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Complicated Comorbidities in Patients with Substance Use Disorders

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Disclosures

- James Latronica, DO, has no conflicts of interest to disclose
- Julie Kmiec, DO, has no conflicts of interest to disclose

Objectives

- Addiction Medicine and Addiction Psychiatry are two closely-related specialties with similar patient populations with many comorbidities
- Differing background training and primary board certification may create unique perspectives in caring for patients with substance use disorders
- Patients with Substance Use Disorders and co-occurring medical and/or psychiatric illness will be described and discussed from perspective of addiction psychiatry and addiction medicine
- Addiction specialists often become the de facto “primary” provider, so fostering inter-disciplinary communication and knowledge of trade net plans between specialties is an eminently rational target to support the best possible clinical outcomes.

Addiction Medicine vs. Addiction Psychiatry

- Addiction Medicine
  - Residency training often in a primary care field
  - May seek fellowship training in addiction medicine
  - May seek certification by clinical pathway (AOA, ABPM)
  - Pathways will be closing in upcoming years
- Addiction Psychiatry
  - Residency training in general psychiatry
  - Fellowship training in addiction psychiatry
  - Sit for ABPN board examination
  - ABPN clinical pathway closed several years back

Medical Complications and Questionable DSM Criteria

T.W. – 39 y/o male

- PMH: Ehlers Danlos
  - Chronic aortic dissection (no repair possible)
  - Non-ischemic cardiomyopathy w/ HFrEF (31%)
  - Chronic back pain (spondylolysis at multiple thoracic and lumbar levels)

- Presented from Pain Clinic for “consult.”
  - Pain Clinic patient x 5 years
  - Alerted: “This might take some digging…” (allotted a full hour appt.)

T.W. – 39 y/o male

- Pain Clinic's Overview
  - Long-time pain clinic patient, suddenly seeing displaying behavior
  - Early fills, many phone calls to Pain Clinic
  - Some missed appts.
  - Is he "drug-seeking" now?
    - Pain relief = rational human behavior
  - Their main concern: repeated withdrawal = increased chance of CV event
    - However, they were effectively "turning him over" to us

T.W. – 39 y/o male

- My Deep Dive Overview
  - Long-time pain clinic patient, appropriate PDMP's (some "early fills")
  - Fall 2018: T.W feels pain is well controlled, and he notices over-sedation
    - At that time on **270 MME** (morphine sulfate-XR + oxycodone)
  - Asks *himself* to be tapered down (confirmed with Pain Clinic)
    - Initial worry about control; told they can stop or increase back at any time
  - October 2019: Now on **80 MME** (oxycodone only)
    - Pain poorly controlled; running out early
    - Pain Clinic: "Let's maximize non-opioid therapy."

T.W. – 39 y/o male

- My Deep Dive Overview (cont'd)

  - August 2020
    - Pain still poorly controlled
    - Duloxetine only adjunct that helps (compliant at 90mg. daily)
      - acetaminophen, gabapentin, lidocaine, capsaicin, TCA ineffective
      - NSAIDs contraindicated per Nephrology and Cardiology
    - 6 ED trips in last 2 months due to inadequate pain control and withdrawal

  - Pain Clinic:
    - "We can't keep writing and filling early."
    - Explained full history; state that he's missed too much and has violated practice guidelines too often

T.W. – 39 y/o male

What do we do with this gentleman?!?!

T.W. – 39 y/o male

- <u>What Do We Know For Sure?</u>

  1.) Serious multi-system medical condition

  2.) Chronic, untreated pain

  3.) Previous well-controlled pain (w/ possible over-sedation)

  4.) He can no longer be a patient at Pain Clinic

T.W. – 39 y/o male

- DSM-5 Opioid Use Disorder (meet at least 2 in last 12 mos)
  - Using larger amounts or for longer time than originally intended?
  - Persistent desire or unsuccessful efforts to cut down or control opioid use?
  - Great deal of time is spent obtaining, using, or recovering from opioid?
  - **Craving or strong desire to use?**
  - Major role obligations at work, school or home affected?
  - Persistent or recurrent social or interpersonal problem?
  - Important social, occupational or recreational activities are given up or reduced?
  - Use where physically hazardous?
  - Use despite physical or psychological problems caused or exacerbated by opioids?
  - ***Tolerance?**
  - ***Withdrawal?**

T.W. – 39 y/o male

What Are Our Options?

- A.) Treat as OUD
  - not convinced he meets criteria
  - 1.) Naltrexone: not considered for this patient
  - **2.) Buprenorphine**
    - Withdrawal = CV danger + ED trips
    - Induction on buprenorphine would be difficult
      - In-office monitored? Admit for observation? TID dosing?
  - **3.) Methadone**
    - Questionable criteria = tough to make case for OTP
    - Transportation issues
    - Once daily dosing likely insufficient for pain control

T.W. – 39 y/o male

What Are Our Options? – can't do "nothing"

- B.) Treat As Chronic Pain Management
  - 1.) Take over this patient's care ourselves (go back to old regimen)
    - This office = general IM (w/ residents) + OBAT (hub and spoke model)
    - Currently only a handful of patients with chronic pain
    - Not ideal
  - 2.) TID Methadone *indicated and written for pain*
    - Pain Management on board!
    - IM office on board!
    - QT_c = 510 (not on board!)

T.W. – 39 y/o male

What Are Our Options? – can't do "nothing"

- C.) Beg and Plead With Pain Clinic
  - After hearing my full story and our options and rationale, Pain Management took this patient back
  - Uptitrating to ~120MME per day
    - Last level w/ pain control w/o over-sedation
  - *Also consulted Palliative Care for input*
    - Implantable device?
    - Nerve blocks?

High MME and Questionable History

M.G. – 34 y/o male

- Military History
  - Post-Gulf service
  - Deployed to Middle East -- some combat
  - Denies MST, TBI, combat injury

- PMH: Chronic pancreatitis (many acute flares), vertebral osteomyelitis (w/ assoc. chronic pain)
  - Hydromorphone: 8mg PO 5x/day
  - Fentanyl transdermal: 125mcg/hr TD Q3 days
  - Total MME: 460

M.G. – 34 y/o male

- PPsyH: PTSD, Borderline Personality Disorder, Bipolar(?)
  - Intermittently treated – Psych consult pending
  - Constantly fractured care
    - Multiple VA sites, multiple civilian sites, multiple regional and distant moves since discharge in 2016
  - Insight and Judgment: very limited

- Social
  - Lives with parents but they are “fed up.”
  - Multiple conversations with mother

M.G. – 34 y/o male

- Chronic Pain
  - Chronic pancreatitis: 2/2 EtOH
    - No biliary, triglyceride, or scorpion issues
  - Vertebral Osteomyelitis (MSSA): IV Abx x 6 weeks + PO Abx x 6 weeks
    - Now finished Abx course (states “I still feel it in there”)
    - Adjuncts
      - 3000mg. acetaminophen
      - 3200mg. ibuprofen
      - 2400mg. gabapentin
      - 90mg. duloxetine

M.G. – 34 y/o male

- Some More History…
  - Initially confused why he was referred to me
    - "I take a lot but it's prescribed."
  - Framed it as "many reasons why pain might not be controlled"
    - e.g., hyperalgesia
    - Asked "have you ever been in so much pain you used more?"
    - Now endorses purchasing hydromorphone or heroin
  - So clearly using more than 460MME
  - Using hydromorphone and heroin IV
    - Has tried to stop this ("I know it's a problem")

M.G. – 34 y/o male

- **Larger amounts/ longer time? –** *460 MME (plus more)*
- **Efforts to cut down or control opioid use? –** *tried to stop using IV*
- **Great deal of time is spent to obtain/use/recover from?** *–sleeps >12 hours per day*
- **Craving or strong desire to use?**
- Major role obligations at work, school, or home affected?
- **Persistent or recurrent social or interpersonal problem?** *– stealing from parents*
- **Giving up activities due to use?** *– unable to work or help around house*
- **Use where physically hazardous? –** *driving (avoided multiple DWI)*
- **Use despite physical or psychological problem caused or exacerbated by opioids?** *-- PTSD*
- ***Tolerance?**
- ***Withdrawal?**

M.G. – 34 y/o male

What do we do with this gentleman?!?!

M.G. – 34 y/o male

- Chronic Pain
  - Chronic pancreatitis and post-infectious spinal pain
    - He is definitely in pain
    - Likely a hyperalgesia picture

M.G. – 34 y/o male

What Are Our Options?

- A.) Treat as OUD
  - meets criteria
  - 1.) Naltrexone: not considered for this patient

  - **2.) Buprenorphine**
    - Significant, long-term fentanyl use
    - Induction onto buprenorphine would be difficult
      - Admit for observation?
      - Even max TID dosing likely not sufficient
      - Buprenorphine-XR? – not yet at VA

M.G. – 34 y/o male

What Are Our Options?

- A.) Treat as OUD
  - **3.) Methadone**
    - Clear criteria
    - Transportation issues
    - Once daily dosing possibly insufficient for pain control
    - VA relies on community programs – additional barrier

M.G. – 34 y/o male

What Are Our Options?

- B.) Treat as Chronic Pain
  - Difficult given dosing and misuse
  - Would require close monitoring and engagement from multiple departments
  - TID methadone?
    - SUD Team at VA has never managed this; Pain Management has not either
  - Implantable device? (available at VA)
  - *Have yet to see in person, complicating everything*

Positive Alcohol Biomarkers but Denying Alcohol Use

AT, 39 y/o woman

- AT is a 39 y/o woman with OUD taking buprenorphine/naloxone (bup/nx).
- Started at clinic about 6 years ago
- In 2014 she was admitted to psych unit for depression and suicidal ideation
  - Started on citalopram 20 mg daily
- She admitted to using up to 90 mg of oxycodone orally daily; using daily for a couple years, amount increased over time
  - Dx with OUD, started on bup/nx 8/2 mg SL daily
- Also admitted to drinking a fifth of vodka daily for months
  - Dx with AUD, underwent medically supervised withdrawal

AT, 39 y/o woman

- MH: HTN on HCTZ
- PH: MDD, OUD, AUD, tobacco use disorder
- SH: Single, has 12 y/o daughter, works for a managed care company

- AT was stable for several years on bup/nx 8/2 mg daily, denied substance use and urines are consistent with self report. She participates in therapy as required and attends physician appointments.
- After 6 months in clinic, no longer feels she needs citalopram for depression

AT, 39 y/o woman

- In January 2020, AT is hit by a car while crossing the street.
- EMS comes to scene, she refuses transport to the hospital.
- Next morning she goes to ED on her own, found to have distal tib-fib fracture for which she undergoes ORIF and is hospitalized.
- She calls clinic to inform us of her status.
- While in hospital, bup/nx is held and she is given oxycodone for pain. Upon discharge she was given a short script of oxycodone.
- AT finishes the oxycodone and gets restarted on bup/nx, dose increased to 16/4 mg for ankle pain.

AT, 39 y/o woman

- When reviewing chart from ED visit and hospitalization it is noted that AT reported she was leaving a bar and then hit by a car.
- No alcohol level done when she reported to the ED.
- BMP and CBC done in the ED were normal except
  - MCV 101.9
  - MCH 35.4
  - RBC 3.79

AT, 39 y/o woman

- During visit, asked AT about concerns regarding report she was leaving a bar and this abnormal lab which may reflect regular/heavy drinking
- She states she was getting take-out from the bar and denies drinking alcohol except for occasional “social” drinking
- Given lab req to complete (CBC, CMP, B12, folate, TSH, iron panel)

AT, 39 y/o woman

- In May, AT reports she has been depressed, reports problems with her daughter who is 12 years old, who doesn't like AT's boyfriend. This has caused several problems at home, AT feels caught in the middle.
- Symptoms of depression: depressed mood, anhedonia, low motivation and energy, increased sleep, low appetite, poor concentration, no SI
- Start citalopram for depression because worked for her in the past
- Denies all substance use; UDS positive for buprenorphine only
- Asks for FMLA certification because she has been missing work
- Still hasn't done blood work

AT, 39 y/o woman

- AT continues monthly doctor visits. Therapist leaves clinic, she is not connecting with new therapist. She reports feeling a bit better in June
- In July went to the ED complaining of sore throat and SOB.
- Reviewed ED note, states that AT felt tremulous in the ED, stated she drinks alcoholic beverages on a regular basis and ED physician believed that she was likely exhibiting some element of alcohol withdrawal syndrome and gave her a dose of lorazepam which alleviated the tremor.
- Labs: K 2.7, ALT 145, AST 138, MCV 101.9, MCH 35.3, RBC 3.87
- AT denies that she reported drinking alcohol regularly, stating she rarely drinks

AT, 39 y/o woman

- In September she reports depression worsened, can't get out of bed, missing several days of work, states she was told she isn't eligible for more FMLA because she missed several weeks at the beginning of the year
- In mid-September she reports drinking every few days, 1-2 drinks
  - Supposed to be seen in clinic, states she can't come because of a flat tire, telemedicine visit is arranged and she is 45 mins late for this appointment
- In late-September states she is drinking 5-6 drinks every other day
  - Supposed to be seen in clinic, arrives late (4:30 PM), when she arrives she smells of alcohol
  - She stated it may be positive because she drank the night prior breathalyzer given
  - Breathalyzer 0.16

AT, 39 y/o woman

- One week later she reports drinking ½ of a fifth of vodka daily
- Complains of being shaky all the time and people noticing this
- Maintains she was accurate about her drinking prior to 1 month ago
- Referred to ambulatory detoxification where she is seen in clinic, provided chlordiazepoxide for withdrawal, arranged telemed follow-up the next day

AT, 39 y/o woman

- On the telemed visit she sounded intoxicated, she reported her boyfriend told her she wasn't acting normal
- Switched to lorazepam
- One day later she calls saying she can't come to clinic due to a funeral
- Two days later she emails and says she is ill with virus and can't come to detox but states she will for sure be at her bup clinic appointment tomorrow
- Phone goes to vmail

AT, 39 y/o woman

- What are the next steps in AT's treatment?
- How do we make sense of her self-report of drinking in light of the alcohol biomarkers and what has been recorded by ED physicians?

How can I use biomarkers for alcohol?

- Screen for alcohol problems
  - May help with differential diagnosis by determining the possible role of alcohol use in a disease process
  - Not to be used as the sole screening tool as they have low-to-moderate sensitivity and specificity
- Motivate change in drinking behavior
  - Biomarkers provide objective evidence on alcohol's effects and may result in one stopping or reducing alcohol use
- Identify return to drinking
  - Important for improved outcomes

Indirect Biomarkers

- Indirectly correlated with alcohol use, not very sensitive
- Suggest heavy alcohol use by detecting the toxic effects that alcohol may have had on organ systems or body chemistry
- GGT
- AST and ALT
- MCV
- CDT

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ASAM Principles of Addiction Medicine, Sixth Edition

Indirect Biomarkers

- Gamma glutamyl transferase (GGT)
  - Elevation caused by liver enzyme induction by alcohol, liver damage, prescription drugs
- Aspartate amino transferase (AST) and alanine amino transferase (ALT)
  - Elevations indicate injury and death of liver cells
- Mean corpuscular volume (MCV)
  - Size may increase with heavy drinking (and other factors)

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Indirect Biomarkers

- Carbohydrate-deficient transferrin (CDT)
  - Transferrin is produced in liver and purpose is to transfer iron from intestines through blood to cells than need iron to function
  - Normal transferrin has carbohydrate side chains; when someone drinks heavily for 2 weeks the transferrin molecules may be lacking in carbohydrate residues in some of the terminal chains
  - Expressed in %CDT
  - 2.6% or higher is clinical cut-off for heavy drinking (>5 drinks per day for 2 weeks)
  - 95% sensitive and 93.3% specific

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Direct Biomarkers

- Most consumed alcohol is metabolized by oxidative processes in the liver, small amount is metabolized nonoxidatively, and about 1-2% is excreted in urine unchanged
  - Alcohol only detected in system for hours
    - Breath alcohol
    - Blood or serum ethanol
    - Ethyl alcohol in urine (about 7-12 hours)
  - EtG and EtS directly measure alcohol exposure or use as they are nonoxidated analytes of alcohol metabolism that can be measured up to 1-3 days
  - PEth can be measured for days to weeks

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ASAM Principles of Addiction Medicine, Sixth Edition

Cut-off Values for EtG and EtS

- Verifying abstinence (EtG>100 ng/mL, EtS>25 ng/mL)
- Some labs use higher cut-offs to minimize positive tests from incidental alcohol use (e.g., EtG>500, EtS>200 ng/mL)

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Cut-off Values for EtG and EtS

- A high positive (>1000 ng/mL) may indicate
  - Heavy drinking in the past day or two
  - Light drinking on the same day
- A low positive (500-1000 ng/mL) may indicate
  - Heavy drinking in the past 1-3 days
  - Light drinking in the past 24 hours
  - Recent intense incidental exposure in the past 24 hours
- A very low positive may indicate
  - Heavy drinking in the past 1-3 days
  - Light drinking in the past 12-36 hours

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Considerations Regarding EtG and EtS

- Specimen should be refrigerated
- Ethanol can be synthesized by Candida albicans and glucose
  - EtG (and not EtS) can be synthesized in vitro in presence of ethanol and E. Coli
- E. Coli contains glucuronidase which can hydrolyze EtG → lower levels of EtG
  - EtS is not sensitive to bacterial hydrolysis

Helander A, Olsson I, Dahl H. Postcollection synthesis of ethyl glucuronide by bacteria in urine may cause false identification of alcohol consumption. Clin Chem. 2007 Oct;53(10):1855-7. doi: 10.1373/clinchem.2007.089482. Epub 2007 Aug 23. PMID: 17717128.

Considerations Regarding EtG and EtS

- Use EtG in concert with EtS
- If EIA is used and the urine sample tests positive, the result should be confirmed by the more accurate GC/MS or LC/MS/MS procedures due to high rates of false positives on EIA.
- Hydration influences concentration of EtG and EtS, so important to look at urine creatinine concentration or SpGr

Helander A, Olsson I, Dahl H. Postcollection synthesis of ethyl glucuronide by bacteria in urine may cause false identification of alcohol consumption. Clin Chem. 2007 Oct;53(10):1855-7. doi: 10.1373/clinchem.2007.089482. Epub 2007 Aug 23. PMID: 17717128.

EtG Cut-offs for Hair

- Hair samples – cut 3 cm from root and this represents about 3 months of time based on hair growing about 1 cm per month
- Chemical processes for hair (e.g., coloring, perming, bleaching) can leach EtG metabolite out of hair
- EtG cut-off levels
  - <7 pg/mg – suggest no use or low use in the past 3 months
  - 7 to 30 pg/mg – suggest repeat alcohol consumption
  - >30 pg/mg suggest chronic and heavy use

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Phosphatidyl Ethanol (PEth)

- Direct serum biomarker
- PEth is a minor metabolite of ethanol, it is a phospholipid that is synthesized and stored in membranes of red blood cells
- PEth is detectable in blood within hours of heavy drinking, elimination half-life 4-12 days resulting in a window of detection of at least 3 weeks
- Measured in blood, can be capillary blood collected on filtered paper (easy collection, storage, and transport)

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Phosphatidyl Ethanol (PEth)

- Can be used to
  - Detect heavy drinking (e.g., 50 g/day of alcohol for several weeks; 14 g of alcohol in a std drink)
  - Can detect single heavy drinking episode for up to 12 days

- Use
  - PHMPs
  - Clinical programs?

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Considerations with Biomarkers

- Each biomarker may have different strengths and weaknesses
- May use biomarkers together to screen for alcohol problems
- Should not be used as a substitute for collecting history from patient and/or using a standardized instrument (e.g., AUDIT-C)
- Biomarkers have differing strengths and weaknesses, they are often used together, especially for screening for alcohol use problems.

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Alcohol Biomarkers

Biomarker	Screening for Heavy Drinking	Identify Relapse, esp to Heavy Drinking	Time to Return to Normal with Abstinence	Monitoring Abstinence
CDT	x	x	2-3 weeks	
EtG, EtS		x	1-3 days	x
GGT	x		2-4 weeks	
MCV	x		Up to several mos	
PEth		x	2-4 weeks	
Sensor Device		x	Continual	
SGOT/AST	x		2-4 weeks	
SGPT/ALT	x		2-4 weeks	

So what are next steps for AT?

- She admits drinking, suspect underreporting
- Monitoring
  - In clinic appointments, difficult to assess her via phone/telemed
  - Breathalyzers at visits
  - Add EtG/EtS to urine testing, possibly other biomarkers?
  - Weekly follow-up visits
- Level of care
  - Referred to IOP already, awaiting completion of alcohol withdrawal management
  - Inpatient withdrawal management?
  - Other higher level of care?

Questions/comments?