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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

Buprenorphine, Naltrexone, and the Liver

Should I ever be concerned?

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ECHO

DISCLOSURES

Speaker and planner disclosures

Speaker: I have no relevant financial disclosures.

Planner disclosures

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

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OBJECTIVES

Session objectives

1. Review the hepatic metabolism of buprenorphine and naltrexone and the burden of liver disease in OUD and AUD.
2. Separate the historical hepatotoxicity signals from the contemporary evidence at therapeutic doses.
3. Apply an evidence-based approach to LFT monitoring and dose adjustment in hepatic impairment.
4. Recognize the clinical scenarios that genuinely warrant concern or a change in management.

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BACKGROUND

Meet the liver

The body's central metabolic organ, and where most medications are processed

- Central metabolic organ: makes bile, albumin, and clotting factors, and stores glycogen.
- Biotransformation: Phase I oxidation, then Phase II conjugation, make drugs water-soluble.
- First-pass metabolism: oral drugs pass through the liver before reaching the circulation.
- Most medications are processed here, so liver function shapes drug levels and clearance.

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A FAIR QUESTION

Wait, buprenorphine and the liver?

Naltrexone's liver reputation is well known. Buprenorphine's? Not so much.

If "buprenorphine and hepatotoxicity" gives you pause, you are not alone.

This session aims to provide clarity on the topic.

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WHY IT MATTERS

The patients we treat usually have sick livers

60%

of a 666-patient buprenorphine cohort had RNA-confirmed hepatitis C

#1

Alcohol-associated liver disease is a leading and rising cause of US cirrhosis

MASLD

an increasingly common comorbidity in this population

Untreated OUD carries far higher mortality than any hepatic risk of these medications.

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Buprenorphine: pharmacology and uses

- Partial mu-opioid agonist with a ceiling effect on respiratory depression.
- Metabolized by CYP3A4 to norbuprenorphine, then cleared by the liver.
- Often combined with naloxone (poorly absorbed orally) as an abuse deterrent.

FORMULATIONS

TREATS

Opioid use disorder

Some formulations are also approved for chronic pain.

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BACKGROUND · 2 OF 2

Naltrexone: pharmacology and uses

- Pure mu-opioid antagonist with no agonist activity.
- Metabolized by dihydrodiol dehydrogenase to 6-beta-naltrexol, with minimal CYP450 involvement.
- Typically 50 mg daily orally, or IM 380 mg monthly.

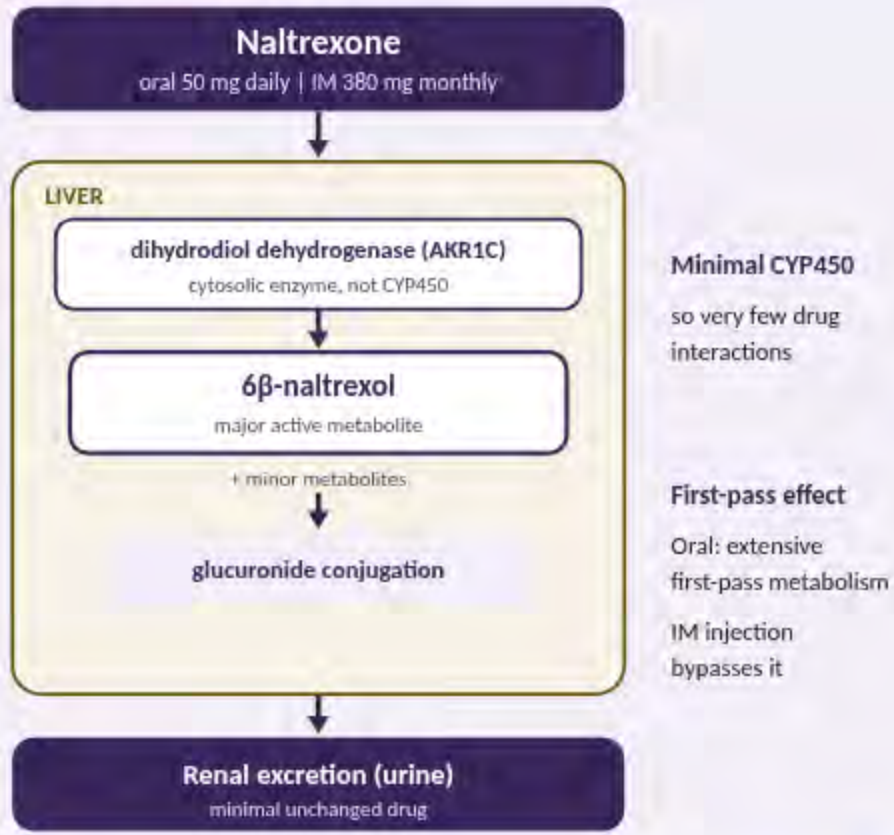
TREATS

Alcohol use disorder **Opioid use disorder**

OFF-LABEL

Methamphetamine use disorder, compulsive and hypersexual behaviors, and binge-eating or bulimia.

HEPATIC METABOLISM



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PART ONE

Buprenorphine and the liver

CONSULT 1

Case 1: opioid use disorder

47-year-old man

- Severe opioid use disorder, seeking medication for the first time.
- Chronic hepatitis C, never treated; ongoing alcohol use.
- CKD stage 2 (eGFR 78) and hypertension.
- Liver labs: AST 150, ALT 175 (elevated); bilirubin 0.9, albumin 4.0, INR 1.0, platelets 190k (preserved synthetic function).

CONSULT QUESTION

His transaminases are up with untreated hepatitis C. Is his liver too sick to start buprenorphine?

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WHERE THE CONCERN BEGAN

Where the concern began: Berson 2001

Berson et al., Journal of Hepatology 2001

13–50×

the ALT rise seen in patients after IV misuse

- Four former heroin users with chronic hepatitis C, on sublingual buprenorphine.
- After injecting it intravenously, ALT rose to 13 to 50 times normal; three became jaundiced.
- Stopping the IV injections led to prompt recovery, even when sublingual dosing continued.
- A companion paper traced the toxicity mainly to mitochondrial dysfunction at high concentrations. *(Berson et al., 2001)*

The signal was real, but it was about IV misuse and high intracellular levels, not sublingual therapy.

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THE OTHER SIDE

The residual concern, and the label

Rare therapeutic-dose cases

Isolated reports of acute hepatitis at conventional sublingual doses, usually with HCV co-infection (Herve 2004; Zuin 2009).

What the FDA label says

A spectrum from asymptomatic transaminase elevation to rare hepatic failure. Baseline and periodic LFTs are recommended.

What LiverTox concludes

Clinically apparent injury usually, though not always, follows misuse or IV administration of sublingual tablets.

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THE EVIDENCE

The reassurance: the START trial

Saxon et al., Drug Alcohol Depend 2013 · NIDA Clinical Trials Network

1,269

patients randomized to buprenorphine/naloxone vs methadone

- Multisite randomized trial across 8 opioid treatment programs, with serial liver panels through 24 weeks.
- **No evidence of liver injury** with either medication over 6 months.
- Built specifically to answer the hepatotoxicity question as buprenorphine prescribing expanded to patients with liver disease.

Local note: led by Andrew Saxon at VA Puget Sound / University of Washington.

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HIGHER-RISK GROUPS

Reassurance across higher-risk groups

- **HIV / HCV cohort (n=666).** ALT, AST, and bilirubin were rarely elevated on buprenorphine; HIV, HCV, or co-infection raised risk and may warrant closer monitoring. *(Tetrault et al., 2016)*

- **Adolescents and young adults.** An exploratory analysis found no evidence of buprenorphine hepatotoxicity, regardless of hepatitis C status. *(Bogenschutz et al., 2010)*

- **LiverTox synthesis.** Across studies, ALT elevations on buprenorphine were minimal and no greater than with methadone. *(NIDDK LiverTox)*

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THE PRACTICAL NUANCE

When the liver is already impaired

Nasser et al., Clin Pharmacokinet 2015

Pharmacokinetics

Moderate to severe impairment raises exposure to both buprenorphine and naloxone two to threefold.

The naloxone problem

Naloxone is cleared even less efficiently, sharply raising the naloxone-to-buprenorphine ratio; this can blunt buprenorphine's effect and worsen tolerability.

Product choice

The combination product is not recommended in severe impairment and may be inappropriate in moderate impairment.

Practical approach

Use the mono-product for induction; in severe impairment, halve the dose and double titration intervals.

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PUTTING IT TO WORK

LFT monitoring: optimal versus practical

Following PCSS-MOUD guidance · PCSS LFT monitoring guidance (Saxon)

Optimal

- Baseline: transaminases, bilirubin, PT/INR, albumin.
- Hepatitis B and C panels if serostatus is unknown.
- Monitor periodically; semi-annual is usually enough.

Practically

- Often impractical in urgent or brief withdrawal.
- Test first when you can, to avoid mislabeling later.
- START: serious injury rare, rises mostly tied to hepatitis, not buprenorphine.

Cannot test first? The data support starting now and checking liver tests when you can.

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RESOLUTION

Case 1: plan and outcome

- Empowered by the START trial, we proceed despite the elevated transaminases.
- Start a high-dose, non-overlapping buprenorphine induction.
- Increase liver monitoring given his untreated hepatitis C.

Outcome: he does great and is now in early remission from opioid use disorder.

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PART TWO

Naltrexone and the liver

CONSULT 2

Case 2: alcohol use disorder

58-year-old man

- Severe alcohol use disorder, wants to stop drinking.
- Alcohol-related cirrhosis, decompensated by ascites; CKD stage 3b (eGFR 38).
- Labs: bilirubin 3.1, albumin 2.4, INR 1.6, platelets 85k; AST 120, ALT 55.

CONSULT QUESTION

Is naltrexone safe to start with decompensated cirrhosis?

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WHERE IT CAME FROM

Where naltrexone's reputation came from

~300

mg per day, about 5 times the standard dose, used in the original studies

- 1980s studies in non-addiction populations, such as obesity, used high doses. *(Pfohl et al., 1986)*
- These produced reversible, asymptomatic transaminase elevations.
- That triggered an FDA boxed warning, later extrapolated to standard therapeutic doses.

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THE REVERSAL

The boxed warning is gone

July 2013: the FDA removed the boxed warning on naltrexone hepatotoxicity.

- Driven by accumulating safety data in alcohol- and opioid-dependent patients, including those with HCV and HIV. *(Vagenas et al., 2014)*
- At standard doses, naltrexone does not raise ALT or AST, and in some studies the enzymes actually fell.

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MODERN DATA

Modern data: safe even in cirrhosis

Thompson et al., JHEP Reports 2024

3,285

patients with cirrhosis started on naltrexone

- **No cases met criteria for drug-induced liver injury;** no deaths or decompensations were attributed to the drug.
- Judged safe across both compensated and decompensated cirrhosis.
- A 2025 review concludes the hepatotoxicity concern has been disproven, yet naltrexone stays underused. *(Kee et al., 2025)*

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SUPPORTING DATA

Naltrexone in decompensated cirrhosis

Thompson et al., 2024

- 31% had prior decompensation: ascites, varices, or encephalopathy.
- 15% were Child-Pugh class B or C; 6% had bilirubin ≥ 3.
- No DILI by RUCAM, and no decompensation or death attributed to naltrexone.

Jahagirdar et al., 2024

- Decompensated alcohol-associated cirrhosis cohort.
- Naltrexone associated with about 17% lower mortality.
- Fewer AKI, spontaneous bacterial peritonitis, and HCC events.
- Treating AUD itself improves survival in alcohol-related cirrhosis.

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REFERENCE

Calculating the Child-Pugh score

Measure	1 point	2 points	3 points	Case 2
Total bilirubin (mg/dL)	<2	2-3	>3	3.1 = 3 pts
Albumin (g/dL)	>3.5	2.8-3.5	<2.8	2.4 = 3 pts
INR	<1.7	1.7-2.3	>2.3	1.6 = 1 pt
Ascites	None	Mild to moderate	Severe or refractory	Present = 2 pts
Encephalopathy	None	Grade 1-2	Grade 3-4	None = 1 pt

Class A: 5-6 · Class B: 7-9 · Class C: 10-15 · Case 2 total: 10 → Child-Pugh Class C

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CLINICAL GUIDANCE

Naltrexone: considerations and contraindications

Contraindications

- Acute hepatitis or acute liver failure.
- Current or recent opioids, or acute withdrawal.
- Known hypersensitivity to naltrexone.

Child-Pugh C: a shared decision

- Class C is a small subset not reported separately; data are limited.
- Weigh benefits of AUD treatment against the paucity of evidence.
- Partner with hepatology; document shared decision-making.

Dosing consideration: favor IM injection (bypasses first-pass) or start oral low at 25 mg to minimize hepatic exposure. *(Diaz et al., 2025)*

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RESOLUTION

Case 2: plan and outcome

- After a shared, patient-centered discussion, he starts oral naltrexone 25 mg daily.
- Close LFT monitoring showed no elevation or evidence of DILI.
- Co-managed with hepatology throughout.

Outcome: he abstains from alcohol and is now listed for liver transplant.

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IN PRACTICE

Practical monitoring and red flags

Routine

- Baseline and periodic LFT monitoring with known liver disease.
- Provider variability exists in obtaining LFTs when initiating naltrexone.
- Consider deferring naltrexone if LFTs are greater than 5× ULN.

Red flags: stop and investigate

- Hepatocellular pattern, jaundice, or symptoms.
- Hy's law: ALT over 3× ULN with bilirubin over 2× ULN.
- Work up other causes (viral, alcohol, other drugs) before blaming the medication.

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DECISION AID

So, should I be concerned?

Clinical scenario	Buprenorphine	Naltrexone (PO / XR)
Normal LFTs or mild elevation	Proceed; safe.	Proceed; safe.
HCV / HIV ± elevated enzymes	Proceed; monitor more closely.	Proceed; safe.
Compensated cirrhosis	Proceed; consider mono-product.	Proceed; safe.
Severe / decompensated (Child-Pugh C)	Mono-product, halve dose, slow titration.	Use with caution; emerging data may support safety.
Active IV misuse	The real hepatotoxic setting; reinforce harm reduction.	Not applicable (antagonist).

The riskiest choice here is the one not listed: not treating.

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SUMMARY

Take-home points

1. Both drugs' liver reputations come from special circumstances: IV misuse for buprenorphine, high-dose trials for naltrexone, not standard therapy.
2. Randomized and large cohort data show no meaningful hepatotoxicity at therapeutic doses, even in HCV, HIV, and cirrhosis.
3. In severe hepatic impairment buprenorphine is safe but may need to be adjusted (mono-product, lower dose).
4. Naltrexone should be used in compensated cirrhosis and may be safe in decompensated Child-Pugh C (consider IM, lower dose).
5. Optimal vs. practical lab monitoring may vary; don't let mild elevations stop treatment.
6. **The riskiest choice is not treating.**

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- FDA decision (July 2013) removing the boxed warning on naltrexone hepatotoxicity.

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Thank you

Questions and discussion

CONNECT TO MEDICATIONS

Washington State

Washington Recovery Help Line -MOUD Finder (can search my medicine type)
https://search.warecoveryhelpline.org/

Washington Telebuprenorphine Hotline (fact sheet pdf attached)
https://doh.wa.gov/community-and-environment/opioids/wa-telebuprenorphine-hotline
206-289-0287

Out of State

FindTreatment.gov - SAMHSA (can search by medication type)
https://findtreatment.gov/locator

Ideal Option - Washington, Oregon, Alaska, Idaho, Montana, North Dakota, New Mexico, Maryland, and Arkansas
Ideal Option: Virtual Clinic Now Open

Patient Use Disorder Identification

DSM-5

Criteria for DSM-5 checklist for patient and with DSM-5 codes (pdf attachment)

12-Step Related

AA - Is AA for you? (self-assessment)
https://www.aa.org/self-assessment

NA - Am I an Addict (pamphlet)
https://na.org/wp-content/uploads/2024/05/EN3107-IP-7-English.pdf

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WA Telebuprenorphine Hotline

Fast and Low-Barrier Opioid Treatment

The Washington Telebuprenorphine (Telebupe) Hotline is a statewide telehealth program providing low-barrier access to buprenorphine, a medication for opioid use disorder (MOUD), to anyone in WA ages 13+ years, including pregnant people. The hotline provides a direct connection from crisis intervention to sustained care to help address Washington's opioid and fentanyl crisis.

No-cost visits - No insurance required - Referrals for long-term care

- **Call the hotline any day of the week from 9 AM-9 PM -** audio or video available
- **Same-day telehealth visit*** with a trained emergency medicine doctor
- **Prescription sent to local pharmacy**
- **Linkage-to-care coordinators** connections to ongoing treatment and support

*Compliant with WA & federal telehealth regulations; DEA-registered providers may prescribe buprenorphine without an in-person visit.

(206) 289-0287
7 days a week, 9:00 AM-9:00 PM

Spread the Word

Share hotline promotional materials with your community.

Give clients the hotline number or call together if they request that support.

Bridge treatment access gaps

Integrate the hotline into your workflow. Include the hotline number on your materials, such as discharge or follow-up plans.

Partner with us

Reach out with questions about our service or ideas on partnering with us.

Fill out the referral partner form to become an organization that receives referrals from the hotline.

Contact WA Telebupe: telebupe@uw.edu **or** learn more at our website

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Client Name ID: _____ Date Completed:_____/_____/_____
Chart #: _____ month day year

Check one Alcohol or Drug Category for Which This Form is Being Filled Out (use a different form for each drug)

___ Alcohol Use	___ Cannabis Use	___ Hallucinogen Use: Phencyclidine (LSD)	___ Hallucinogen Use: Other Hallucinogen
___ Inhalants Use	___ Opioid Use	___ Sedative, Hypnotic, Anxiolytic **Use**	___ Stimulant Use: Amphetamines
___ Stimulant Use: Cocaine	___ Stimulant Use: Other	___ Tobacco Use	Other Substance Use (or ___ unknown)

Past Alcohol or Drug Use Questions

The following statements are about your alcohol or drug use over the *past 12 months.* Please check *YES* for those statements that describe your drinking or drug use during the past 12 months, and check *NO* for those statements that are not true for you.

	YES	NO
1. **In the past 12 months,** I often used alcohol or drugs in large amounts over longer periods of time than I intended.		
2 **In the past 12 months**, I often wanted or tried to cut down or **control** my alcohol or drug use.		
3. **In the past 12 months,** I spend a lot of time either (a) using alcohol or drugs, (b) in activities trying to obtain alcohol or drugs, or (c) recovering from the effects of my drinking or drug use.		
4. **In the past 12 months,** I gave up or reduced my involvement in important social, occupational, or recreational activities because of my alcohol or drug use.		
5. **In the past 12 months,** I continued to use alcohol or drugs despite knowing that it likely caused or made worse psychological or physical problems I had (for example, continued drinking or drug use knowing it was making my ulcer or depression worse).		
6. **In the past 12 months,** I found I needed greater amounts of alcohol or drugs than I use to in order to feel intoxicated or to get a desired effect, **OR** I got much less of an effect by using the same amount of alcohol or drugs as in the past.		
7. **In the past 12 months,** I experienced withdrawal symptoms when I tried to cut down or stop my drinking or drug use **OR** I drank alcohol or used drugs to relieve or avoid withdrawal symptoms. **IF YES, PLEASE DESCRIBE YOUR WITHDRAWAL SYMPTOMS:** _____ _____		
8. **In the past 12 months**, my continued alcohol or drug use resulted in my not fulfilling major obligations at work, school, or home (for example, repeated absences or poor performances at work or school; neglecting my children or home).		
9. **In the past 12 months,** I repeatedly used alcohol or drugs in situations that were physically hazardous (for example, driving a car or operating machinery).		
10. **In the past 12 months,** I have experienced strong desires, urges, or cravings to use alcohol or drugs.		
11. **In the past 12 months,** I continued to use alcohol or drugs despite having persistent or recurrent social or interpersonal problems caused or made worse by the effects of my drinking or drug use (e.g., arguments with friends or family about my drinking or drug use or physical fights).		

DSM 5 Drug Classes (part 2 for trainees)

- **Alcohol**
- **Caffeine**
- **Cannabis**
- **Hallucinogens**
  - **Phencyclidine**
  - **Other hallucinogens**
- **Inhalants**
- **Opioids**
- **Sedatives, hypnotics, or anxiolytics**
- **Stimulants**
- **Tobacco**
- **Other (or unknown)**

For some drug classes, you can use the class name in the diagnosis, rather than the specific substance. For example, for someone who uses cocaine, you would not use Stimulant Use Disorder rather you would use Cocaine Use Disorder. However, for Xanax it would be better to say Anxiolytics Use Disorder.

Severity Coding:
Mild; 2-3 symptoms endorsed
Moderate; 4-5 symptoms endorsed
Severe; 6 or more symptoms endorsed

Specifiers:

- **Early Remission: No symptoms except cravings (item 10 in checklist) for at least 3 months but less than 12 months.**
- **Full remission: No symptoms except cravings (item 10 in checklist) for at least 12 months.**

Note: Withdrawals (item 7) are not considered a symptom for hallucinogens or inhalants as it has not been established that they occur. The severity categories remain the same, however.

Note: For substances medically prescribed and taken in compliance with medical prescriptions: Tolerance and withdrawals are not considered symptoms if they occur solely under appropriate medical supervision.

Disorder	DSM 5 Code (Mild 2-3 Symptoms)	DSM 5 Code (Moderate 4-5; Severe ≥ 6 Symptoms)
Alcohol Use Disorder	305.00	303.90
Cannabis Use Disorder	305.20	304.30
Hallucinogen Use Disorder Phencyclidine (LSD)	305.90	304.60
Hallucinogen Use Disorder Other Hallucinogen	305.30	304.50
Inhalant Use Disorder	305.90	304.60
Opioid Use Disorder	305.50	304.00
Sedative, Hypnotic, Anxiolytic Use Disorder	305.40	304.10
Stimulant Use Disorder Amphetamine-type	305.70	304.40
Stimulant Use Disorder Cocaine	305.60	304.20
Stimulant Use Disorder Other	305.70	304.40
Tobacco Use Disorder	305.1	305.1
Other/Unknown Substance Use Disorder	305.90	304.90