches for the public or everyone
- Selective: strategies aimed at a subgroup determined to be at the highest risk for substance use
- Indicated: strategies designed to prevent the onset of substance use problems in individuals who are showing early danger signs

SAMHSA. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. 2016

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Harm Reduction

- Programs aimed toward minimizing negative health, social and legal impacts associated with drug use while grounded in human rights

https://www.hri.global/what-is-harm-reduction, Health, Rights, and Drugs UNAIDS 2019

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Harm Reduction Services	Harm Reduction Supplies
• Overdose reversal education and training services • Navigation services to ensure linkage to HIV and viral hepatitis prevention, testing, treatment and care services, including antiretroviral therapy for HCV and HIV, pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), prevention of mother to child transmission and partner services • Referral to hepatitis A and hepatitis B vaccinations to reduce risk of viral hepatitis infection • Provision of education on HIV and viral hepatitis prevention, testing, and referral to treatment services • Provision of information on local resources and/or referrals for PrEP	• Overdose reversal supplies, including the purchase of naloxone kits (this may include syringes for the purpose of administering injectable naloxone only) • Substance test kits, including fentanyl test strips • Safer sex kits, including condoms • Sharps disposal and medication disposal kits • Wound care supplies • Medication lock boxes • Supplies to promote sterile injection and reduce infectious disease transmission through injection drug use, exclusive of sterile needles, syringes, and other drug paraphernalia* • Safer smoking kits to reduce infectious disease transmission, excluding pipes/pipettes and other drug paraphernalia**

https://www.samhsa.gov/find-help/harm-reduction

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Evidence-Based Prevention Interventions

- Programs and policies supported by research that reduce unhealthy substance use and related threats to public health
- Long-term and cost saving benefits
- Prevent other undesirable outcomes among youth: delinquency, psychiatric conditions, violence, and school dropout
- Vast majority of studies have been conducted on children, adolescents, and young adults
- Remain underutilized

SAMHSA. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. 2016

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School-Based Interventions

- Strong study habits, academic support, bonding to school, self-efficacy and assertiveness, social problem-solving, emotional awareness and strong communication skills are correlated with decreasing risk of future drug use among youth
- Focus on building social, emotional, cognitive, and substance refusal skills and provide accurate information on rates and amounts of peer substance use

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School-Based Interventions

- Good Behavior Game
- Classroom-centered Intervention
- The Fast track Program
- Life Skills Training

- Delayed and lowered rates of alcohol, tobacco, and other substance use in adulthood

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Family-Based Interventions

- Focus on enhancing parenting skills
  - Nurse-Family Partnership
  - Strengthening Families Program: for Parents and Youth
  - Coping power
  - I Hear What You're Saying
  - Parent Handbook
- Reduce early alcohol and substance use

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Healthcare-Based Interventions

- Brief alcohol screening:
  - associated with significant reductions in alcohol consumption and alcohol-related problems in both adults and adolescents
  - recommended by USPSTF and American Academy of Pediatrics
- Motivational interviewing
  - associated with reductions in drinking

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Community Coalition-Based Interventions

- Change community-level physical, social and economic risk and protective factors
- Composed of representatives from multiple community sectors or organizations- government, law enforcement, health, and education
- Achieve community- wide reductions in substance use by planning and implementing prevention strategies

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Community Coalition-Based Interventions

- Communities that Care: community coalition tailors interventions to results of high school survey
  - associated with lower rates of alcohol and tobacco initiation in high school
- Communities Mobilizing for Change on Alcohol: aimed at reducing youth access to alcohol, increased enforcement of underage drinking laws, reduced availability of alcohol at community events, and media campaigns against underage drinking
  - associated with significant reductions in alcohol-related problem behaviors in young adults including DUIs

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Drinking-Oriented Interventions

- Policies that reduce alcohol availability and increase the costs of alcohol have immediate benefits in reducing drinking and harms from alcohol use:
  - Decrease morbidity
  - Decrease mortality
  - Decrease crime and violence
- Drinking-oriented policies include:
  - Raising alcohol taxes
  - Reducing alcohol production
  - Reducing alcohol sales
  - Preventing alcohol sales to minors

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Driving-Oriented Interventions

- Policies that prevent an intoxicated person from driving have been found to:
  - Reduce rates of drinking and driving
  - Traffic crashes
  - Injuries
  - Deaths
- Driving-oriented policies include:
  - Driving under influence (DUI) blood alcohol content (BAC) limits
  - Sobriety checkpoints
  - Lower BAC limits for people convicted of DUI
  - Mandatory assessment and treatment of persons convicted of DUI
  - Raising minimum legal drinking age
  - Zero tolerance laws
  - Use/lose laws

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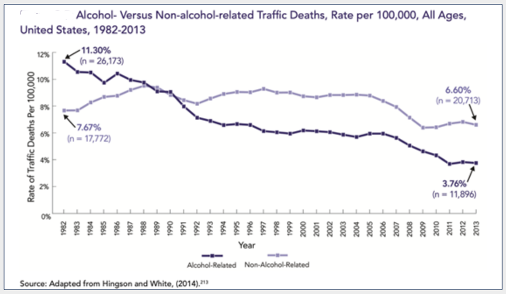
Driving-oriented Prevention Policies



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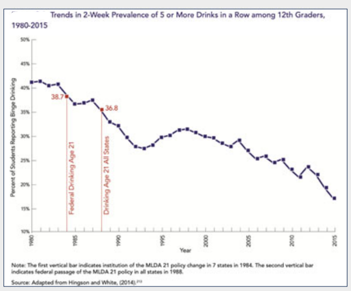
Driving-oriented Prevention Policies



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Overall Benefits of Prevention Interventions

- Cost saving benefits for personal and public health
- Long-term positive effects that can last for generations

Economics of Prevention

The Washington State Institute for Public Policy developed a standardized model using scientifically rigorous standards to estimate the costs and benefits associated with various prevention programs. Benefit-per-dollar cost ratios for EBIs ranged from small returns per dollar invested to more than $64 for every dollar invested. These estimates are illustrated below in Table 3.3.

Table 3.3: Cost-Benefit of EBIs Reviewed by the Washington State Institute for Public Policy, 2016

Program	Benefit per Dollar Cost
Nurse-Family Partnership	$1.61
Raising Healthy Children/SSDP	$4.27
Good Behavior Game	$64.18
LifeSkills Training	$17.25
keepin' it REAL	$11.79
Strengthening Families Program 10-14	$5.00
Guiding Good Choices	$2.69
Positive Family Support/ Family Check Up	$0.62
Project Towards No Drug Abuse	$6.54
BASICS	$17.61

*Cost estimates are per participant, based on 2015 United States dollars.

Note: This is a general indication of the potential health and social value of EBIs. It is not possible to estimate specific cost-benefit for every EBI due to challenges in calculating accurate intervention effect sizes, the failure to document costs, the variation of methods used, and few mandates or incentives to complete this research. Reaching a consensus on standards for cost-benefit analyses and making them a routine part of prevention program evaluation could help policymakers choose EBIs that both prevent substance misuse and ensure that investments return benefits over the life course.

Source: Washington State Institute for Public Policy, (2016).

SAMHSA. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. 2016

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Conclusions

- A well-established body of evidence-based interventions exists
- More implementation, systematic monitoring and research are needed

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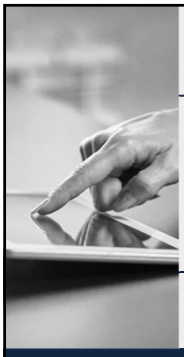

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Deb Dupnik, CAE, CCSM-A
Director, American Osteopathic Board of Family Physicians, Addiction Medicine Conjoint, Distinct Osteopathic Examination Committee, Geriatric Medicine CAQ
Cara Poland, MD, MEd, FACP, DFASAM
Program Director, Trinity Health Grand Rapids Addiction Medicine Fellowship
Associate Professor, OB/GYN and Reproductive Biology, Michigan State University

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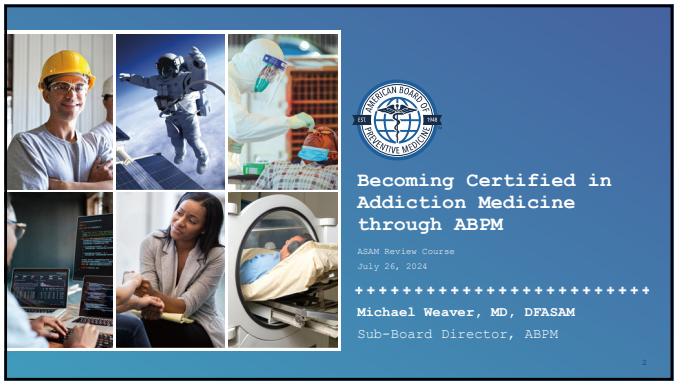
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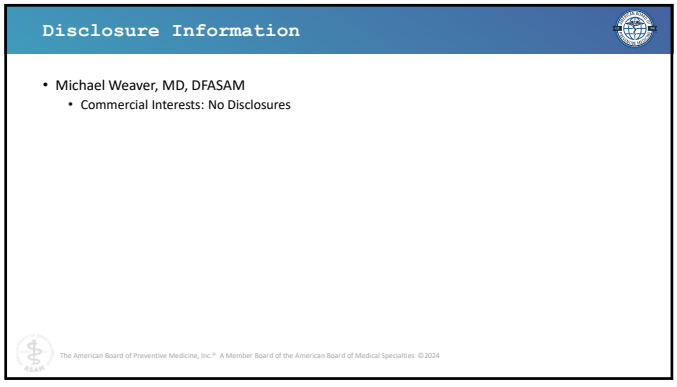
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Key Eligibility Requirements

- **Primary Specialty Certification**
  - American Board of Medical Specialties (ABMS) Member Board
  - American Osteopathic Association (AOA)
  - Royal College of Physicians and Surgeons of Canada (RCPSC)
  - College of Family Physicians of Canada (CFPC)
- **Medical Degree**
- **Medical License**
  - Current, unrestricted and valid in US or Canada; no license may be restricted, revoked, suspended, or currently under such notice
- **Training or Experience in Addiction Medicine**
  - Practice Pathway (through 2025)
  - ACGME-Accredited Fellowship in Addiction Medicine

4

Practice Pathway

- **Eligible physicians have significant Addiction Medicine practice experience or training but who have not completed an ACGME-accredited Addiction Medicine fellowship to qualify for the certification exam**
- **Open through 2025 Exam Cycle**

5

Practice Pathway: Time & Experience

- **1,920 hours of relevant Addiction Medicine practice at the subspecialty level**
  - Completed over at least 24 months
  - Must be completed within 60 months immediately preceding June 30 of the application year
  - Need not be continuous
- **Broad-based, professional activity with significant addiction medicine responsibility**
  - Comprehensive approach to preventing diagnosing, and managing patients with various substance use disorders and addictions
  - Minimum of 480 hours of direct patient care including prevention and treatment of individuals at risk for substance use disorders
  - May include up to 1,440 hours of teaching, research and/or administration activities

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ACGME-Accredited Fellowship Pathway

- Successful completion of an ACGME-accredited fellowship training
  - At least 12 months in duration
  - If fellowship is longer than 12 months of training, physicians must successfully complete all years of training for which the fellowship program is accredited
- Addiction Medicine fellowship programs began ACGME accreditation process in February 2018
- Beginning in 2026, ACGME-Accredited Fellowship Pathway will be the sole pathway to ABPM certification in Addiction Medicine

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Examination Content, Questions & Timeline

8

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Exam Content

- Assesses ability to apply knowledge rather than to recall isolated facts
- Focuses on high-frequency and/or high-impact patient problems
- Emphasizes clinical situations and decisions arising in the experienced addiction medicine specialist's practice

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Core Exam Content Areas

Proportion	Content Area
25%	01 Definitions 02 Genetics 03 Pharmacokinetic and Pharmacodynamic Principles 04 Pharmacology 05 Neurobiology of Addiction
20%	06 Epidemiological Concepts 07 Epidemiological Trends of Substance Use Disorders 08 Prevention
40%	09 Screening, Assessment, and Brief Intervention 10 Overview of Addiction Treatment 11 Management of Inpatient and Outpatient Intoxication and Withdrawal 12 Pharmacologic Interventions for Addictions 13 Behavioral Interventions 14 Co-Occurring and Medical Disorders among Patients with Alcohol and Other Drug Use and Addiction 15 Co-Occurring Psychiatric Disorders among Patients with Alcohol and Other Drug Use and Addiction 16 Pain and Addiction
15%	17 Ethical, Legal, and Liability Issues in Addiction Practice

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Exam Content by Substance/Addiction

Proportion of Exam	Substance/Addiction
15–20%	Alcohol
15–20%	Nicotine
10–15%	Opioids
7–10%	Sedatives
7–10%	Stimulants
7–10%	Cannabinoids
0.5–3%	Hallucinogens
0.5–3%	Dissociatives
0.5–3%	Inhalants
0.5–3%	Anabolic Steroids
1–3%	Other Substances
1–3%	Nonsubstance addiction
1–5%	General/All Substances Combined

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What is on the Exam?

- **Multiple-Choice questions**
  - **Recall:** specific important facts
  - **Interpretation:** e.g., identify a fatal study flaw, diagnose a patient
  - **Problem Solving:** e.g., judgment about clinical treatment, healthcare administration, study design, 2x2 tables, etc.
- **Single-best answer**
- **Calculator, drug name list, and normal range values are provided**

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What is NOT on the Exam?

- True/False questions
- K-type questions
  - Choose appropriate set of correct answers (e.g., "A and B" or "A,B, and C")
- Trick questions
- "Experimental" questions

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Certificate

- Attests that all requirements of Addiction Medicine certification have been met.
- Effective January 1 of the year following the exam.
  - Subject to continuing compliance with Continuing Certification Program (CCP) requirements, Certificate will expire December 31, ten years after issuance.
    - E.g., for those passing the 2024 examination, certification is effective beginning January 1, 2025, through December 31, 2034.
- All Addiction Medicine Diplomates certified by the ABPM are subject to the Annual Fee

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Important Dates

March 13, 2024	Application window opens
May 22, 2024	Exam registration opens
June 30, 2024	Application window closes
July 1, 2024	Late application window open (additional fee applies)
July 15, 2024	Late application window closes
September 13, 2024	Exam registration closes
October 14 – November 3, 2024	Exam administration
Late January 2025	Exam scores released to examinees

15

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Questions?
www.theabpm.org
abpm@theabpm.org
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AOA Certification in Addiction Medicine
Deb Dupnik, CAE, CCSM-A
Director, American Osteopathic Board of Family Physicians,
Addiction Medicine Conjoint, Distinct Osteopathic Examination Committee, Geriatric Medicine CAQ
AMERICAN OSTEOPATHIC ASSOCIATION

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Financial Disclosure
• Deb Dupnik, CAE, CCSM-A
• No relevant disclosures
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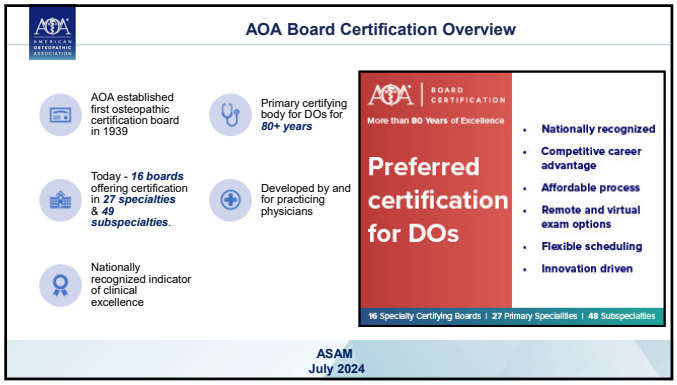
AOA Board Certification Overview
AOA established first osteopathic certification board in 1939
Primary certifying body for DOs for 80+ years
Today - 16 boards offering certification in 27 specialties & 49 subspecialties.
Developed by and for practicing physicians
Nationally recognized indicator of clinical excellence
BOARD CERTIFICATION
More than 80 Years of Excellence
Preferred certification for DOs
Nationally recognized
Competitive career advantage
Affordable process
Remote and virtual exam options
Flexible scheduling
Innovation driven
16 Specialty Certifying Boards | 27 Primary Specialties | 48 Subspecialties
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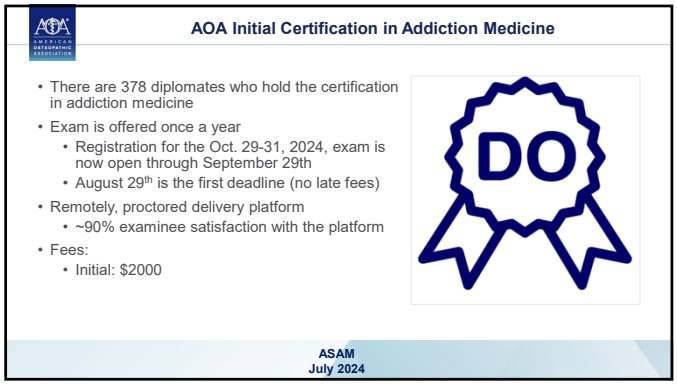
AOA Initial Certification in Addiction Medicine
There are 378 diplomates who hold the certification in addiction medicine
Exam is offered once a year
Registration for the Oct. 29-31, 2024, exam is now open through September 29th
August 29th is the first deadline (no late fees)
Remotely, proctored delivery platform
~90% examinee satisfaction with the platform
Fees:
Initial: $2000
DO
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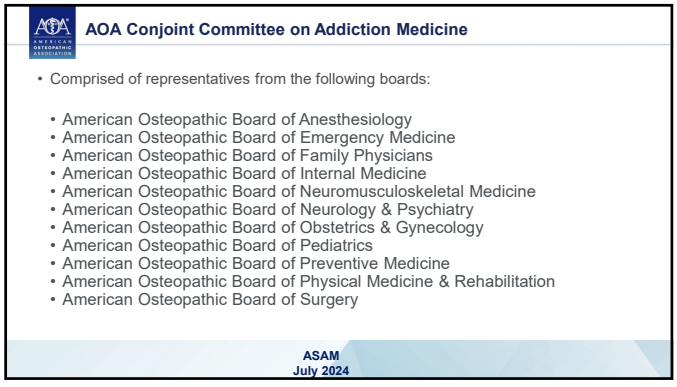
AOA Conjoint Committee on Addiction Medicine
Comprised of representatives from the following boards:
American Osteopathic Board of Anesthesiology
American Osteopathic Board of Emergency Medicine
American Osteopathic Board of Family Physicians
American Osteopathic Board of Internal Medicine
American Osteopathic Board of Neuromusculoskeletal Medicine
American Osteopathic Board of Neurology & Psychiatry
American Osteopathic Board of Obstetrics & Gynecology
American Osteopathic Board of Pediatrics
American Osteopathic Board of Preventive Medicine
American Osteopathic Board of Physical Medicine & Rehabilitation
American Osteopathic Board of Surgery
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Achieving Certification

1. Hold an active primary certification in an AOA or ABMS specialty.
2. Maintain a valid, unrestricted license to practice
3. Adhere to the AOA Code of Ethics
4.
   - Pass the Addiction Medicine written certification exam
   - 200 items
   - 4-hour exam, 15-minute break

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Pathways to Certification

Pathway 1: Complete an AOA or ACGME Fellowship in Addiction Medicine.

Pathway 2: Clinical Pathway – Open through 2026

- Complete 1000 hours of practice time within a 2-year period
  - May be a combination of direct patient care and published research, teaching activities within an accredited medical school or ACGME residency, and/or live or recorded live ACCME and/or AOA CME activities.
  - No more than 500 hours may come from CME activities.
- An active ABAM certificate will waive the need for the 1000-hour attestation.
- Certificate of completion of an American College of Academic Addiction Medicine (ACAAM) (formerly the Addiction Medicine Foundation (TAMF) and the American Board of Addiction Medicine (ABAM) fellowship within the five years before the application start date for that year will waive the need for the 1000-hour attestation.

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Addiction Medicine Exam Content

CONTENT	PERCENT RANGE ON EXAM
1. Pharmacology	24%
2. Epidemiology and Genetics	18%
3. Treatment	15%
4. Legal Aspects	14%
5. Diagnosis	12%
6. Special Populations	11%
7. Prevention	6%

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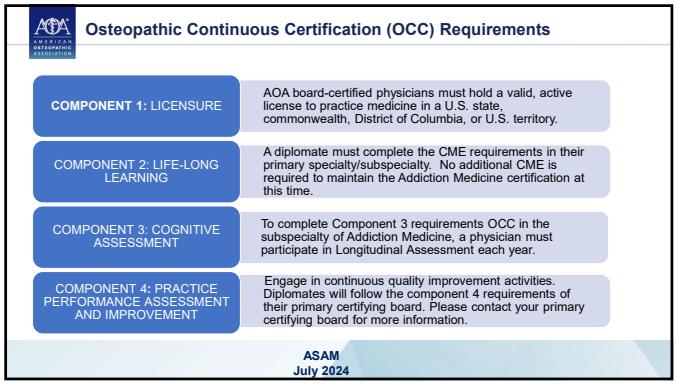
Osteopathic Continuous Certification (OCC) Requirements
COMPONENT 1: LICENSURE
AOA board-certified physicians must hold a valid, active license to practice medicine in a U.S. state, commonwealth, District of Columbia, or U.S. territory.
COMPONENT 2: LIFE-LONG LEARNING
A diplomate must complete the CME requirements in their primary specialty/subspecialty. No additional CME is required to maintain the Addiction Medicine certification at this time.
COMPONENT 3: COGNITIVE ASSESSMENT
To complete Component 3 requirements OCC in the subspecialty of Addiction Medicine, a physician must participate in Longitudinal Assessment each year.
COMPONENT 4: PRACTICE PERFORMANCE ASSESSMENT AND IMPROVEMENT
Engage in continuous quality improvement activities. Diplomates will follow the component 4 requirements of their primary certifying board. Please contact your primary certifying board for more information.
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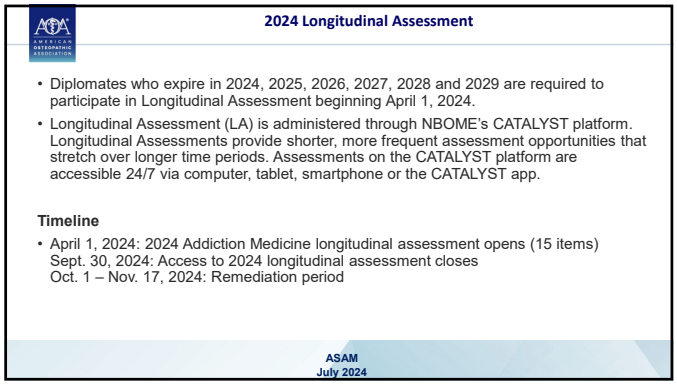
2024 Longitudinal Assessment
• Diplomates who expire in 2024, 2025, 2026, 2027, 2028 and 2029 are required to participate in Longitudinal Assessment beginning April 1, 2024.
• Longitudinal Assessment (LA) is administered through NBOME's CATALYST platform. Longitudinal Assessments provide shorter, more frequent assessment opportunities that stretch over longer time periods. Assessments on the CATALYST platform are accessible 24/7 via computer, tablet, smartphone or the CATALYST app.
Timeline
• April 1, 2024: 2024 Addiction Medicine longitudinal assessment opens (15 items)
Sept. 30, 2024: Access to 2024 longitudinal assessment closes
Oct. 1 – Nov. 17, 2024: Remediation period
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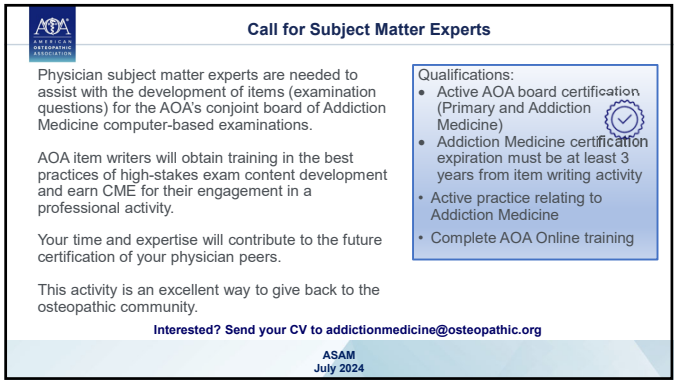
Call for Subject Matter Experts
Physician subject matter experts are needed to assist with the development of items (examination questions) for the AOA's conjoint board of Addiction Medicine computer-based examinations.
AOA item writers will obtain training in the best practices of high-stakes exam content development and earn CME for their engagement in a professional activity.
Your time and expertise will contribute to the future certification of your physician peers.
This activity is an excellent way to give back to the osteopathic community.
Qualifications:
• Active AOA board certification (Primary and Addiction Medicine)
• Addiction Medicine certification expiration must be at least 3 years from item writing activity
• Active practice relating to Addiction Medicine
• Complete AOA Online training
Interested? Send your CV to addictionmedicine@osteopathic.org
ASAM
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AMERICAN OSTEOPATHIC ADDICTION MEDICINE EXAMINATION COMMITTEE

Questions?

Please contact us:

Phone: (312) 202-8478
Email: addictionmedicine@osteopathic.org

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July 2024

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ASAM REVIEW COURSE 2024

Becoming Certified: Pathways, Insights and Preparation Strategies

Cara Poland, MD, MEd, FACP, DFASAM
Program Director, Trinity Health Grand Rapids Addiction Medicine Fellowship
Associate Professor, OB/GYN and Reproductive Biology, Michigan State University

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Financial Disclosure

Cara Poland, MD, MEd, FACP, DFASAM

- No Relevant Disclosures

Thank you Dr. Ruchi Fitzgerald for use of her slides!

REVIEW COURSE 2024

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Content

- Assessment of the ability to apply knowledge rather than recall of isolated facts
- Focus on high-frequency and/or high-impact patient problems
- Focus of clinical situations and decisions arising in the experienced addiction medicine specialist's practice

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Some quick suggestions

- Focus studying on topics and material you don't see regularly in your clinical work
  - e.g., the Hallucinogens and Dissociatives—in each applicable section, i.e, pharmacology, intoxication, withdrawal, treatment.
- Review/skim the topics you know well
- **Do Not Neglect "**Soft Topics,"
  - Ethical, Legal, Liability; Harm Reduction; Non-Pharmacologic Treatments (MI, CBT, DBT)
- May be expected to know "classic" articles, e.g. MOTHER study

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Additional Tips

- High yield topics include *neurotransmitters*, *receptors*, *neurobiology*
- Read questions carefully before answering
- Work with a study partner to keep oneself accountable to a study plan – especially helpful for those in the Practice Pathway

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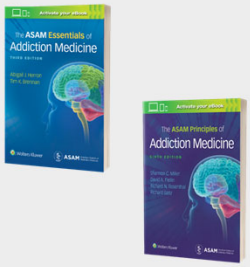
Study Tools

- Publications

  The ASAM Principles of Addiction Medicine Textbook and The ASAM Essentials of Addiction Medicine (condensed version) – *if you have time to read this book and complete the questions at the end of each chapter, you will have confidence for the board exam.*



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Study Tools

- ASAM Board Exam Study Tool (BEST)
  - 500+ board exam-style questions
  - 40 ***AMA PRA Category 1 Credits™***
- Review Course Weekly Office Hours
  - Complimentary to Review Course attendees
  - Connect with faculty and fellow exam takers, review practice questions and get your questions answered by our renowned experts

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MI CARES

- Provides support on the various practice pathways
- Over 20 hours of FREE CME provided by Michigan State University's Dean
- General overview/gap analysis – not comprehensive review course

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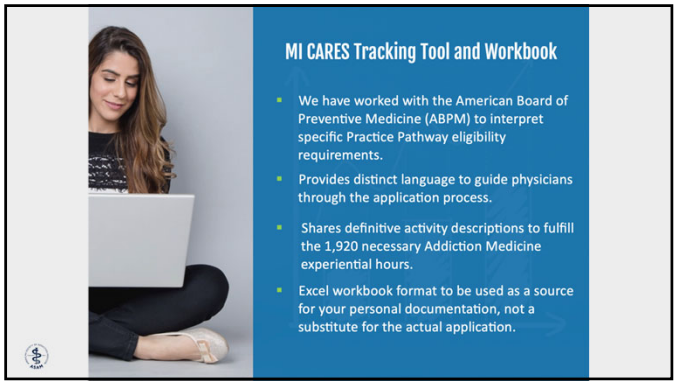

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MI CARES Assistance

Coaching calls designed to:

- Provide personalized assistance with completing application documentation requirements
- Enhance your learning experience by interacting with MI CARES staff and fellow colleagues

- We will review 2 versions of Tracking Tools
- Comment on 4 entries

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Tips from Other Faculty

- Don't wait until the last minute to study
- Have confidence in your answers
- Know how to calculate NNT, etc.
- Understand the studies for substance use/misuse (NSUDH), and epidemiology for different substances.
- Do at least one practice exam – and then retake it if possible.
- Results do not arrive until February.

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Questions?

REVIEW COURSE 2024

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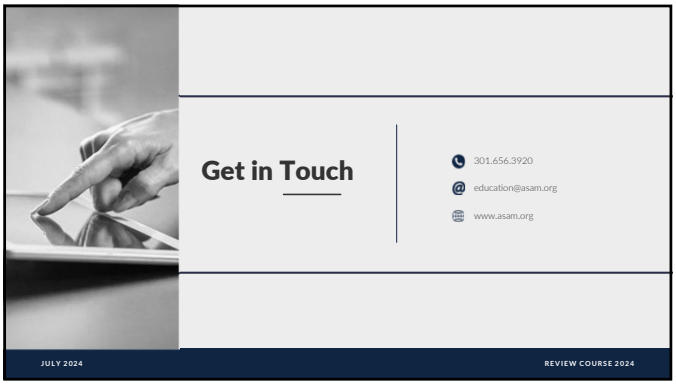

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