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Psychiatric Comorbidities: Diagnosis and Treatment of Comorbid Psychiatric Disorders and Opioid Use Disorders - Revised

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Frances Levin, MD: Disclosures

- Frances Levin, MD has no conflicts of interest or disclosures relevant to the content of this presentation

The content of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose this information.

Elizabeth Evans, MD: Disclosures

- Elizabeth Evans, MD has no conflicts of interest or disclosures relevant to the content of this presentation.

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Target Audience

- The overarching goal of PCSS is to train a diverse range of healthcare professionals in the safe and effective prescribing of opioid medications for the treatment of pain, as well as the treatment of substance use disorders, particularly opioid use disorders, with medication-assisted treatments.

Educational Objectives

- At the conclusion of this activity participants should be able to:
 - Recognize that psychiatric illnesses and substance use disorders commonly co-occur
 - Describe how to screen for and identify comorbid psychiatric diagnoses
 - Identify the distinction between independent psychiatric illness and substance-induced disorders
 - Demonstrate comfort in developing treatment plans when comorbidities are identified

Outline

- Epidemiology
- Comorbidity theories
- Clinical Relevance
- Case 1: Depression
- Case 2: Post traumatic stress disorder (PTSD)
- Case 3: Attention deficit hyperactivity disorder (ADHD)
- Conclusions

Epidemiology

- Substance use disorders (SUD) and psychiatric illnesses frequently co-occur
- Data from the National Survey on Drug Use and Health (NSDUH) revealed that among the 19.6 million adults with a past year substance use disorder, 41% (8.4 million adults) had co-occurring mental illness in 2015
- In comparison, among all adults, 17.9% had any mental illness.

Clinical Relevance: Why does this matter?

- Co-occurring psychiatric illness and SUD has:
 - Worse prognosis: worse treatment outcomes, higher risk of relapse and hospitalizations¹
 - Poorer quality of life ²
 - Increased risk of suicide, particularly with bipolar disorder ³
- Effective treatment of co-occurring psychiatric disorders, such as bipolar disorder or major depression generally improves the outcome of the substance use disorder ⁴



1. Drake et al. 2001; Swofford et al. 1996; Haywood et al. 1995; Hasin et al. 2002; Levin et al. 2004

2. Carpentier et al. 2009

3. Dalton et al. 2003; Levy and Deykin 1989; Tondo et al. 1999

4. Nunes and Weiss et al. 2015

Comorbidity Theories: Why so common?

- Developmental Factors (i.e. one causes the other):
 - Substance abuse usually starts in adolescents when the brain is undergoing significant developmental changes.
 - Early exposure to drugs of abuse can change the brain in ways that increase the risk for mental illness, and early symptoms of a mental disorder may increase vulnerability to drug abuse.¹
- Shared Risk Factors: For example, shared genetic vulnerability or environmental stressors--stressful life events, trauma.²
- Indirect risk factor: 'Self medicating' one psychiatric disorder transitions into a substance use disorder.³

1. Volkow 2004; Bolanso et al. 2003; Carlezon et al. 2003, NIDA Topics in Brief: Comorbid Drug Abuse and Mental Illness
2. Pettinati 2004; Kendler et al. 2003; Schuckit 1986; Tambs et al. 1997
3. Gros et al. 2013

Clinical Relevance:

Diagnostic and Treatment Implications

- The DSM-5 distinguishes between independent psychiatric illness and one that is substance-induced (i.e. secondary)
- Evidence of an independent disorder could include per DSM-5:
 - Symptoms precede the onset of the substance use
 - Symptoms persist for a substantial period (e.g. about 1 month) after the cessation of substance use
 - Past episodes not substance-related

Clinical Relevance: Diagnostic and Treatment Implications

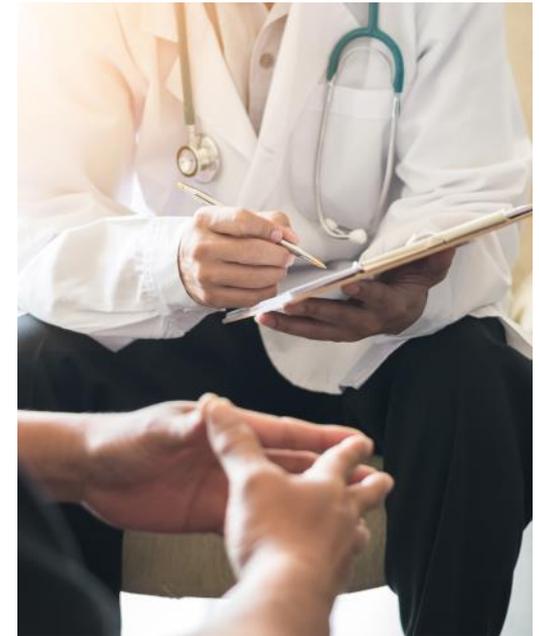
- The Psychiatric Interview for Substances and Mental Diseases (PRISM) is a diagnostic tool designed to distinguish between independent and secondary symptoms
 - PRISM places section on substance use disorders early in the interview, and an effort is made to establish age of onset of substance and psychiatric syndromes
 - When querying criteria for a disorder such as major depression, PRISM asks the interviewer to judge whether each symptom of depression (e.g. insomnia) is, or is not, better explained as a usual effect of substances

Clinical Relevance: Diagnostic and Treatment Implications

- When evaluating someone with both a substance use disorder and psychiatric symptoms, careful diagnosis, evaluating for substance-induced disorders is important
- A different clinical course may be expected if psychiatric symptoms are substance induced.
 - Substance-induced symptoms should improve rapidly with abstinence¹
 - However, other work suggests both primary and substance-induced depression predict future depression, relapse and suicide ideation, warranting clinical attention and consideration for specific treatment²

Clinical Relevance: Diagnostic and Treatment Implications

- It is important to note that sometimes even with the most prudent evaluation it can be very difficult to differentiate independent from secondary disorders without reduction/abstinence period
 - Reduction/abstinence can be difficult and delaying treatment for psychiatric symptoms can have serious consequences.



Clinical Relevance: Diagnostic and Treatment Implications

- For co-occurring independent depressive disorder + SUD
 - Antidepressant treatment improves depression symptoms
 - Improvement in drug/alcohol use is less consistent across studies¹
- For co-occurring bipolar + SUD
 - Fewer studies but lithium or mood stabilizers appear to improve both mood and substance use²

1. Nunes and Levin 2004; Pettinati et al. 2013
2. Nunes and Weiss et al. 2015

Clinical Relevance: Diagnostic and Treatment Implications

- Reasonable clinical guideline for managing co-occurring substance use disorder + other psychiatric syndromes¹
 - Initiate treatment for the substance use disorder
 - Try to get patient abstinent, or reduce substance use, and observe what happens to co-occurring psychiatric symptoms: Do they resolve? Or persist?
 - Differentiating independent from substance-induced disorders may be difficult in practice, especially if patient does not rapidly achieve abstinence
 - If psychiatric symptoms are severe, or entail risks (e.g. poor functioning, suicide) it may be better to initiate treatment for co-occurring psychiatric syndrome right away, rather than delay to await abstinence.

Case 1: Depression

History

- Mr. K is a 55-year-old married man whom you have been seeing for many years and have been treating his hypertension
- Mr. K recently had a right hip replacement surgery.
- He comes to you today for a routine check up.
- He reports that since his surgery 3 months ago, he has been increasingly feeling down, with low energy, and poor sleep and appetite.
- You know that Mr. K was depressed before, first in his 20s and again about age 33 and 46.
 - It is important to obtain details about prior depressive episodes to determine severity (e.g. hospitalizations? suicide attempts?) and past treatments (why repeat a failed trial?)
- You believe he might be depressed again



Case 1: Depression

Steps to evaluate for depression

- What are the steps you take to evaluate for depression?
 - DSM-5 criteria for major depressive episode: 5 (or more) of the following x 2-week period at least 1 of the symptoms must include depressed mood or anhedonia:
 - depressed mood (most of day, nearly every day),
 - anhedonia,
 - change in appetite/weight,
 - insomnia or hypersomnia,
 - psychomotor agitation or retardation,
 - fatigue,
 - guilt or worthlessness,
 - change in concentration,
 - recurrent thoughts of death or suicidal ideation.

Case 1: Depression

Steps to evaluate for depression

- Must cause clinically significant distress/impairment
- Evaluate for Persistent Depressive Disorder (Dysthymia)
- Important to consider duration, severity, intensity of the symptoms as this will help guide treatment (e.g. therapy, medication, combined treatment, outpatient, intensive outpatient, outpatient)
- Self reports can assist in screening for current symptom severity¹ but clinical history, ideally assisted by diagnostic instrument such as PRISM or Structured Clinical Interview for DSM, is needed for diagnosis²
 - For QIDS go to: <http://www.ids-qids.org/>

1. e.g. Beck Depression Inventory (BDI), Quick Inventory of Depressive Symptomatology (QIDS-SR) (Beck et al. 1961; Rush et al. 2003)

2. Nunes and Weiss et al. 2015

Case 1: Depression

Steps to evaluate for depression-continued

- Determine if depression is unipolar or bipolar
 - Bipolar disorder is highly comorbid with SUDs. In the National Comorbidity Survey, lifetime comorbidity of any SUD in individuals with DSM-IV bipolar I disorder was 60.3%¹
 - Treatment is different, and treating bipolar patients with antidepressants alone can be de-stabilizing
- Ask about psychosis
 - Psychotic symptoms can occur with severe depression and have prognostic and treatment implications
- Ask about other psychiatric disorders (e.g. anxiety)

Case 1: Depression

Steps to evaluate for depression-continued

- Evaluate for medical etiologies
 - Medical conditions e.g. hypothyroidism can cause symptoms that mimic depression
- Are there any substances (medications, illicit drugs, alcohol) that could be causing depressive symptoms?
- Safety: Screen for suicide. Depression is a risk factor for suicide. Other risk factors include (but not limited to): substance use disorders, prior suicide attempts, family history of suicide, hopelessness, impulsivity
 - The Columbia Suicide Severity Rating Scale (C-SSRS) can be used to assess suicidal ideation and behavior.¹
 - Go to <http://www.cssrs.columbia.edu/> for C-SSRS training and scale

Case 1: Depression

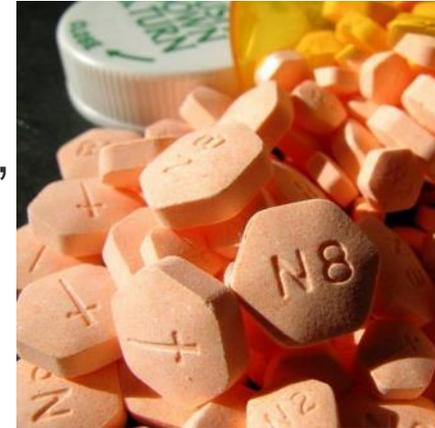
- As you are asking about depressive symptoms, Mr. K asks for a prescription for oxycodone/acetaminophen (Percocet[®])
- You find this surprising as his surgery was months ago
- You then ask him more about his Percocet[®] use, and Mr. K reveals he has been misusing Percocet[®], taking 10-15 oxycodone 10mg/325mg acetaminophen per day, has begun to purchase on the street, and recently began snorting his Percocet[®]
 - When evaluating for depression, it is important to ask about substance use and substance use disorder
 - 45.6 % = lifetime prevalence MDD in those with opioid use disorder¹

Case 1: Depression

- You ask Mr. K more about his Percocet[®] misuse, and he tells you that prior to his surgery he began feeling down, but this only worsened after surgery when he had trouble with mobility and concerns about returning to work as a construction worker
- He found the Percocet[®] to help “numb” his emotional pain.
 - It is important to ask about motivation for misuse
- He also reveals that in his 20s he was dependent on heroin but had been in remission for 30 years
 - Ask about prior substance use. Could this have been avoided if his surgeon had been aware of his prior heroin dependence?
- You ask about other substance use, which he denies
 - Polydrug use is not uncommon

Case 1: Depression

- After further discussion, you diagnose Mr. K with opioid use disorder (OUD) and discuss treatment options as he states he very much wants to stop abusing Percocet[®], but has “terrible” withdrawal each times he has attempted to cut back on his own. After discussion about treatment options, you agree to treat his OUD with buprenorphine/naloxone (e.g. Suboxone[®], Zubsolv[®]).
- You also discuss sending blood work to evaluate his liver function given the amount of acetaminophen he has been ingesting.
- You identify symptoms of depression ongoing for 4 months including: daily low mood, anhedonia, low energy, early insomnia, weight loss of 10 lbs, constant guilty ruminations about past mistakes.



Case 1: Depression

- He has been spending more time isolating at home, and tells you his family and friends have commented upon this. He does not feel he has the energy to return to work. He denies manic/hypomanic symptoms or psychotic symptoms.
- On mental status exam you found him to have a depressed mood, a blunted affect, and evidence of psychomotor retardation. No homicidal or suicidal ideation. He reports that his wife and children hope that he can feel better. He states that he wants to get better so they don't have to worry about him (protective factor).



Case 1: Depression

Question 1:

Does the knowledge about Mr. K's OUD impact how you see his mood symptoms?

Case 1: Depression

- Opioid intoxication (e.g. apathy, dysphoria, psychomotor agitation or retardation, impaired memory and attention) and withdrawal (e.g. insomnia, dysphoria, irritability) can look like depression
- Reasons to suggest independent mood disorder in Mr. K's case:
 - Prior episodes of depression beginning in his 20s (the mean age of onset of depression is mid-20s; about 50% of people with one episode of major depression will have a second, this number rises to 70% after two episodes and the recurrence rate is about 90% after three episodes)
 - Prior depressive episodes that occurred in the absence of other substance misuse
 - Current depressive symptoms that began prior to reported onset of opioid misuse. It appears in this case, Mr. K may have been “self medicating” with the Percocet®
- After much thought, you believe Mr. K meets criteria for Major Depressive Disorder, recurrent in addition to your diagnosis of Opioid Use Disorder

Case 1: Depression

Question 2:

Should you treat his depression
and if so, how?

Case 1: Depression

- A number of clinical trials have evaluated pharmacotherapy for depression in those with opioid use disorder¹.
 - The data suggest antidepressant treatment is effective for improving depressive syndromes
 - Some studies² suggest both depression and substance use improve, but improvement in substance use is less consistent across studies³
- Lack of treatment of depression in those needing it, carries risk (e.g. poor functioning, suicide)
- Factors to consider when weighing risks vs. benefits of initiating antidepressant medication: severity of depression (more severe may warrant more intense treatment environment or combination treatment), past trials, co-morbid medical conditions, potential medication interactions

1. Nunes, Sullivan, and Levin 2004
2. e.g. Nunes et al. 1998
3. Nunes and Levin 2004; Pettinati et al. 2013

Case 1: Depression

Question 2-continued

Treatment options for depression include:

- **Pharmacotherapy:**
 - Selective serotonin reuptake inhibitors (SSRIs): (e.g. fluoxetine, sertraline)
 - “First line” due to safety profile, generally well tolerated, affect the hepatic P450 system thus pay attention to potential for drug-drug interactions.
 - Serotonin and norepinephrine reuptake inhibitors (SNRIs) (e.g. venlafaxine, duloxetine): Monitor blood pressure, particularly with venlafaxine
 - Tricyclic antidepressants (TCAs): Contraindicated in those with cardiac conduction delays, fatal in overdose.
 - Some positive evidence for treating depression in those on methadone maintenance¹

Case 1: Depression

Question 2-continued

- Monoamine oxidase inhibitors (MAO-I): Required dietary restrictions, wash out period required when switching from irreversible MAO-I to another antidepressant
 - Other: bupropion (norepinephrine and dopamine reuptake inhibitor), mirtazapine (alpha 2 adrenergic blocker), trazodone/nefazodone (5HT2 antagonists)
- **Psychotherapy:** Evidence-based psychotherapies for depression include: Cognitive Behavioral Therapy (CBT) and Interpersonal Psychotherapy (ITP) ^{1,2}

Case 1: Depression

Question 2-continued

- You consider having Mr. K come back after 4 wks with the assumption that he will be off opioids (and taking buprenorphine/naloxone) but decide not to wait given your belief that he has independent depression in addition to OUD. He also reports that while he has never attempted suicide he has had suicidal thoughts and has been quite debilitated by prior depressions.
 - the value of diagnostic clarity with abstinence should be weighed with evidence for independent disorder that is impacting function and perhaps substance use

Case 1: Depression

Question 2-continued

- You decide to prescribe bupropion (Wellbutrin[®]) as Mr. K has responded to this in the past
- You check for potential drug interactions with buprenorphine/naloxone (e.g. Suboxone[®], Zubsolv[®]) and learn there are none
- Buprenorphine is metabolized by CYP450 3A4 isoenzyme
 - Inhibitors of CYP3A4 include some antidepressants (e.g. fluoxetine, fluvoxamine)
 - Due to ceiling effect of buprenorphine, not thought to be clinically significant but should be monitored and discussed with patients



Case 1: Depression Treatment Plan

- You discuss possible side effects of bupropion with Mr. K and that it can take weeks to see the full treatment effect.
- You discuss plans for buprenorphine/naloxone (Suboxone[®]) induction and follow-up appointments.
- You discuss involving Mr. K's wife to maximize his support system.
- You discuss therapy referral with Mr. K.
 - Therapy for depression and substance use can sometimes be given by the same provider. However, sometimes individuals may need two therapists.

Case 2: Post Traumatic Stress Disorder (PTSD)

History

- Ms. M is a 28-year-old woman who comes to you requesting buprenorphine for treatment of opioid use disorder.
- Ms. M reports that she was first prescribed oxycodone 2 years ago after a fall in which she fractured her arm requiring surgical intervention. She reports about 1 month later she fractured her jaw, again after a fall, receiving another prescription for oxycodone. She tells you that since this time she has had a number of other injuries, and “aches and pains,” for which she was taking oxycodone.
- She reports initially the “oxys” were “magic pills” not only treating her physical pain, but helped her “stay numb and emotionally checked out.”



Case 2: PTSD

History-continued

- However, she tells you that over time she began to need increasing doses of oxycodone to achieve the same effect (tolerance). She describes using more than she planned, trying to cut back but being unable to, describes symptoms of opioid withdrawal when she has tried to stop, cravings that are “impossible to resist,” and reports that financially she is “in trouble,” as she is spending all of her money on oxycodone; she was recently fired from a job due to repeated absences, “I was out getting high.” She is using about 150mg orally per day.
- She reports the desire to stop using oxys, stating “they’ve ruined my life,” and has heard that you can prescribe buprenorphine/naloxone (e.g. Suboxone[®], Zubsolv[®]).

Case 2: PTSD

- You diagnose Ms. M with opioid use disorder, and believe that Suboxone[®] is a reasonable treatment option.
- However, you begin to wonder about her “aches and pains,” and the many fractures she has reported, particular given she is only 28 years old.
- You ask Ms. M a bit more about the circumstances leading to her injuries.
- Ms. M opens up to you and reveals that she had been in a domestic violence relationship for 4 years; she tells you her injuries are the result of the physical abuse she suffered.
- Ms. M says that with the help of friends she was able to leave the relationship and is currently living with a friend in a “safe environment.”
- You begin to wonder if Ms. M might have post traumatic stress disorder (PTSD) .

Case 2: PTSD

- PTSD and substance use disorders (SUDs) commonly co-occur
 - Lifetime prevalence rate of PTSD in those with SUDs has been found to be 36-50% ¹
 - Some studies indicate particularly high comorbidity of PTSD and OUD (relative to alcohol and other drugs). Mills et al. reported 33% of those with OUD had PTSD ^{2,3}
 - Among veterans, psychiatric diagnoses, particularly PTSD, were associated with increased risk of receiving opioids for pain, high risk opioid use and adverse clinical outcomes ⁴
- Trauma and stress are risk factors for many forms of psychopathology, including depression, anxiety disorders, and substance abuse ⁵
- When evaluating someone with a SUD, always be alert for possible PTSD (and other psychiatric comorbidities)

1. Jacobsen LK 2001
2. Meier A 2014
3. Mills KL 2006
4. Seal KH 2012
5. Brady et al. 2010

Case 2: PTSD

Screening Instruments

- Screening tools, while not diagnostic, can be helpful in indicating the presence of symptoms consistent with the disorder and if positive, a more thorough assessment should be conducted.
- The Primary Care PTSD (PC-PTSD) Screen is commonly used in primary care settings and in studies has had a reported sensitivity of 70-78% and specificity of 87%-92%^{1,2}
 - A list of PTSD screens, including the PC-PTSD, can be found on the U.S. Department of Veterans Affairs website:
<http://www.ptsd.va.gov/professional/assessment/screens/index.asp>
- Ms. M screens positive for PTSD on the PC-PTSD, so you review the DSM-5 criteria for PTSD to see if she meets criteria.

1. Prins et al. 2003
2. Gore et al. 2008

Case 2: PTSD

What are the symptoms of PTSD?

- DSM-5 criteria for PTSD include the following symptoms lasting longer than 1 month, and causing significant distress or impairment:
 - **A. Exposure** to actual or threatened death, serious injury, or sexual violence in **one (or more)** of the following ways:
 - Directly experiencing the traumatic event(s).
 - Witnessing, in person, the event(s) as it occurred to others.
 - Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
 - Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse).

Case 2: PTSD

DSM-5 criteria-continued

- **B. Presence of one (or more) of the following intrusion symptoms** associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
 - Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).
 - Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).

Case 2: PTSD

DSM-5 criteria-continued

- Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)
- Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
- Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

Case 2: PTSD

DSM-5 criteria-continued

- **C. Persistent **avoidance**** of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by **one or both** of the following:
 - Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
 - Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

Case 2: PTSD

DSM-5 criteria-continued

- **D. Negative alterations in cognitions and mood associated** with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by **two (or more)** of the following:
 - Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
 - Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., “I am bad,” “No one can be trusted,” “The world is completely dangerous,” “My whole nervous system is permanently ruined”).
 - Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
 - Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
 - Markedly diminished interest or participation in significant activities.
 - Feelings of detachment or estrangement from others.
 - Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

Case 2: PTSD

DSM-5 criteria-continued

- **E. Marked alterations in arousal and reactivity** associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by **two (or more)** of the following:
 - Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
 - Reckless or self-destructive behavior.
 - Hypervigilance.
 - Exaggerated startle response.
 - Problems with concentration.
 - Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

Case 2: PTSD

Diagnostic Challenges

- There is overlap between symptoms of PTSD and symptoms of drug/alcohol intoxication and withdrawal
- Hyperarousal symptoms of PTSD (e.g. problems with concentration, sleep disturbance, irritability) can be caused by opioid intoxication or withdrawal
- Negative alteration in mood/cognition symptoms (e.g. feeling detached, diminished interest/participation in activities) could also be caused by opioid use
- Intrusion symptoms (e.g. recurrent dreams, images, flashbacks) are relatively specific to PTSD
- To distinguish those symptoms that may be common to both, ask about relationship of the symptoms to the traumatic event
- If the symptoms started shortly after a traumatic experience and/or are linked to distressing recollections of the traumatic event, the symptoms are likely secondary to PTSD. ¹

Case 2: PTSD

- You now believe Ms. M has PTSD in addition to OUD
- Next, you screen Ms. M for suicide and she denies any thoughts that life is not worth living, ever having an attempt, plan or intent, and is hopeful about the future, has many protective factors including her religion, family and friends. You believe her acute risk of suicide is low.
 - The prevalence of suicidal behavior in patients who have been exposed to trauma is significantly greater among those with a diagnosis of PTSD in comparison to other diagnoses. ¹
 - PTSD is associated with an increased incidence of prior attempted suicide and prior and current suicidal ideation. Controlling for other psychiatric disorders (including depression) weakened, but did not eliminate, this association. ²

1. Ferrada-Noli et al. 1998
2. Krysinska and Lester 2010

Case 2: PTSD

You now wonder how to treat Ms. M.

- Question 1:
How is PTSD treated?
- Question 2:
Should I treat her OUD first?
- Question 3:
Will treating her PTSD worsen her OUD?



Case 2: PTSD

Question 1: How is PTSD treated?

Treatments for PTSD can include the following:

- **Psychotherapy:**
 - Evidence-based psychotherapies for PTSD include Cognitive Behavioral Therapy (CBT), including exposure-based CBT. CBT for PTSD involves a combination of psychoeducation, relaxation and anxiety management techniques, cognitive techniques, imagined and in vivo exposure to trauma-related stimuli, and relapse prevention.¹
- **Pharmacotherapy:**
 - Meta-analyses and several randomized controlled trials published generally support the superiority of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) over placebo for non-combat-related PTSD. Less work has been done for the treatment of PTSD and concurrent Substance Use Disorders². The data for SSRIs and combat-related PTSD is more mixed; the most recent (2004) APA guidelines recommended SSRIs as first-line.
 - Tricyclic antidepressants and monoamine oxidase inhibitors showed improvement in intrusive and depressive symptoms, but SSRIs are considered first-line in part due to safety profiles.
 - Mirtazapine and nefazodone have also been shown to be superior to placebo in treating PTSD.
 - Prazosin has been found to be effective for PTSD-related nightmares and sleep disturbance.
 - Other medications with some indication, often in uncontrolled reports, include: carbamazepine, beta-blockers, lithium, clonidine, benzodiazepines, to name a few.
 - Adjunctive treatment with a second-generation antipsychotics in patients who have partially responded to an SSRI or an SNRI have also been shown to be effective³

1. Gabbard et al. 2007
2. Hien et al. 2015
3. Gabbard et al. 2007; Brady et al. 2010

Case 2: PTSD

Question 1-continued

- Relatively little data exists addressing the treatment of comorbid PTSD and OUD.
- Seeking Safety (SS) is one of the most widely studied non-exposure based treatments for co-occurring PTSD and SUD.
 - SS is a standard cognitive behavior treatment with both safety/trauma and substance use components integrated into each session.¹
 - SS has shown positive results in PTSD symptoms and SUD in a number of studies.²
 - SS has been shown to be more effective than ‘standard community care’ for both PTSD and SUD symptoms.³ However, it does not demonstrate better outcomes than relapse prevention (a SUD only treatment) or health education.⁴

1. Najavits et al. 1998
2. Hien et al. 2004; Hien et al. 2009; Najavits and Hien 2013
3. Hien et al. 2004
4. Hien et al. 2004; Hien et al. 2009

Case 2: PTSD

Question 1-continued

- In addition to non-exposure-based treatments (e.g. Seeking Safety) more recently a number of treatment protocols have involved exposure-based treatments for those with comorbid PTSD and SUD.
- Six recent studies were reviewed by Najavits and Hien and found to have positive outcomes, and notably no negative outcomes. The studies did, however, modify the classic exposure for PTSD in varying ways; this flexibility in classic exposure may be a key component.¹
- The literature examining pharmacological approaches to treating PTSD and SUD is limited and has been done only with alcohol use disorder²; no studies have looked at medications for comorbid PTSD and OUD.

1. Najavits and Hien 2013

2. Hien et al. 2015

Case 2: PTSD

Question 2: Should I treat her OUD first?

- In the past, individuals were treated for SUD and treatment of PTSD was deferred. However, this approach is now considered problematic because symptoms of PTSD may drive relapse for SUD.¹
- The few studies thus far suggest that the usual treatments for OUD are effective for OUD but do not impact PTSD symptoms.²

1. Brady et al. 2004
2. Mills et al. 2007; Trafton et al. 2006; Fareed et al. 2013

Case 2: PTSD

Question 3: Will treating her PTSD worsen her OUD?

- Growing literature shows that treatment for PTSD, including exposure therapy, is not harmful for individuals with SUD and PTSD and can lead to improvement in SUD outcomes¹
- Integrated treatments are therefore recommended at this time

Case 2:PTSD

Treatment Plan

- After a discussion with Ms. M, you decide to refer her to a trauma treatment program specifically for women with SUD and a history of trauma (i.e. Seeking Safety)
- In addition to buprenorphine/naloxone (e.g. Suboxone[®], Zubsolv[®]) maintenance, Ms. M was started on sertraline (Zoloft[®]) 50mg, titrated up to 100mg as she continued to have depressed mood and sleep troubles after her first six weeks in treatment.
- Ms. M completes the treatment program and returns to you for management of her buprenorphine/naloxone, while continuing with weekly therapy and medication management with a psychiatrist. She also attends a weekly aftercare group.

Case 3: Attention Deficit Hyperactivity Disorder (ADHD)

- Mr. C is a 38-year-old divorced man, without children, living alone, employed as realtor, who comes to you seeking treatment for his substance use disorder.
- Mr. C reports he has been abusing opioids for about 8 years. He reports he started using oxycodone/acetaminophen (Percocet[®]), but after about 2 years, transitioned to heroin as it was cheaper. He is using 5-7 bags of heroin IV daily. He describes both tolerance and withdrawal, noting that he no longer enjoys using heroin; “I need it to avoid withdrawal; that’s the only reason I use.” He reports his divorce was largely due to his heroin use, and reports he has increasingly isolated from his friends. He has been increasingly less productive at work. He denies other drug or alcohol use.

Case 3: ADHD

History

- Mr. C has never been in substance use treatment before. He has never overdosed on heroin.
- Mr. C reports denies any psychiatric history.
- He reports growing up he struggled in school, noting he never read a book “cover-to- cover” because he would get “bored and distracted.” He describes significant difficulty in school sitting still, would often get into troubles with teachers as result. He reports his family would always complain that he was impulsive, frequently interrupting and appeared “driven like a motor.” His mother in particular used to complain about the fact that he was constantly losing things, something Mr. C said his ex-wife used to do as well. Mr. C has been at his current job for 10 years and feels it suits him as he does not have to sit at a desk all day and can make his own schedule, although he often forgets about appointments and has lost a few clients for this reason.

Case 3: ADHD

History

- Mr. C denies any past or present medical problems, and is not taking any medications.
- Mr. C denies any medical complications from IV drug use (e.g. abscess).
- You test Mr. C for HIV and Hepatitis B, C and he is negative.



Case 3: ADHD

Course of Treatment

- Mr. C is interested in buprenorphine/naloxone (e.g. Suboxone[®], Zubsolv[®]) maintenance as his brother who also abused opioids has done very well with in buprenorphine/naloxone.
- You plan for an outpatient in buprenorphine/naloxone induction and Mr. C is ultimately maintained on 10mg SL in buprenorphine/naloxone daily.
- Three months into treatment, Mr. C is doing well, not abusing opioids, and has begun to exercise and spend more time with his friends and family. He feels he is “getting back to my old self.”
- However, Mr. C tells you he is having trouble organizing his day, still missing appointments, and recently lost a potential client due to his disorganization.
- He asks you if there is anything you can do to help him.
- You recall Mr. C’s history of trouble in school and wonder if he might have ADHD.

Case 3: ADHD

- ADHD is a disorder that by definition presents before the age of 12 (*represents a change in DSM-5 from DSM-IV in which age was 7 years).
- It is estimated that ADHD symptoms will persist into adulthood in approximately 50-60% of cases¹.
- ADHD and SUD frequently co-occur. Adults in substance abuse treatment have rates of ADHD ranging from 8-33% ².
- Rates of comorbidity of ADHD in those with OUD range from 19%-33% ³

1. Barkley et al. 2002; Biederman et al. 2000; Kessler et al. 2005; Rasmussen and Gillberg 2000

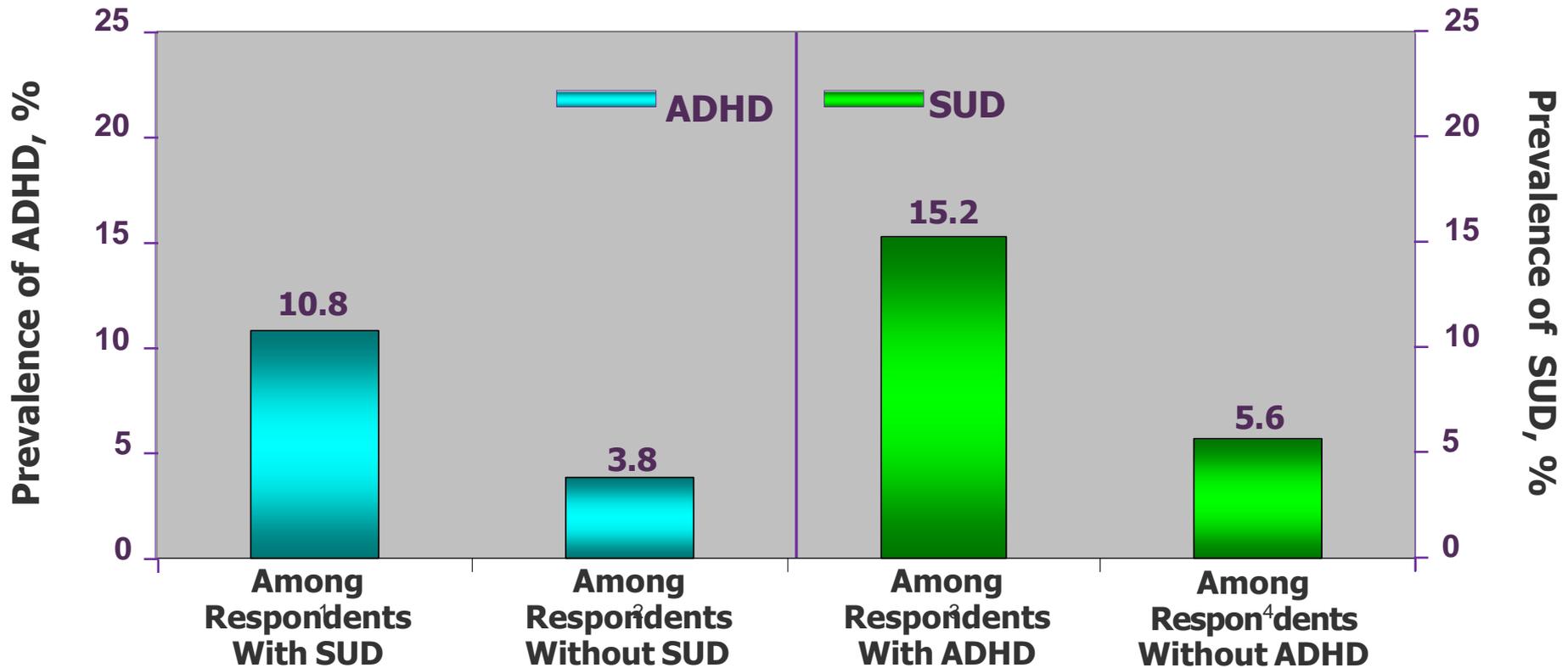
2. Clure et al. 1999; Levin et al. 1998; Schubiner et al. 2000; van de Glind et al. 2014

3. King et al. 1999; Peles et al. 2012

Case 3: ADHD

Comorbidity of Adult ADHD and SUD in Adults: Epidemiologic Data

National Comorbidity Survey Replication (N=3199)



Case 3: ADHD

For substance abusers coming for treatment: Why is ADHD important?

- Earlier onset of SUD when ADHD present
- A reduced likelihood of going into remission if dependence develops
- Higher relapse rates for both adolescents and adults
- If remission achieved, longer time to reach remission
- More treatment exposure, yet do less well in treatment
- Higher rates of other psychiatric comorbidities (e.g., conduct/antisocial disorders)

Case 3: ADHD

How to diagnose ADHD DSM-5 criteria

A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development as characterized by (1) and/or (2):

- 1. Inattention:** 6 (or more) of the following x 6+mos (For older adolescents and adults (ages 17 and older) at least five symptoms are present):
 - Fails to give close attention to details/makes careless mistakes
 - Difficulty sustaining attention in tasks
 - Does not seem to listen when spoken to
 - Does not follow through with instructions and fails to finish work/duties
 - Difficulty organizing tasks and activities
 - Avoids/dislikes/reluctant to engage in tasks that requires sustained mental effort
 - Loses things necessary for tasks/activities
 - Easily distracted by extraneous stimuli
 - Forgetful in daily activities

Case 3: ADHD

How to diagnose ADHD DSM-5 criteria

2. Hyperactivity and impulsivity: 6 or more of the following for 6+mos (For older adolescents and adults (ages 17 and older) at least five symptoms are present):

- Fidgets with or taps hands or feet/squirms in seat
- Leaves seat in situations when should not
- Runs about/climbs in inappropriate situations
- Unable to play/engage in leisure activity quietly
- “On the go,” acting as if “driven by a motor”
- Talks excessively
- Blurts out answers before a question has been completed
- Difficulty waiting his/her turn
- Interrupts or intrudes on others



- Several symptoms must be present before age 12
- Present in 2 or more settings (e.g. work, home)
- Interfere with function
- Not better accounted for by another mental disorder

Case 3: ADHD

Screening Instruments

Screening/self-report instruments can be helpful in identifying those at high likelihood of ADHD

Instruments include:

- Adult ADHD Self-Report Scale (ASRS)
 - 67-88% sensitivity and 66-82% specificity in substance abusers¹
 - http://www.hcp.med.harvard.edu/ncs/ftplib/adhd/18Q_ASRS_English.pdf
- Conners Adult ADHD Rating Scale (CAARS)
 - 94% sensitivity and 70% specificity in those with cocaine dependence²
- Wender Utah Rating Scale (WURS)
 - 93% sensitivity and 70% specificity in those with cocaine dependence³
 - http://www.uvm.edu/medicine/ahec/documents/Wender_Utah_Rating_Scale.pdf

1. Ramos-Quiroga et al. 2009; Dakwar et al. 2012; Van de Glind et al. 2013

2. Dakwar et al. 2012

3. Dakwar et al. 2012

Case 3:ADHD

Challenges to diagnosing ADHD in those with SUD

Factors leading to **underdiagnosis**:

- Inability to recall symptoms prior to age 12
 - Alcohol-dependent, opiate-dependent, methamphetamine-dependent have cognitive deficits compared to non-substance abusers.¹ Deficits shown to persist with abstinent alcoholics²
 - Early-onset cannabis use (< 17 years old) exhibit poorer cognitive performance compared to late-onset users³
- Lack of corroboration from older family members
 - May have estranged relationships, do not want family to be contacted
 - Parents may not remember details

1. Maxwell et al. 2005; Davis et al. 2002
2. Davies et al. 2005
3. Pope et al. 2003

Case 3:ADHD

Challenges to diagnosing ADHD in those with SUD

Factors leading to **overdiagnosis**:

- Ongoing SUD can mimic ADHD
 - Acute effects: opioids: agitation, impaired concentration
 - Withdrawal: opioids: restlessness, irritability, agitation
- Relying on screening instruments/computer testing alone
 - May not take into account impact of ongoing substance use or other psychiatric diagnoses
- Chaotic early childhood
 - Inattentive or impulsive symptoms may be secondary to difficulties at home, no structure
- Learning disabilities
- Desire to get stimulant medication

Case 3: ADHD

Other helpful tips when assessing ADHD in substance abusers

- Complete a timeline for ADHD symptoms: onset of symptoms, what types of symptoms, did they change over time
- Complete a timeline for substance use, onset of use, heavy substance use, problematic use, and periods of abstinence or reduced use
- Determine presence/absence of ADHD symptoms prior to drug use and during periods of abstinence
- If symptoms not present during abstinence or come and go, not consistent with ADHD diagnosis

Case 3: ADHD

- You have Mr. C fill out the ADHD Rating Scale which shows that he has symptoms “highly consistent with ADHD.”
- You go through the DSM-5 criteria for ADHD and Mr. C appears to meet criteria for ADHD, predominantly inattentive type
- You review a timeline of his symptoms and substance abuse which reveals symptoms of ADHD began long before his opioid abuse. Mr. C did have a period of daily, heavy cannabis use in his mid-teens as he felt the cannabis allowed him to “slow down and sit still.” However, his symptoms of ADHD both predate his cannabis use and occurred during times of abstinence from all substances.
- You now wonder, “How should I treat his ADHD?”



Case 3: ADHD

Treatment

Treatments for ADHD include **non pharmacological and pharmacological interventions.**

- Non pharmacological interventions which encompass a wide-range of interventions including behavior therapy, academic interventions, family therapy, care coordination have been well studied in children but not adults¹
- Pharmacologic interventions can be broken down into stimulants and non-stimulants

Case 3: ADHD

Treatment

- Stimulants have demonstrated efficacy in numerous double-blind, placebo controlled trials. Considered first-line treatments.
 - Examples include: methylphenidate and related compounds: dexamethylphenidate, and longer-acting methylphenidate agents (e.g. Concerta[®], Metadate CD[®], Ritalin LA[®]) and dextroamphetamine and mixed amphetamine salts and longer acting related compounds (e.g. Vyvanse[®], Adderall XR[®])
- Non-stimulants: atomoxetine (Strattera[®]) is the first/only non-stimulant medication FDA-approved for treatment of ADHD in adults. Other medications demonstrating some efficacy include: bupropion, alpha agonists (guanfacine, clonidine—both FDA approved for treatment of ADHD in children and adolescents), modafinil, TCAs, MAOIs

Case 3: ADHD

Treatment-continued

- Literature of treatment for ADHD and SUD is still limited, but the emerging trend is that medications that are effective for adult ADHD are likely to be effective for adults with ADHD and SUD, though the therapeutic benefit may be less¹
- Available evidence supports the use of stimulants over non-stimulants for adult (and pediatric) ADHD

Case 3: ADHD

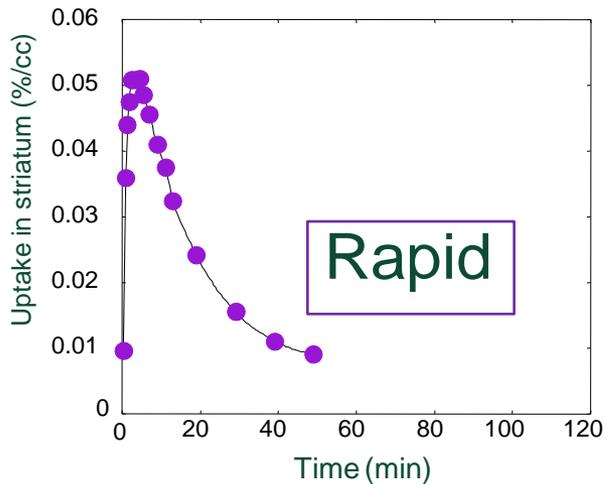
How do we treat ADHD in those with SUD

- Question 1: Do I have to worry about making people “high” and precipitate relapse if I give stimulants?
- Question 2: How much do I have to worry about diversion if we give stimulants?
- Question 3: Which are the best medications/formulations to use?
- Question 4: If I prescribe a stimulant, how should I monitor for abuse?

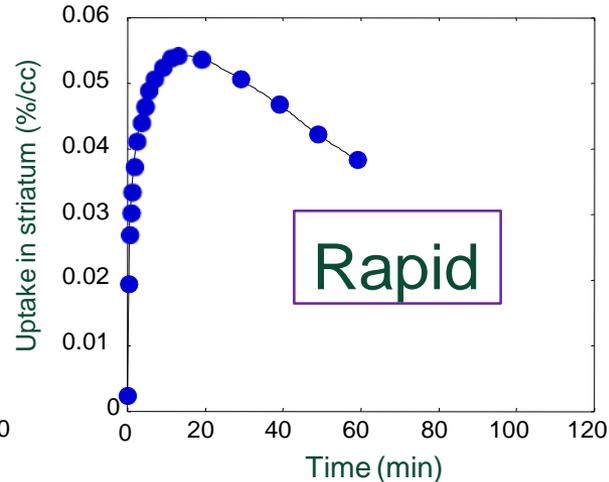
Case 3: ADHD

Question 1: Rate of drug uptake into brain affects “high”

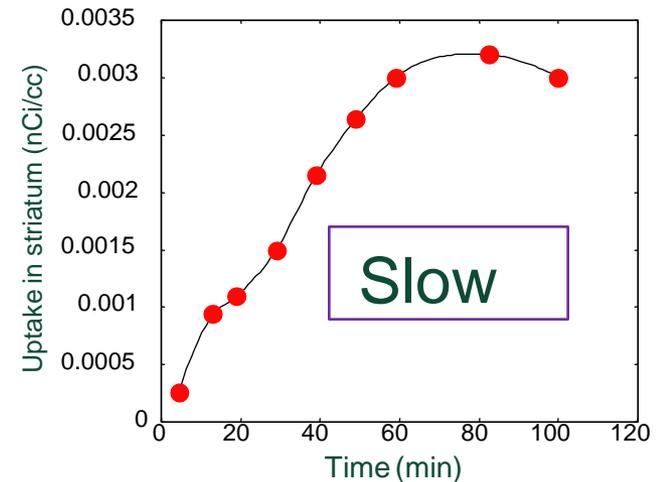
iv cocaine



iv MPH



oral MPH



- Cocaine (iv) and methylphenidate (iv) produce a “high” but methylphenidate (oral) does not (10-60 mg), or at least much less
- The slow brain uptake of oral methylphenidate permits effective treatment

Case 3: ADHD

Question 2: How much do I worry about diversion?

- None of the clinical trials report diversion or misuse, but doesn't preclude that this is happening to some degree
- Desantis et al 2009: Survey of 333 fraternity members in U.K. Twenty-six (8%) had legal prescription for ADHD. Of remaining 307 students (55%) reported nonmedical use of stimulants
- Bright (2008) 545 subjects in ADHD clinic, 14% abused stimulants (80% abused short-acting stimulants, 17% long acting, 2% both)

Case 3: ADHD

Question 3: What medication to choose? Treatment Recommendations

No data in ADHD-OUD to guide treatment; however, based on studies with ADHD-SUD¹ :

- Atomoxetine: First-line treatment, particularly shown helpful for abstinent alcohol-dependent individuals, those with tic disorder. High drop-out rate when given to cocaine abusers with ADHD²
- Bupropion (“Off-Label” – not FDA approved for ADHD)
 - Efficacy in smoking cessation
 - Useful in comorbid mood disorders
 - Open studies show improved ADHD/SUD/Mood outcome
- Guanfacine, modafinil, tricyclic antidepressants (Off-label)

1. Wilens 2004; Riggs 1998; Schubiner 2005; Wilson and Levin 2005; Mariani and Levin 2007.
2. Levin et al. 2009

Case 3: ADHD

Question 3: What medication to choose? Treatment Recommendations

- **Stimulants**
 - Use in substance-abusing patients is complex and requires close monitoring
 - Use extended-release formulations of stimulants (e.g., OROS MPH, d-MPH XR, MAS XR, or MPH SR)
 - Monitor closely- both ADHD symptoms and pattern of alcohol/drug use
 - If severe SUD may refer for intensive intervention prior to starting medication
 - May need to avoid stimulants if they have current use disorder on prescription stimulants or high risk of diversion of medication (i.e., sold medication in past)

Case 3: ADHD

Question 3: What medication to choose? Treatment Recommendations

- **Non-pharmacologic approaches adjunctively**
 - For SUD: Group and individual psychotherapy (e.g. cognitive-behavioral therapy); Family therapy for adolescents and young adults
 - For ADHD: Cognitive-behavioral therapy, organizational coaches



Case 3: ADHD

Question 4: Monitoring when prescribing medications with abuse potential

- Misuse/Diversion/Use Disorder are inherent risks of prescribing controlled medications
- All patients prescribed controlled substances should be assessed at each visit for signs of misuse, abuse, or addiction
- Evaluate patient using a matter-of-fact and non-threatening manner

Case 3: ADHD

Question 4: Monitoring when prescribing medications with abuse potential

- Red flags:
 - Symptoms of intoxication or symptoms associated with heavier use (agitation, psychosis, SOB, palpitations)
 - Demands for a particular, usually fast acting, medication (amphetamine IR)
 - “Extended-release doesn’t work for me”
 - Repeated lost prescriptions
 - Discordant pill count (escalation of doses)
 - Excessive preoccupation with securing medication supply
 - Multiple prescribers



Case 3: ADHD

Treatment Plan

- You discuss treatment options with Mr. C
- Mr. C reports feeling “a little nervous” about the idea of a stimulant medication given “misusing pills (oxycodone/acetaminophen) are what got me into this mess.”
- You discuss a trial of atomoxetine
- You confirm there is no interaction between atomoxetine and buprenorphine/naloxone
- You start Mr. C on atomoxetine 40mg po daily

Conclusions

- Psychiatric illnesses and substance use disorders frequently co-occur
- When treating someone for a substance use disorder, it is important to be mindful of the likelihood of psychiatric comorbidities
- A host of screening instruments can assist in identifying those that warrant for investigation of a psychiatric comorbidity
- Data thus far support need for concurrent therapy directly targeting the SUD in addition to treatment of co-occurring psychiatric comorbidity

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