Addiction Medicine Review Track
Co-Occurring Disorders

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EDUCATIONAL OBJECTIVES

After attending this presentation, participants will be able to:

1. Identify diagnoses of commonly co-occurring psychiatric conditions based on clinical presentation.

2. Differentiate between substance-induced versus primary psychiatric disorders.

3. Identify how psychiatric disorders affect the clinical course of substance use disorders and vice versa.

4. Identify how treatments affect co-occurring psychiatric and substance use disorders.

QUESTION #1

A 55 yo male presents for inpatient alcohol withdrawal management. He reports feeling severely depressed with passive thoughts of suicide and symptoms of fatigue, insomnia, and poor concentration for the past 3 months. His symptoms began just after he returned to drinking alcohol. He denies any episodes of depression during times of abstinence from alcohol. At 1 month follow-up he reports having significant improvement in his depression over the first two weeks of alcohol abstinence with complete resolution by the end of the third week. What is the most likely diagnosis?

A. Alcohol-induced depressive disorder

B. Major depressive disorder

C. Persistent depressive disorder

D. Cyclothymic disorder

ANSWER #1

A. Alcohol-induced depressive disorder

Substance-induced mood disorders occur only during periods of substance use and improve or resolve with abstinence. These mood symptoms exceed what would be expected by typical intoxication or withdrawal from the substance. Symptoms of substance-induced depression may be severe enough to warrant treatment with medication.

For a diagnosis of co-occurring major depressive disorder (MDD), you would expect symptoms to occur during times of abstinence from alcohol and/or to persist >1 month after discontinuation of drinking.

For co-occurring persistent depressive disorder, you would expect depressed mood to occur most days over a period of at least 2 years while not meeting full criteria for MDD. For co-occurring cyclothymic disorder, you would expect periods of hypomanic and depressive symptoms, not meeting full criteria for hypomanic or major depressive episodes, to occur over a period of at least 2 years.

ASAM Principles of Addiction Medicine, 6th Ed, pg 1369
DSM. 5th ed.

Major Depressive Disorder DSM-5 Criteria

5+ symptoms (including either depressed mood or loss of interest) in a 2+ week period:

- ***Depressed mood***
- ***Loss of interest/pleasure***
- *Change in weight or appetite*
- *Insomnia or hypersomnia*
- *Psychomotor retardation or agitation*
- *Loss of energy or fatigue*
- *Feelings of worthlessness or guilt*
- *Impaired concentration*
- *Thoughts of death or suicide*

DSM. 5th ed.

QUESTION #2

A 38 yo female presents to your clinic asking for help to discontinue alcohol use. She reports daily alcohol use since she was 17 years old. She drinks one bottle of wine per night and has been unable to reduce or discontinue use. She reports feeling down and depressed, with decreased appetite, trouble concentrating, loss of interest in activities she used to enjoy, and insomnia. She denies any thoughts of self-harm or suicide and she has been able to care for herself at home. She reports having been depressed since her childhood. She denies any episodes of mood elevation consistent with mania or hypomania.

In regards to treating her depression and alcohol use disorder, you recommend:

A. Treating her depression first, then addressing alcohol use disorder at her next visit
B. Treating alcohol use disorder first, then reassessing depression after 1 month of abstinence
C. Starting treatment for both depression and alcohol use disorder today
D. Recommend she be admitted to a psychiatric hospital

ANSWER #2

C. Starting treatment for both depression and alcohol use disorder today

It is no longer recommended to wait to start treatment for depression for patients who are actively drinking alcohol. She reports feeling depressed since she was a child and it is likely that her depression preceded alcohol use. Additionally, alcohol use disorder is the most common co-occurring substance use disorder with major depressive disorder (MDD), with women more likely to have co-occurring MDD than substance-induced depression.

A randomized controlled trial of patient with co-occurring alcohol use disorder and MDD showed that patients treated with both naltrexone and sertraline had a higher likelihood of complete abstinence, a significant delay to return to heavy drinking, and lower rates of depression compared to groups taking either medication alone or placebo.

As she denies thoughts of self-harm and is able to care for herself at home, inpatient psychiatric hospitalization is not warranted at this time.

Pettinati HM, Oslin DW, Kampman KM, Dundon WD, Xie H, Gallis TL, Dackis CA, O'Brien CP. A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. Am J Psychiatry. 2010 Jun;167(6):668-75

QUESTION #3

You are treating a 19 yo female for stimulant use disorder and depression. She was recently started on an SSRI. All of the following are risk factors for completed suicide, EXCEPT:

A. Stimulant use

B. Depression

C. Patient's age

D. Initiation of an SSRI

ANSWER #3

D. Initiation of an SSRI

While there have been reports of increased thoughts of suicide in adolescents and young adults <25 yo starting SSRI treatment (including an FDA black box warning), a review of 15 trials involving >2000 patients showed similar rates of suicidal ideation and behavior between youth treated with antidepressants and those treated with placebo. There were **no completed suicides** in any study patients. In general, the risk of suicide secondary to untreated depression is considered much higher than the risk of treatment with an SSRI.

Both depression and substance use are risk factors for suicide. Other factors that increase acute risk include agitation/irritability, impulsivity, hopelessness, recent stressful life event, and recent discharge from a psychiatric hospital. Long-term risk factors include a history of prior suicide attempts, family history of suicide, history of trauma/abuse, comorbid medical illnesses, and demographic factors (young adults <24 or elderly, living alone, male).

1. American College of Neuropsychopharmacology. Preliminary report of the Task Force on SSRIs and Suicidal behavior in Youth. January 21, 2004.
2. Fazel, S., & Runeson, B. (2020). Suicide. New England Journal of Medicine, 382(3), 266–274.
3. ASAM Principles of Addiction Medicine, 6th Ed, pg 1377-78

QUESTION #4

You are seeing a 39 yo female in the emergency room. She was brought in by police after being found wandering in the street. She is agitated and states “they are out to get me! I need to get out of here! They’re watching me!” She endorses hearing voices. Her vital signs are Temp 99.1, BP 173/95, HR 112, SpO2 98%. Her urine drug screen is positive for methamphetamine.

What is your first step in managing the psychological and behavioral effects of her stimulant intoxication?

A. Give haloperidol 5mg intramuscular injection

B. Place her in restraints

C. Place her in a quiet environment with minimal sensory stimulation

D. Given diazepam 10g intramuscular injection

ANSWER #4a

C. Place her in a quiet environment with minimal sensory stimulation

The first step in managing anxiety, agitation, and paranoia from acute stimulant intoxication is to provide reassurance and place the patient in a quiet, non-threatening environment (in reality this can be difficult to do in a busy ED!)

If medication is needed, the next step is to treat with benzodiazepines (such as diazepam 10mg IM or lorazepam 2mg IM). Benzodiazepines are preferred as next line over antipsychotics because they treat the sympathomimetic toxidrome caused by catecholamine excess (protecting against the CNS and cardiovascular effects of stimulants). Antipsychotics may be necessary as a 3rd line measure, but they can also increase the risk of hyperthermia, lower the seizure threshold, and precipitate extrapyramidal reactions.

Physical restraints should be avoided if possible and can increase the risk for rhabdomyolysis. When used, they should be removed as soon as possible.

ASAM Principles of Addiction Medicine, 6th Ed, pg 758-9

QUESTION #4 Continued

You are seeing a 39 yo female in the emergency room. She was brought in by police after being found wandering in the street. She is agitated and states "they are out to get me! I need to get out of here! They're watching me!" She endorses hearing voices. Her vital signs are Temp 99.1, BP 173/95, HR 112, SpO2 98%. Her urine drug screen is positive for methamphetamine.

She is placed in a quiet area of the emergency room and treated with benzodiazepines as needed. Within 36 hours she is calm, cooperative with her providers, and is no longer experiencing paranoia or hallucinations. What is the most likely diagnosis?

A. Stimulant-induced psychosis
B. Expected effect of methamphetamine intoxication
C. Schizophrenia
D. Borderline personality disorder

ANSWER #4b

B. Expected effect of methamphetamine intoxication

Symptoms of psychosis including paranoia, delusions, and hallucinations are an expected effect of methamphetamine intoxication. If symptoms resolve when the patient is no longer experiencing intoxication/withdrawal, then they do not meet criteria for a substance-induced psychotic disorder.

Stimulant-induced psychosis lasts beyond the intoxication and withdrawal period and typically resolves within 1 week, but in cases of heavy prolonged use can persist upwards of 3-6 months. Beyond 1 month of symptoms it becomes more difficult to differentiate between a schizophrenia spectrum disorder and prolonged stimulant-induced psychosis.

While patients with borderline personality disorder can experience transient symptoms of psychosis, the patient's recent use of methamphetamine is the more likely cause of her symptoms. There is also insufficient evidence in the question stem to diagnose borderline personality disorder.

Glasner-Edwards S, Mooney LJ. Methamphetamine psychosis: epidemiology and management. CNS Drugs. 2014 Dec;28(12):1115-26.

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QUESTION #5

You are seeing a 35 yo female in your outpatient clinic. She began having anxiety episodes at age 17 yo where she would hyperventilate, sweat and have tremors and palpitations. She felt like she was going to die during these episodes and was fearful of when they would recur. She began using cannabis when she was 20 yo to self-manage her anxiety. While using cannabis seemed to initially help her anxiety, it is no longer effective. She reports using cannabis by smoking throughout the day, with increased use over the past year. She has noticed mental fogginess and difficulty performing her duties at work. Her husband is concerned, and her cannabis use has put a strain on their relationship. She developed insomnia and cravings when she attempted to stop smoking and quickly returned to use. What are the most likely diagnoses?

A. Cannabis-induced anxiety disorder and moderate cannabis use disorder

B. Panic disorder and moderate cannabis use disorder

C. Cannabis-induced anxiety disorder and severe cannabis use disorder

D. Panic disorder and severe cannabis use disorder

ANSWER #5

D. Panic disorder and severe cannabis use disorder

The patient had symptoms of panic disorder that preceded the onset of her cannabis use. She meets DSM-5 criteria for panic disorder based on having 4+ symptoms of panic attacks (palpitations, tremors, diaphoresis, hyperventilation) with an accompanying sense of fear, and persistent worry (>1 mo) that these episodes could recur.

She additionally meets criteria for a severe cannabis use disorder based on loss of control of her cannabis use, cravings, tolerance, withdrawal symptoms, and continued use despite consequences in both her personal life and work.

Several studies suggest that for the majority of adults, anxiety precedes the onset of cannabis use. There is also evidence suggesting that cannabis use to self-manage anxiety can lead to an avoidance-anxiety cycle that ultimately increases anxiety in the long-term.

ASAM Principles of Addiction Medicine, 6th Ed, pg 1396
APA. DSM. 5th ed. Arlington, VA: APA, 2013

QUESTION #6

A 45-year-old male presents to your office to discuss smoking cessation. He has a history of schizophrenia that is well controlled with medication. He has affective blunting but has not experienced auditory hallucinations since starting this medication. He works as a truck driver and has found that because of the stress at work he has increased his cigarette use from ½ to 1 pack per day. He asks if you can prescribe him nicotine replacement therapy. You provide him with both nicotine patches and gum.

One month later you receive a call from the hospital consult psychiatrist who is taking care of the patient after he experienced a seizure. They report the patient stopped all tobacco use one week ago. Which medication is most likely responsible for the patient's seizure?

A. Escitalopram

B. Clozapine

C. Benztropine

D. Alprazolam

ANSWER #6

B. Clozapine

Polycyclic aromatic hydrocarbons found in tobacco (and cannabis) smoke are metabolic inducers of hepatic CYP450 1A2. Smoking decreases blood levels of several antipsychotics, including haloperidol, fluphenazine, thiothixene, olanzapine, and clozapine. **When patients discontinue smoking, CYP1A2 is no longer induced resulting in increased blood levels of the antipsychotic medication.** Clozapine toxicity includes seizures, and there are reports of seizures precipitated by a tobacco quit attempt. This case highlights the importance of counseling patients taking certain antipsychotics on the risk for seizures if they reduce or discontinue tobacco use. This patient would have benefited from checking clozapine levels and adjusting his dose to avoid toxicity.

Both escitalopram, a selective serotonin reuptake inhibitor, and benztropine, an anticholinergic agent, are metabolized by different CYP pathways and are not associated with increased blood levels or seizure risk with smoking cessation. Alprazolam is a benzodiazepine and would be protective against seizures unless the patient was experiencing withdrawal from chronic benzodiazepine use.

1. ASAM Principles of Addiction Medicine, 6th Ed, pg 1409-1410
2. McCarthy RH. Seizures following smoking cessation in a clozapine responder. Pharmacopsychiatry. 1994 Sep;27(5):210-1.

CYP1A2

Inducers

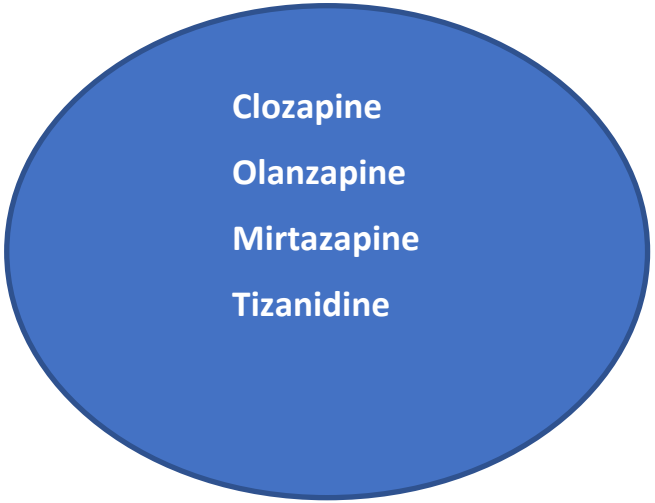
Smoking (aromatic hydrocarbons)

Barbiturates

Carbamazepine

Rifampin

Substrates



Inhibitors

Cimetidine

Ciprofloxacin

Fluvoxamine

1. Horn, JR and Hansten PD. Get to Know an Enzyme: CYP1A2. Pharmacy Times. 2007.

QUESTION #7

A 28 yo male presents to the hospital for alcohol withdrawal management. He states that he has been admitted several times in the past, and during his last hospitalization he required ICU admission for delirium tremens and withdrawal seizures. He has been drinking a half-gallon of liquor per day for the past 2 months. His current medications are naltrexone 50mg daily, omeprazole 20mg daily, bupropion 200mg BID, escitalopram 10mg daily, and prazosin 2mg at bedtime. As you write his admission orders, which of his medications do you decide to hold?

A. Escitalopram

B. Omeprazole

C. Bupropion

D. Prazosin

ANSWER #7

C. Bupropion

Bupropion can lower the seizure threshold, and while the risk for seizures is extremely rare (about 0.1%) in the general population, providers should consider holding bupropion when patients are being treated for acute alcohol withdrawal due to increasing the risk for withdrawal seizures. **In this patient's case, since he has experienced a withdrawal seizure in the past he is at high risk for recurrent seizures and bupropion should be held during his admission.** If he continues to consume alcohol in the future, his outpatient providers should consider discontinuing bupropion and using an alternative medication.

Escitalopram is not associated with increased risk for seizures when taken at therapeutic doses. There have been reports of seizures from toxicity in overdose. Omeprazole and prazosin do not increase the risk for seizures.

1. Detoxification and Substance Abuse Treatment [Internet]. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2006. (Treatment Improvement Protocol (TIP) Series, No. 45.) 5 Co-Occurring Medical and Psychiatric Conditions. Available from: https://www.ncbi.nlm.nih.gov/books/NBK64105/
2. Richmond R, Zwar N. Review of bupropion for smoking cessation. Drug Alcohol Rev. 2003 Jun;22(2):203-20

QUESTION #8

You are seeing a 23 yo female for treatment of opioid use disorder. She has been using heroin 1g per day IV and would like to discontinue use. In exploring her psychiatric history, she reports experiencing nightmares, feeling on edge, occasionally feeling outside of her own body, and avoiding certain streets in town due to a prior traumatic experience. She began using opioids in her teen years to “fill a void” and found that for a time they helped her to feel normal. She has also used self-harm behaviors such as cutting and has restricted her eating in the past. All of the following may be a beneficial part of her treatment plan, EXCEPT:

A. Buprenorphine

B. Alprazolam

C. Sertraline

D. Referral for dialectical behavioral therapy

ANSWER #8

B. Alprazolam

This patient likely has PTSD in addition to opioid use disorder given her report of a prior traumatic experience with associated avoidance, re-experiencing via nightmares, feeling on edge, and occasional depersonalization. She may also meet criteria for borderline personality disorder (history of self-harm, chronic feelings of emptiness) and an eating disorder, although further investigation of these is needed.

In addition to treating her opioid use disorder with buprenorphine, she could benefit from starting an SSRI (both sertraline and paroxetine are FDA approved to treat PTSD) and a referral to learn DBT skills. In the future she could consider Cognitive Processing Therapy.

Benzodiazepines are NOT recommended to treat PTSD given their unproven efficacy and risk for dependence and adverse effects (particularly when combined with other CNS depressants such as buprenorphine). There is also evidence that treatment with benzodiazepines after a recent trauma increases the risk for developing PTSD.

Of note, certain populations including Black women have higher rates of co-occurring PTSD and substance use disorders than the general population, while also having less treatment access and retention.

1. Guina J, Rossetter SR, DeRHODES BJ, Nahhas RW, Welton RS. Benzodiazepines for PTSD: A Systematic Review and Meta-Analysis. J Psychiatr Pract. 2015 Jul;21(4):281-303.
2. Management of Posttraumatic Stress Disorder and Acute Stress Reaction 2017; https://www.healthquality.va.gov/guidelines/MH/ptsd/
3. Bauer AG, Ruglass LM, Shevorykin A, Saraiya TC, Robinson G, Cadet K, Julien L, Chao T, Hien D. Predictors of therapeutic alliance, treatment feedback, and clinical outcomes among African American women in treatment for co-occurring PTSD and SUD. J Subst Abuse Treat. 2022 Aug;139:108766.

QUESTION #9

A 23 yo female who is 9 weeks pregnant is brought to the hospital by her family due to concern about her behavior. Her mother tell you that for the past week the patient has not slept and has been very irritable. This morning she told her mother that she will be "giving birth to the next messiah" and that she is the "savior of all humanity." She has a history of severe opioid use disorder for which she takes methadone via daily dispensing at an opioid treatment program. She has continued methadone, but stopped taking all of her psychiatric medications when she found out she was pregnant. All of the following may be a part of her treatment plan, EXCEPT:

A. Initiate haloperidol 5mg BID

B. Contact her opioid treatment program to confirm her dose of methadone

C. Initiate valproate 500mg BID

D. Obtain a baseline ECG

ANSWER #9

C. Initiate valproate 500mg BID

While valproate would be a reasonable treatment for acute bipolar mania, it is contraindicated in pregnancy due to the risk for teratogenicity (i.e. neural tube defects).

Antipsychotics are the first line treatment of acute bipolar mania in pregnancy. These medications carry the risk of QTc prolongation which may become problematic given that she has been receiving maintenance methadone therapy. Next steps in her care include obtaining a baseline ECG to check her QTc and confirming her methadone dose. If her QTc is within normal limits it is reasonable to start haloperidol.

If her QTc were to be prolonged, other options for management could include transitioning from methadone to buprenorphine, treatment with lithium (after consideration of risks including fetal cardiac malformation), and electroconvulsive therapy.

Eberhard-Gran M, Eskild A, Opjordsmoen S. Treating mood disorders during pregnancy: safety considerations. Drug Saf. 2005;28(8):695-706.

QUESTION #10

A 21 yo male presents requesting treatment for ADHD. He reports having difficulty with focus and concentration that began in early grade school. He struggled to complete projects on time due to procrastination and would often skip steps. He would lose things at home and would forget to do his chores. He was never able to sit still and had difficulty with following directions. When he was 16 yo he dropped out of school and has been working at a grocery store. Due to showing up late to work and forgetting tasks, he is now at risk for losing his job. He was never treated for ADHD in childhood and says his parents did not believe in seeking mental health treatment.

At age 19 he began using methamphetamine by smoking with the hope of improving his ability to focus and concentrate. While it was helpful, more recently he has noticed that he needs to use more to achieve the same effect and that he feels profoundly fatigued on days he does not use. He has also been experiencing shortness of breath when smoking and is concerned about his health. He has noticed having cravings for methamphetamine in the morning when he wakes up. He states that if he receives treatment for ADHD, it will be easier for him to discontinue methamphetamine use.

QUESTION #10 (Continued)

With his permission, you call his mother who confirms his report of childhood inattention symptoms. Based on the patient's symptoms and collateral information you diagnose him with ADHD, inattentive type and moderate stimulant use disorder. What is the best initial medication to prescribe?

A. Fluoxetine

B. Modafinil

C. Mirtazapine

D. Atomoxetine

ANSWER #10

D. Atomoxetine

This patient has co-occurring ADHD and stimulant use disorder. In consider treatment options, a non-stimulant such as atomoxetine is a very reasonable first choice. Atomoxetine, a selective norepinephrine reuptake inhibitor, is FDA-approved to treat ADHD in children and adults. It is not a controlled substance and has a negligible potential for misuse. Unlike stimulant medications, it can take 4-6 weeks to see the full effect of atomoxetine after starting treatment.

Modafinil is a non-amphetamine central nervous system stimulant and would not be an appropriate initial treatment for this patient. Modafinil is not FDA-approved to treat ADHD and has not been shown to be beneficial in the treatment of stimulant use disorder. Mirtazapine has been studied as a treatment for stimulant use disorder but is not a treatment for ADHD. Selective serotonin reuptake inhibitors, including fluoxetine, do not treat symptoms of ADHD but may help with co-occurring depression and anxiety.

1. ASAM Principles of Addiction Medicine, 6th Ed, pg 1429-1430
2. Upadhyaya HP, Desaiah D, Schuh KJ, Bymaster FP, Kallman MJ, Clarke DO, Durell TM, Trzepacz PT, Calligaro DO, Nisenbaum ES, Emmerson PJ, Schuh LM, Bickel WK, Allen AJ. A review of the abuse potential assessment of atomoxetine: a nonstimulant medication for attention-deficit/hyperactivity disorder. Psychopharmacology (Berl). 2013 Mar;226(2):189-200.
3. Chan B, Freeman M, Kondo K, Ayers C, Montgomery J, Paynter R, Kansagara D. Pharmacotherapy for methamphetamine/amphetamine use disorder-a systematic review and meta-analysis. Addiction. 2019 Dec;114(12):2122-2136.

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ANSWER #10 (Continued)

D. Atomoxetine

While atomoxetine is a reasonable first approach, if not effective, treatment with a long-acting stimulant such as extended-release methylphenidate (Concerta) or lisdexamfetamine (Vyvanse) may be considered. If treatment with stimulant medication is pursued, it should be done with proper monitoring including regular office visits, monitoring of vitals (blood pressure, heart rate), and urine drug screening.

Most point-of-care urine drug screens test for amphetamines and will not detect methylphenidate. If there is concern for diversion, special testing must be ordered to confirm compliance with methylphenidate therapy.

At this point, there is currently not enough evidence to support the use of stimulants for the treatment of stimulant use disorder in patients without co-occurring ADHD. This is an area of active research.

1. Mariani JJ, Levin FR. Treatment strategies for co-occurring ADHD and substance use disorders. Am J Addict. 2007;16 Suppl 1(Suppl 1):45-54; quiz 55-6.
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SUMMARY/TAKEAWAYS

1. Differentiate between substance-induced vs primary psychiatric disorders by the timeline of symptom onset/resolution and whether symptoms occurring during periods of abstinence.
2. Be aware of psychiatric medications patients are taking and how these may interact with treatment of substance use disorders and withdrawal management.
3. Recognize that medications prescribed for psychiatric conditions (e.g. stimulants, benzodiazepines) are in themselves substances that can cause addiction and may not be first-line for patients with co-occurring disorders.

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2. American College of Neuropsychopharmacology. Preliminary report of the Task Force on SSRIs and Suicidal behavior in Youth. January 21, 2004.
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