New Psychiatric Medications and Clinical Pearls

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Disclosures

No disclosures or conflicts of interest to report

Learning Objectives

- Increase familiarity with newer antipsychotics and antidepressants
- Understand common actionable psychiatric side effects seen in primary care settings
- Differential between substance induced psychiatric disorders vs primary psychiatric disorders

Case Presentation

Michael Myers comes into your outpatient clinic for his annual primary care visit. He just turned 21 and is otherwise healthy, but in the last 6 months he's dropped out of college, moved back home, and stopped seeing his friends. His mother presents with him and is concerned that he's spending most of his time in his room and is not engaging with the family unless necessary. He used to come down for family dinners but now only eats pre-packed food in his room. You interview Michael alone and he confides that he has been in his room more because a group of people are after him, they watch him on the internet constantly, and they have been breaking into his house at night. He's concerned about being poisoned so he's stopped eating food that isn't sealed. You work in a very rural area and the wait time to see a psychiatrist is months. A preliminary lab work-up is all wnl. He denied any intent to harm himself and wants to avoid going to the hospital. A urine drug screen is negative. What do you start him on?

Choices

A) Olanzapine (Zyprexa)
B) Brexpiprazole (Rexulti)
C) Xanomeline/Trospium (Cobenfy)
D) Lurasidone (Latuda)
E) Clozapine (Clozaril)
F) I have no idea
G) I’m sending him to the emergency room

Antipsychotic Side Effect Profile

Generic	Brand	Parkins-onism	Prolactin elevation	Hypo-tension	Akathisia	Weight gain	Sedation	Prolonged QT	Anticholi-nergic	Other
Asenapine	Saphris	+	+	-	+	+	+	-	-	
Brexpiprazole	Rexulti	-	-	-	+	+	-	-	-	
Cariprazine	Vraylar	-	-	-	+	+	-	-	-	Possibly more effective for Negative symptoms
Iloperidone	Fanapt	+	-	+	+	++	-	++	-	
Lurasidone	Latuda	+	-	-	+	+	+	-	-	
Aripiprazole	Abilify	-	-	-	+	+	-	-	-	
Ziprasidone	Geodon	-	-	+	+	-	+	++	-	Must be taken with 500 cal meal
Xanomeline / Trospium	Cobenfy	-	-	-	-	-	-	-	+	Other s/e include GI
Lumateperone	Caplyta	-	-	-	-	-	++	-	-	

Cobenfy

- FDA Approved for treatment of Schizophrenia in 2024
- First novel mechanism of action in decades
- MoA:
  - Xanomeline – M1/M4 muscarinc agonist. Works to modulate dopamine via stimulatory M1 receptor activation and inhibitory M4 activation, leading to decreasing presynaptic DA release in striatal regions. Centrally and peripherally acting.
  - Trospium – peripheral muscarinic antagonists. Blocks/mitigates the muscarinic receptor activation by Xanomeline reducing cholinergic s/e.

Cobenfy

- Side effects:
  - Anticholinergic OR muscarinic
  - Nausea, vomiting, dyspepsia, constipation, hypertension, dry mouth, abdominal pain, diarrhea, tachycardia
- Considerations:
  - Antimuscarinic drugs can increase anticholinergic s/e
  - CYP2D6 inhibitors may increase serum concentration of Xanomeline
  - CYP3A4 substrates (Buspirone) may be increased
  - Substrates of P-glycoprotine with narrow therapeutic (ie – digoxin, colchicine) may be increased
- Who is appropriate?
- What don’t we know?

Clozapine Pearls

- Still the winner for most effective tx in Schizophrenia
- Indicated after 2 failed antipsychotics
- Several side effects to watch out for in primary care setting:
  - Constipation
  - Myocarditis
  - Excessive salivation
  - Orthostasis
  - Weight gain
  - Neutropenia
  - Inc risk for seizure

Newer Long-Acting Antipsychotics

Generic	Brand	Frequency	Comments
Aripiprazole	Abilify Maintena	Monthly	
Aripiprazole	Abilify Asimtufi	Q 2 months	
Aripiprazole	Aristada	4 - 8 wks	
Zyprexa	Relprev	Monthly	Risk for post-injection delirium sedation syndrome
Risperidone	Consta	Q 2 weeks	
Risperidone	Uzedy	Q 2 months	
Paliperidone	Invega	Monthly	
Paliperidone	Trinza	Q 3 months	
Paliperidone		Q 6 months	

Is it the substances or something else?

Let’s say Michael Myers’ UDS did come back for cannabis

- How does this change what we do?

Cannabis and Psychosis

Table 1
Longitudinal studies in the general population about the role of cannabis as risk factor for schizophrenia.

Country in which the study was conducted	Study design	Number of participants	Follow up	Odd ratio (95% CI) (adjusted risk)
United States (Tien and Anthony, 1990)	Population based	4494	NA	2.4 (1.2–7.1)
Sweden (Andreasson et al., 1987; Zammit et al., 2002)	Conscript cohort	50,053	15 years	2.3 (1.0–5.3)
			27 years	3.1 (1.7–5.5)
The Netherlands (NEMESIS) (Van Os et al., 2002)	Population based	4045	3 years	2.8 (1.2–6.5)
Israel (Weiser et al., 2002)	Population based	9724	4–15 years	2.0 (1.3–3.1)
New Zealand (Christchurch) (Fergusson et al., 2003)	Birth cohort	1265	3 years	1.8 (1.2–2.6)
New Zealand (Dunedin) (Arseneault et al., 2002)	Birth cohort	1034	15 years	3.1 (0.7–13.3)
The Netherlands (Ferdinand et al., 2005)	Population based	1580	14 years	2.8 (1.79–4.43)
Germany (EDSP) (Henquet et al., 2005a)	Population based	2437	4 years	1.7 (1.1–1.5)
United Kingdom (Wiles et al., 2006)	Population based	8580	18 months	1.5 (0.55–3.94)
Greece (Stefanis et al., 2004)	Birth cohort	3500	NA	4.3 (1.0–17.9)

Antipsychotic Pearls

- Aside from Clozapine there is no clear winner for symptom management
- Metabolic syndrome is a high risk for most all second generation antipsychotics (SGAs)
  - Metformin should be offered prophylactically
  - GLP-1 can be offered if weight gain is already substantial
  - Metabolic monitoring at least annually
- Long acting injectables (LAIs) are superior to oral medications
- Motivational interviewing and psychoeducation for cannabis use
- TD can happen even with low dose SGAs
- Smoking cessation can have an impact on antipsychotic levels
- Consider what is important to the patient

Case Presentation

Pamela Voorhees is a 40 year-old female who presents for her annual physical. She has previously been healthy, with current PMH of HTN and an elevated BMI of 27. She's wants to talk more about depression treatments, which is new. She's noticing feeling down more, waking up earlier in the morning, having low energy, poor focus, and not wanting to see her friends as much as she use to. Chat GPT told her she might have depression and should start a medication. She'd like to start "one of those newer ones" she's seen on TV. She'd like to not gain much weight since she's already trying to lose some. Her lab work-up is wnl. What do you start her on?

A) Vortioxetine (Trintellix)
B) Bupropion (Wellbutrin)
C) Mirtazapine (Remeron)
D) I’m going to try to talk her into an older SSRI like Sertraline (Zoloft)

Newer Antidepressants

Generic	Brand	MoA	Contraindicated	Notes
Bupropion	Wellbutrin	Dopaminergic and adrenergic actions	- Seizures - Eating disorders - Use caution with AUD	Indicated for smoking cessation (nicotinic acetylcholine receptor antagonist)
Mirtazapine	Remeron	central presynaptic alpha$_2$-adrenergic antagonist, resulting in increased release of norepinephrine and serotonin; potent agonist of 5HT2, 5HT3, H1, peripheral a1 and muscarinic antagonist	- Use with caution if elevated BMI or other metabolic concerns	Some evidence for methamphetamine use disorder
Venlafaxine	Effexor	SNRI at higher dose > 225; lower doses function as SSRI		Consider in cases with chronic neuropathic pain
Desvenlafaxine	Pristiq	SNRI; Major metabolite of venlafaxine (Effexor)		Consider in cases with chronic neuropathic pain
Vilazodone	Viibryd	SSRI		
Vortioxetine	Trintellix	SSRI		
Zuranolone	Zurzuvae	GABA A Receptor Positive modulator		Only for postpartum depression

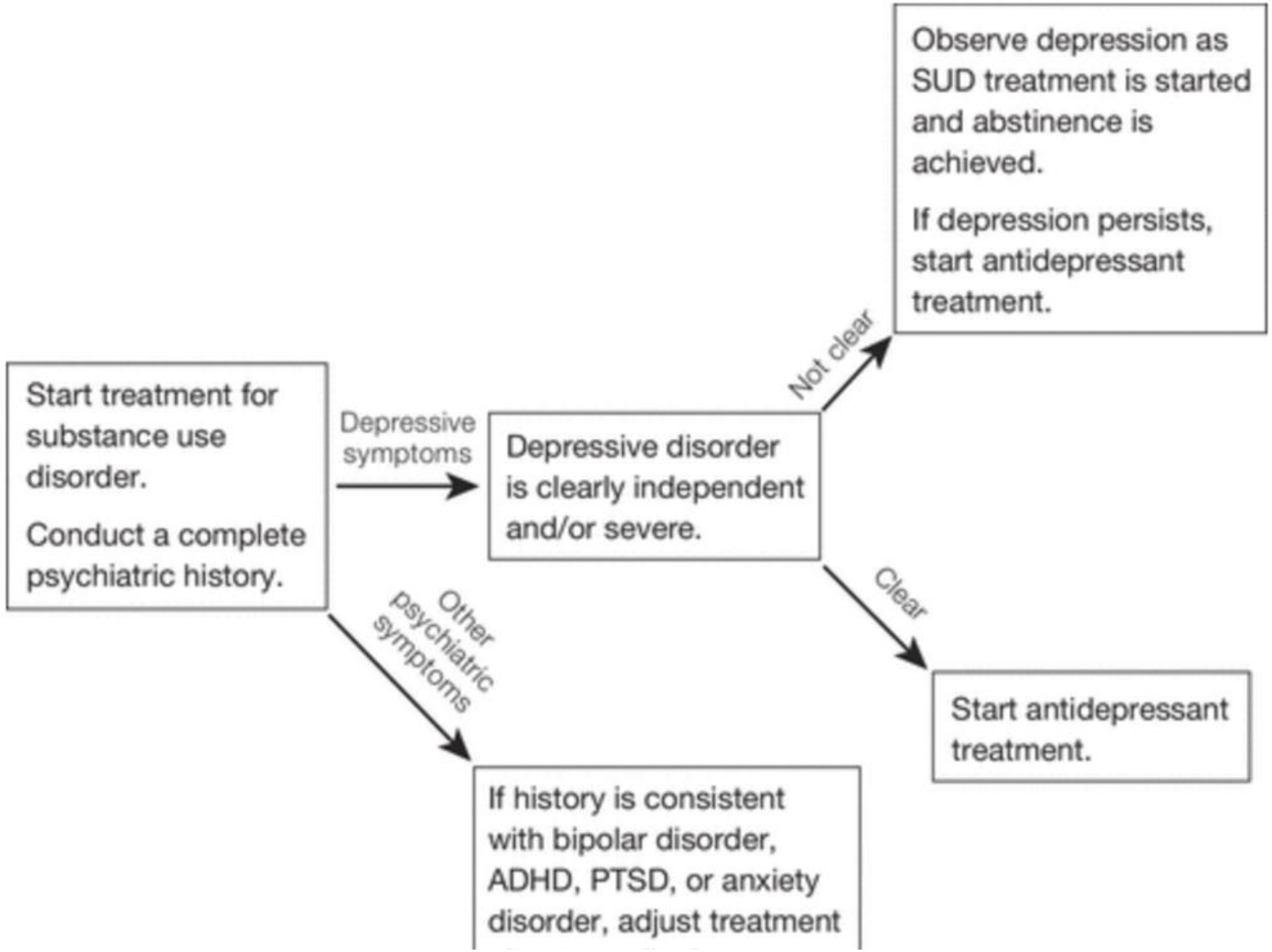
Newer Antidepressant S/E

Generic	Brand	Sedation	Postural hypotension	QT prolongation*	Hyponatremia risk	Sexual dysfunction	GI upset
Bupropion	Wellbutrin	-	-	-	-	-	+
Mirtazapine	Remeron	+++	+	-	-	-	+
Venlafaxine	Effexor	-	-	-	+	+++	+++
Desvenlafaxine	Pristiq	-	-	-	+	+++	+++
Vilazodone	Viibryd	-	-	-	+	++	+
Vortioxetine	Trintellix	-	+	-	+	+	+
Zuranolone	Zurzuvae	++					+

You find out later that Ms. Voorhees has been drinking heavily for the past 10 years after the death of her son in a tragic camp accident. She’s drinking three 750 ml bottles of wine a night. How does this change your management?

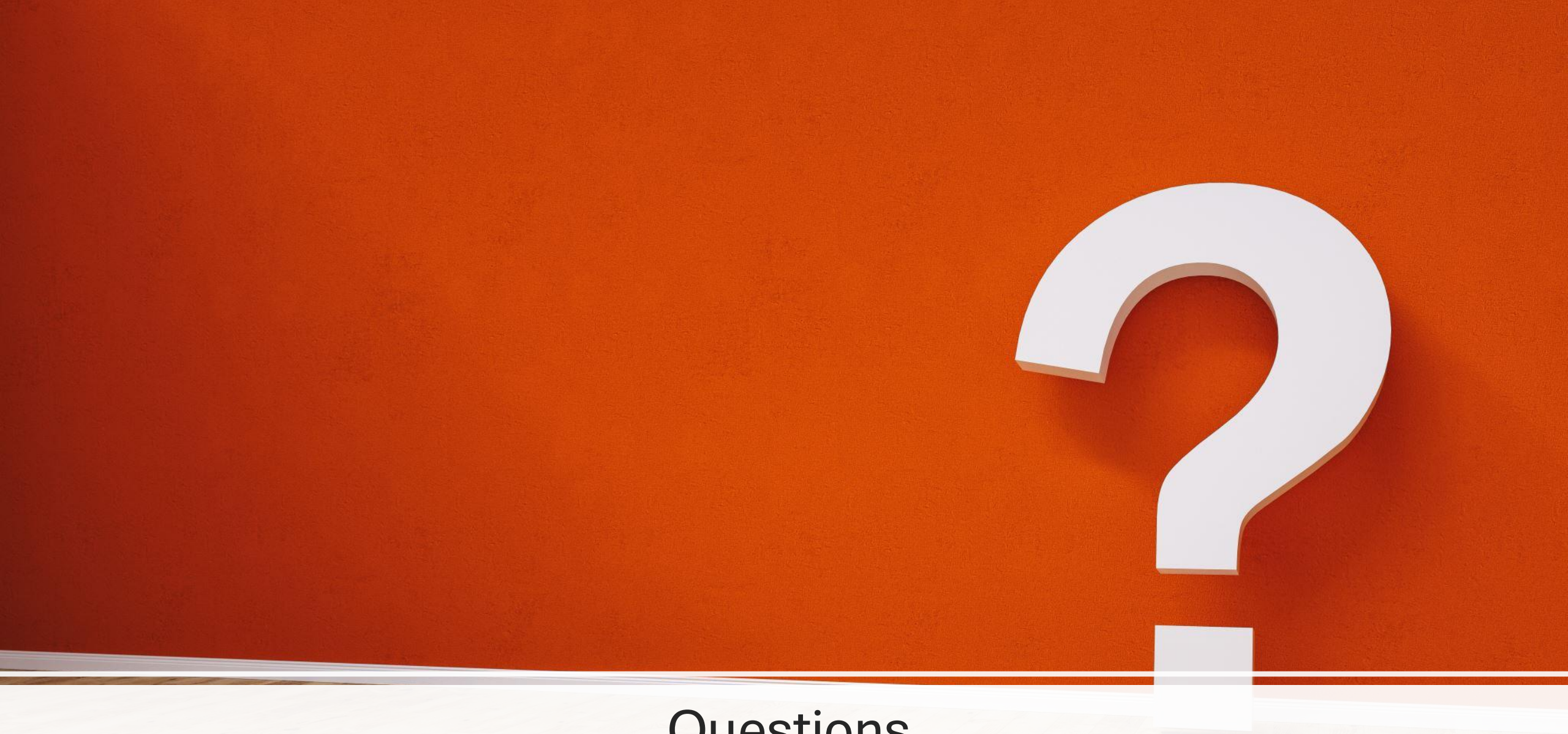
MDD or Substance Induced Depression?

- Thorough clinical assessment is key
  - Duration of symptoms and symptom onset?
  - Concurrent use of substances around symptom onset?
  - Symptom course during periods of prolonged abstinence?
  - Family history?
  - Personal history of mood symptoms?
  - Severity of current symptoms?
- Discussion with patient of risk/benefits of treatment


Start treatment for substance use disorder.
Conduct a complete psychiatric history.
Depressive symptoms
Depressive disorder is clearly independent and/or severe.
Not clear
Observe depression as SUD treatment is started and abstinence is achieved.
If depression persists, start antidepressant treatment.
Clear
Start antidepressant treatment.
Other psychiatric symptoms
If history is consistent with bipolar disorder, ADHD, PTSD, or anxiety disorder, adjust treatment

Antidepressant Pearls

- No particular antidepressant is superior to another as first line
  - Keep to SSRIs, Mirtazapine, Bupropion or SNRI as first line over MAOI or TCA
- Decision should be made with patient preference in mind
- Risks of treatment vs watchful waiting and psychotherapy can be discussed with patient, especially if concurrent SUD in play
- Avoid power struggles



Questions

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