Guideline-Driven Treatment of Mental Illnesses and Substance Use Disorders

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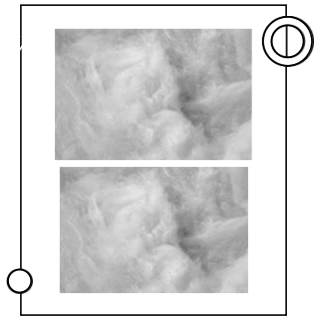

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Disclosures

Dr. Waters is a consultant with Janssen Pharmaceuticals. She will discuss all drugs without bias. All financial interests with ineligible companies (as noted) have been mitigated.

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Learning Objectives

- Describe first- and second-line treatment options for the following disease states:
  - Schizophrenia
  - Bipolar disorder
  - Alcohol use disorder
  - Opioid use disorder
- Identify where long-acting injectable medications fit into treatment guidelines for each disorder
- Apply clinical treatment guidelines to select optimal pharmacologic treatment for a patient diagnosed with these disorders

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Treatment of Schizophrenia & Schizoaffective Disorder

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Schizophrenia Treatment Background

- Antipsychotics are mainstay of treatment
- Non-adherence to antipsychotic treatment may occur in up to **50%** of patients with schizophrenia
  - **Impact of nonadherence:**
    - Risk of **relapse**
    - Risk of **rehospitalization** or requirement of **emergency care**
    - Inpatient **cost**
    - Risk of **substance use**
    - Risk of being a **victim of a crime**
    - Risk of **legal problems**
    - ↓ **Quality of life**
- Longer duration of untreated psychosis = **increased severity of symptoms** and may be more refractory to treatment

Kishimoto T, et al. *Schizophr Bull*, 2017;44:603-19
Haddad P, et al. *Patient Relat Outcome Meas*, 2014;5:43-62

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Schizophrenia and Nonadherence

- Wide variety of reasons for antipsychotic non-adherence in patients with psychiatric illness
  - Stigma
  - Attitude and insight about medications and/or mental illness
  - Feel better → discontinue
  - Cost
  - Comorbid conditions (i.e. substance use disorder)
  - Complex medication regimens
  - Adverse effects

Kishimoto T, et al. *Schizophr Bull*, 2017;44:603-19
Haddad P, et al. *Patient Relat Outcome Meas*, 2014;5:43-62

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Antipsychotic Mechanism of Action

- Simplified explanation:

First-generation antipsychotics (FGAs)	Second-generation antipsychotics (SGAs)
• "Typical" antipsychotics • Block post-synaptic D2 receptors in mesolimbic pathway • Other receptors may be affected and cause adverse effects	• "Atypical" antipsychotics • Block post-synaptic D2 and 5-HT2A receptors

Chokhawala K, et al. *StatPearls [Internet]*. 2023

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Antipsychotic Basics

Both FGAs and SGAs are considered first-line treatment

- Oral antipsychotics
  - Usually scheduled
  - May be used prn for breakthrough symptoms (ex: while hospitalized)
- Short-acting injectable antipsychotics
  - Used on prn basis for agitation or behavior that may cause harm to patient or others
- Long-acting injectable (LAI) antipsychtoics
  - Administered IM/SQ from every 2 weeks to every 6 months depending on medication

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Antipsychotic Agents

First-Generation Antipsychotics (FGAs)	Second-Generation Antipsychotics (SGAs)
Chlorpromazine	Aripiprazole*
Droperidol	Asenapine
Fluphenazine*	Brexpiprazole
Haloperidol*	Cariprazine
Loxapine	Clozapine
Perphenazine	Iloperidone
Pimozide	Lumateperone
Prochlorperazine	Lurasidone
Thioridazine	Olanzapine*,Δ
Thiothixene	Paliperidone*
Trifluoperazine	Quetiapine
	Risperidone*
	Ziprasidone

*Available in long-acting injectable formulation(s)
ΔAlso available in combination with samidorphan

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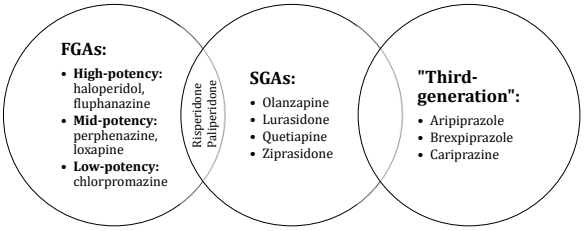
Antipsychotic Categories (Clinically)



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Schizophrenia Treatment Guidelines

	NICE 2014	APA 2020
First-line	SGA FGA	SGA FGA -Includes LAI FGAs or SGAs
Second-line	SGA FGA	SGA FGA Clozapine* -Includes LAI FGAs or SGAs
Third-line	Clozapine	Clozapine

*If significant risk of suicide or aggressive behavior remains "despite other treatments"

Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association, 2020;
Psychosis and schizophrenia in adults: prevention and management. National Institute for Health and Care Excellence, 2014

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Treatment of Schizoaffective Disorder

Treatment of **thought** symptoms: same as treatment for schizophrenia

Treatment of **mood** symptoms: same as treatment for bipolar disorder or major depressive disorder (depending on subtype)

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Antipsychotic Dose Titration & Discontinuation

- **Titration:**
  - Dose increased until acute symptoms improve or intolerable adverse effects (ADEs)
- **Discontinuation:**
  - No specific guidelines including for duration of taper
  - Dose usually decreased over several weeks to months to avoid withdrawal symptoms and risk of relapse
    - Withdrawal: GI upset, malaise, headache
      - Typically begins 2-3 days after abrupt discontinuation → may last 14 days

Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association, 2020

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Switching Between Antipsychotics

5 options for switching antipsychotics:

1. **Abrupt switch:** Abruptly discontinuing one antipsychotic and starting another
   - May lead to withdrawal symptoms if receptor affinity differs between agents
2. **Descending taper switch:** Starting new antipsychotic at full dose and slowly taper down existing antipsychotic
3. **Ascending taper switch:** Abruptly decreasing existing antipsychotic while slowly increasing dose of new antipsychotic
4. **Cross-titration:** Slowly tapering the existing antipsychotic while slowly increasing dose of new antipsychotic
5. **Plateau cross-taper switch:** Slowly increasing dose of new antipsychotic to therapeutic dose and then slowly tapering existing antipsychotic

Takeuchi H, et al. *Schizophr Bull.* 2017;43:862-71

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Antipsychotic Polypharmacy

- Lack of evidence supporting use of ≥ 1 antipsychotic
- Significantly increased risk of adverse effects
- May be appropriate in the following scenarios:
  - **≥ 3 failed trials** of antipsychotic monotherapy
  - **Cross-titration** of antipsychotic medications
  - **Augmentation of clozapine**
  - Treatment with an **antipsychotic + aripiprazole** to treat **hyperprolactinemia** induced by the initial antipsychotic

Lähteenvuo M, et al. *Drugs.* 2021;81:1273-84

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Schizophrenia Treatment Duration

- **First-episode psychosis:**
  - Continue antipsychotic for **≥ 1 year after adequate symptom control** to prevent relapse
    - 60-70% relapse rate within 1 year and 90% relapse within 2 years without maintenance treatment
  - "Functional remission" rates may be higher for pts who have antipsychotic discontinued or dose reduced during maintenance treatment
- **Multiple episodes:**
  - Maintain on antipsychotic for **2-5 years**
  - If multiple prior episodes or ≥ 2 episodes within 5 years → consider lifelong treatment

Kane JM, et al. *J Clin Psychiatry.* 2019;80
Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association, 2020

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Antipsychotic Adverse Effects

- Extrapyramidal symptoms
- Metabolic
- Hyperprolactinemia/sexual dysfunction
- Sedation
- Cardiovascular
- Seizures
- Anticholinergic effects

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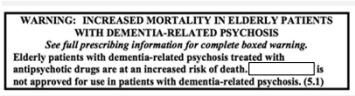
Antipsychotic Boxed Warning(s)

- Death in elderly patients with dementia-related psychosis



WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. [redacted] is not approved for use in patients with dementia-related psychosis. (5.1)

- Some SGAs have a warning for increased suicidal thoughts/actions in children, adolescents, young adults
  - Any medication with FDA-approval for major depressive disorder

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Extrapyramidal Symptoms (EPS)

- Group of potentially serious adverse effects associated with blockade of D_2 receptors in nigrostriatal pathway

EPS Type	Description
Dyskinesia	Repetitive, involuntary, purposeless body or facial movements Ex: Lip smacking, tongue movements, finger movements
Tardive dyskinesia	Occurs after longer duration of use, may be permanent
Akathisia	Extreme form of internal or external restlessness, inability to sit still, urge to move constantly
Dystonia	Muscle tension disorder → strong muscle contractions, unusual twisting of parts of body especially neck
Pseudoparkinsonism	Mask-like facies, resting tremor, cogwheel rigidity, shuffling gait, bradykinesia

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EPS Risk

High-potency (binding most specifically to D_2 receptors)

	High Risk	Medium Risk	Low Risk
First-Generation Antipsychotics	• Haloperidol • Thiothixene • Fluphenazine	• Perphenazine • Loxapine	• Chlorpromazine
Second-Generation Antipsychotics	• Paliperidone • Risperidone	• Asenapine • Cariprazine • Lurasidone	• Aripiprazole* • Brexpiprazole • Clozapine • Iloperidone • Olanzapine • Quetiapine • Ziprasidone

***Exception:** Aripiprazole associated with highest risk of akathisia

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Acute Dystonic Reactions

- Involuntary skeletal muscle contractions that usually occur within **24-96 hours** of drug initiation or dose increase
- Most commonly affects **facial** muscles:
  - Grimacing
  - Trismus (inability to open mouth/jaw)
  - **Oculogyric crisis:**
    - Bilateral involuntary elevation of visual gaze (seconds to hours)
- **Risk Factors:**
  - High potency FGAs, risperidone, paliperidone
  - Younger age
  - Males
  - Large muscle mass
  - Early in course of antipsychotic treatment

Lewis K, et al. *StatPearls[Internet].* 2023

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Tardive Dyskinesia

- Neurological disorder characterized by hyperkinetic movements
  - Occurs after prolonged dopamine blockade → may be irreversible
  - Movements due to *overstimulation* of supersensitive D2 receptors
  - May not be bothersome to the patient
- Abnormal Involuntary Movement Scale (AIMS) can help to detect symptoms
  - Pharmacists can become AIMS raters to improve monitoring and patient care

Butala N, et al. *Ment Health Clin.* 2021;11:248-53
Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association. 2020

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EPS Treatment & Prophylaxis

Akathisia
- Anticholinergic*
- Propranolol (30-120 mg/day divided)

Dystonia
- Anticholinergic* (IM preferred if acute dystonic reaction)

Pseudo-parkinsonism
- Dose reduction or switch
- Avoid anticholinergics

Tardive dyskinesia
- VMAT2 inhibitors (valbenazine, deutetrabenazine)
- Clonazepam

*Benztropine 1-2 mg/day or Diphenhydramine 25-50 mg/day

Lewis K, et al. *StatPearls[Internet].* 2023
Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association. 2020

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Metabolic Syndrome and Mental Illness

- >30% of general population in U.S. meet criteria for metabolic syndrome
  - Increased risk of CV disease, diabetes, mortality
  - Higher prevalence among people with mental illness:
    - **Schizophrenia:** 37-63%
    - **Bipolar disorder:** 30-49%
  - May be due to **medications, pathophysiology of disease**, or combination
- Study assessed **drug-naïve** patients with schizophrenia:
  - Increased **visceral adiposity** (despite no significant difference in total body fat)
  - Increased levels of **cortisol**
- **Smoking status**:
  - Patients with schizophrenia 3-4 times more likely to smoke

Toalson P, et al. *Prim Care Companion J Clinical Psychiatry,* 2004;6:152-8
Hert M, et al. *World Psychiatry,* 2009;8:15-22 Thakore JH, et al. *Int J Obes Relat Metab Disord,* 2002;26:137-41

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Antipsychotic-induced Weight Gain

- **All** SGAs can cause significant **weight gain, dyslipidemia**, and **insulin resistance**
  - Most occurs in first 6 weeks of treatment
  - Higher rates in antipsychotic-naïve patients
- Mechanisms of weight gain:
  - Increased food intake
  - Reduction in **resting energy expenditure**
  - Antagonism of **histamine, serotonin**, and dopamine receptors
  - **Insulin homeostasis** affected by serotonergic receptor blockade
  - Changes to neuropeptides associated with appetite control and energy metabolism
  - Genetic polymorphisms

Raben AT, et al. *Front Neurosci*, 2018;11:741
Dayabandara M, et al. *Neuropsychiatr Dis Treat*, 2017;13:2231-41 Pillinger T, et al. *The Lancet Psychiatry*. 2020;7:64-77

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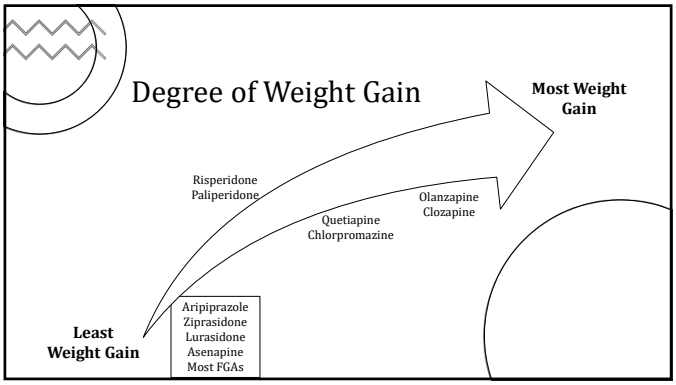

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Metabolic Monitoring Recommendations

Parameter	Baseline	Week 4	Week 8	Week 12	Every 3 Months Thereafter	Annually
Personal and family history of obesity, diabetes, dyslipidemia, hypertension or cardiovascular disease	x					x
BMI	x	x	x	x	x	
Waist circumference	x					x
Blood pressure	x	Every visit				
Fasting glucose, Hgb A1c	x			x		
Lipid panel	x			x (and every 5 years thereafter)		

American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care. 2004

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Metabolic ADE Management & Prevention

- **Non-pharmacologic:**
  - Behavioral interventions (diet, exercise)
  - Smoking cessation
  - Cognitive behavioral therapy
- **Pharmacologic:**
  - Consider antipsychotic with fewer metabolic ADEs for **initial treatment**
  - **Switch** to alternative antipsychotic
  - **Adjuvant medications**:
    - Weight loss: Metformin, topiramate, liraglutide, reboxetine
    - Lipid-lowering: Treatment per ACC/AHA guidelines, metformin

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
Dayabandara M, et al. *Neuropsychiatr Dis Treat*. 2017;13:2231-41 Kanagasundaram P, et al. *Front Psychiatry*. 2021;12:642403

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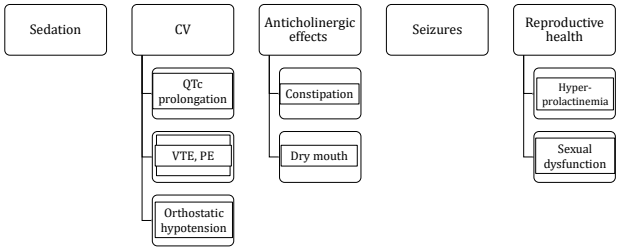
Additional Antipsychotic ADEs



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Audience Question 1

A 22-year-old patient with schizophrenia is being treated by a psychiatrist for the first time. Which of the following medications would be a first-line option for this patient?

A. Oral valproic acid
B. Long-acting injectable haloperidol
C. Oral clozapine
D. Long-acting injectable quetiapine

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Treatment of Bipolar Disorder

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Bipolar Disorder Treatment Goals

Acute Treatment Goals		Maintenance Treatment Goals
• Rapid control of mood, behavioral symptoms • Sleep restoration • Discontinue antidepressants if manic/hypomanic	Following 3 months of mood stability	• Functional improvement • Prophylaxis • Monotherapy if possible

2018 Guidelines for the management of patients with bipolar disorder. Canadian Network for Mood and Anxiety Treatments (CANMAT)

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Bipolar Disorder Medication Categories

Classic Mood Stabilizers	SGAs		Other Agents
Lithium Valproic acid (VPA) Lamotrigine Carbamazepine (CBZ)	**Available as long-acting injectable med**	Risperidone Paliperidone Olanzapine Aripiprazole	Oxcarbazepine Phenytoin (limited data) Not recommended: Topiramate, zonisamide, gabapentin, levetiracetam
	Not available as long-acting injectable med	Quetiapine Cariprazine Lurasidone Asenapine Clozapine	

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Acute Treatment: Manic, Hypomanic, and Mixed Episodes

	Manic/Hypomanic Episode Treatment	Mixed Episode Treatment
First-line[δ]	Lithium Valproic acid (VPA) Second-generation antipsychotic (SGA) Lithium + SGA VPA + SGA	VPA Carbamazepine (CBZ) SGA
Second-line	Alternative first-line agent CBZ Haloperidol	Same as second-line manic*

[δ]Monotherapy preferred in most cases BUT may utilize two agents especially with severe manic/mixed episodes or if psychotic features present

*Mixed features often predictor of nonresponse to lithium

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2018, National Institute for Health and Care Excellence (NICE) 2016, British Association of Psychopharmacology (BAP) 2016

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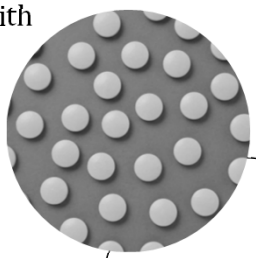
Bipolar Disorder with Psychotic Features

- Most common in manic episodes
- Antipsychotics recommended first-line
  - Monotherapy or in combination with mood stabilizer
- Consider electroconvulsive therapy (ECT)



2018 Guidelines for the management of patients with bipolar disorder. Canadian Network for Mood and Anxiety Treatments (CANMAT)

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Acute Treatment: Depressive Episodes

	Depressive Episode Treatment
First-line	Lithium Lamotrigine Quetiapine IR or ER* Lurasidone* Olanzapine/fluoxetine* Limited data: VPA, CBZ Bipolar I: Consider combination of lithium + VPA
Second-line	Alternative first-line agent Combination of 2 first-line agents (not 2 SGAs)

*FDA-approved for bipolar depression

Guidelines: WFSBP 2010, CANMAT 2018, NICE 2016, BAP 2016

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Antidepressants in Bipolar Disorder

- Controversial
- No demonstrated benefit in depressive symptoms
- **May precipitate a switch from depressive episode into a mixed or manic/hypomanic episode**
  - Mood change may not occur for over 10 weeks after antidepressant is initiated
  - If used → in combination with mood stabilizer

Berkol TD, et al. *Neurosciences (Riyadh).* 2019;24:45-52

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Maintenance Treatment

- Medications have differing abilities to **treat** and **prevent** manic and depressive episodes

	Maintenance Treatment
First-line	• Continuation of medication used to treat manic/depressive episode • Lithium • Lamotrigine (limited efficacy in preventing mania) • Quetiapine, olanzapine, LAI risperidone
Second-line	• Lithium + VPA or lamotrigine • CBZ • Alternative SGA

Guidelines: WFSBP 2010, CANMAT 2018, NICE 2016, BAP 2016

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Bipolar Disorder Treatment Duration

- **Duration of therapy is lifelong for all mood stabilizers (or SGA)** once a definitive diagnosis of bipolar disorder has been made unless:
  - Worsening mood or inadequate response
  - Change in diagnosis
  - Nonadherence
  - Adverse effects
  - Intolerance

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Antipsychotics in Bipolar Disorder

- Not all SGAs are equally effective
  - Some are **not recommended** as monotherapy for acute bipolar depression due to negative results in trials:
    - Aripiprazole
    - Ziprasidone

DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium.
a, level 1 evidence; a, level 2 evidence; c, level 3 evidence; -, level 4 evidence; ▲, level 1 negative evidence; ▲, level 2 negative evidence; ▲, level 3 negative evidence; n.d., no data. (Limited impact on treatment selection; ↓, minor impact on treatment selection; ↓↓, moderate impact on treatment selection; ↑↑↑, significant impact on treatment selection.
*Although monotherapies are listed above combination therapies in the hierarchy, combination therapies may be indicated as the preferred choice in patients with previous history of partial response to monotherapy and in those with psychotic mania or in situations where rapid response is desirable.
†Did not separate from placebo in those with index mania; no studies available in index depression.
‡No controlled trials, however, clinical experience suggests that it is a useful strategy.
§Did not separate from placebo on core symptoms of depression.
¶Divalproex and carbamazepine should be used with caution in women of childbearing age.

2018 Guidelines for the management of patients with bipolar disorder. Canadian Network for Mood and Anxiety Treatments (CANMAT)
Munoyer A. *Cureus.* 2016;8:e567 Gardner DM, et al. *Ann Gen Psychiatry.* 2013;12:1

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Antipsychotics in Bipolar Disorder

- SGAs Can improve manic symptoms within several days
  - Longer for depressive symptoms
- **Clozapine:** Not FDA-approved but may be used for resistant bipolar disorder
- Lower doses of SGAs required than for schizophrenia in many cases
- FGAs may be effective to treat acute mania however lack efficacy for maintenance therapy
- LAI antipsychotics not specifically mentioned in guidelines but used routinely

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Audience Question 2

A patient with bipolar disorder begins treatment with long-acting injectable aripiprazole to treat a depressive episode. Two weeks later, you notice that he is unable to stop pacing and cannot sit still when waiting to pick up his medication. What is the most likely explanation?

A. The patient is experiencing akathisia from aripiprazole
B. The patient has switched from a depressive episode to a manic episode
C. The patient is experiencing tardive dyskinesia from aripiprazole
D. The patient is agitated due to his diagnosis of bipolar disorder

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Treatment of Opioid Use Disorder & Alcohol Use Disorder

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OUD & AUD Treatment Background

- Focus on maintenance phase (not acute intoxication or withdrawal)
- Nonpharmacologic treatment also an option:
  - Pharmacologic treatment more effective than nonpharmacologic for OUD

Wakeman SE, et al. *JAMA Netw Open.* 2020;3:e1920622

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OUD & AUD Goals of Treatment

- **Long-term goal:**
  - Abstinence (??)
- **Short-term goals:**
  - Decrease in the number of **days** of use/drinking
  - Decrease in the number of **days** with **heavy use/drinking**
  - Decrease the **number of drinks/doses** per day
  - Minimize the physical, psychological, financial, and social harm

Stancliff S. *Baltimore (MD): Johns Hopkins University*, 2019
Taylor JL, et al. *J Gen Intern Med.* 2021;36:3810-19 Maremmani I, et al. *Int J Environ Res Public Health.* 2015;12:14828-41

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Harm Reduction

- Abstinence may not be possible for all patients
- Improve wellbeing including during active substance use
- Strategies to minimize harm to self or others:
  - **OUD:**
    - Syringe services
    - Teaching safe injection practices
    - Naloxone distribution programs
  - **AUD:**
    - Self-monitoring with breathalyzer
    - Count number of standardized drinks consumed
    - Avoid mixing alcohol with other substances

Stancliff S. *Baltimore (MD): Johns Hopkins University*, 2019
Taylor JL, et al. *J Gen Intern Med.* 2021;36:3810-19 Maremmani I, et al. *Int J Environ Res Public Health.* 2015;12:14828-41

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OUD Treatment Guidelines

	OUD Maintenance Treatment
First-line	Methadone Buprenorphine*/naloxone
Second-line	Naltrexone*

*Available in LAI formulation

Opioid Agonist Therapy (OAT) strongly preferred due to superior efficacy

Also sometimes called:
- Medication assisted treatment (MAT)
- Opioid replacement therapy (ORT)

American Society of Addiction Medicine, *The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update*
Canadian Medical Association, *Management of opioid use disorders: a national clinical practice guideline*, 2018

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OUD Treatment: Buprenorphine +/- naloxone

- **MOA:**
  - **Buprenorphine:** Partial mu opioid agonist, reduces cravings and withdrawal symptoms
    - May precipitate withdrawal in person currently taking full opioid agonist
  - **Naloxone:** Opioid antagonist, functions as abuse deterrent (if injected, snorted)

Common ADEs	Serious ADEs
Injection site reactions (implant) Constipation Nausea, vomiting, diarrhea Headache Somnolence, fatigue Insomnia	Hypotension Bowel obstruction Hepatic injury/liver failure Drug withdrawal

Buprenorphine. (2023). In Merative Micromedex [Electronic version].Merative US L.P.

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Buprenorphine Prescribing Considerations

- As of 2023, prescribers no longer required to hold X-DEA number (DATA-Waiver)
- Prescribed for at-home use
  - Can be prescribed via in-person or telehealth appointment

Buprenorphine. (2023). In Merative Micromedex [Electronic version].Merative US L.P.

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Buprenorphine Formulations

Formulation	Available Products
Sublingual	Buprenorphine/naloxone SL film (Suboxone®, Cassipa®) Buprenorphine/naloxone SL tablet (Zubsolv®)
Transdermal	Buprenorphine patch (Butrans®)
Buccal	Buprenorphine buccal film (Belbuca®) Buprenorphine/naloxone buccal film (Bunavail®)
Intradermal	Buprenorphine intradermal implant (Probuphine)
Subcutaneous	Long-acting injectable SQ buprenorphine (Sublocade®, Brixadi™)

Buprenorphine. (2023). In Merative Micromedex [Electronic version].Merative US L.P.

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OUD Treatment: Methadone

- **MOA:** Full opioid agonist
- **FDA-approved Indications:** Detoxification, OUD, pain (moderate to severe)
  - Schedule II
- **PK:**
  - Onset within hours --> duration 24-36 hours
  - Extensive hepatic metabolism: CYP3A4, CYP2B6, CYP2C19, CYP2C9, CYP2D6

Common ADEs	Serious ADEs
Hypotension Diaphoresis Constipation Nausea, vomiting Dizziness, sedation	QTc prolongation Respiratory depression Serotonin syndrome

Methadone. (2023). In Merative Micromedex [Electronic version].Merative US L.P.

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Methadone Prescribing Considerations

- Methadone cannot be prescribed outpatient for OUD
- Pts must participate in an Opioid Treatment Program (OTP) aka "methadone clinics"
- **Goal:** Achieve stable maintenance dose that suppresses withdrawal, reduces opioid cravings, and blocks effects of illicit opioids to eliminate or reduce elicit opioid use
- **Maintenance dosing:**
  - In most cases patients must obtain medication daily at the OTP
    - Initiate with 30-40 mg daily
    - Increase up to 80-120 mg daily
  - **Take-home dosing:**
    - Single take-home doses are approved on days OTP is closed (i.e. Sundays, holidays)

Methadone. (2023). In Merative Micromedex [Electronic version].Merative US L.P.

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AUD Treatment Guidelines

	AUD Maintenance Treatment
First-line	Naltrexone* Acamprosate
Second-line	Disulfiram
Alternative	Gabapentin Topiramate
Supportive Care	Thiamine

*Available in LAI formulation

American Psychiatric Association, *Practice guideline for the pharmacologic treatment of patients with alcohol use disorder*, 2018

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AUD Treatment: Naltrexone

- **MOA:** Mu-opioid antagonist
  - Blocks pleasurable effects of alcohol by decreasing dopamine release
  - May reduce cravings, reinforcing properties, experience of intoxication, heavy drinking
- **Contraindications:**
  - **Opioids use within 7 days (14 days if buprenorphine or methadone)**
  - Acute hepatitis or severe hepatic impairment

Common ADEs	Serious ADEs
Nausea, abdominal pain Arthralgia, myalgia Low energy Anxiety, nervousness Insomnia Rash (IM) Injection site reactions (IM)	Hepatitis, hepatotoxicity Opioid withdrawal

Naltrexone. (2023). In Merative Micromedex [Electronic version].Merative US L.P.

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Naltrexone Formulations

Formulation	Available Products
Oral	Generic (ReVia, Depade)
Intramuscular (long-acting injection)	Vivitrol®

- **Onset and Duration:**
  - **Oral:** 15-60 min onset, duration 24h
  - **IM:** 2-3 day onset, duration 4 weeks
- Continue treatment for 6 months to 1 year

Naltrexone. (2023). In Merative Micromedex [Electronic version].Merative US L.P.

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AUD Treatment: Acamprosate (Campral®)

- **MOA:**
  - NMDA receptor antagonist
  - Enhances GABA receptor activation and restores GABA/glutamate balance
  - May decrease cravings and alleviate negative reinforcement
- Dosed TID
  - Renal dose adjustments
- **Onset and Duration:**
  - Within 3-8 hours but **may take several days for full effect**

Common ADEs	Serious ADEs
Diarrhea Insomnia	Attempted and completed suicides

Acamprosate. (2023). In Merative Micromedex [Electronic version].Merative US L.P.

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AUD Treatment: Disulfiram (Antabuse®)

- **MOA:**
  - Blocks aldehyde dehydrogenase, causing the accumulation of acetaldehyde if alcohol is consumed
  - **Aversive agent:** Anticipation of unpleasant reaction:
    - Warmness, flushing of skin
    - Increased HR, palpitations
    - Decreased BP
    - N/V
    - SOB, sweating, anxiety, dizziness
    - Blurred vision
    - Confusion
- Abstinence must be goal
  - Pts must be h**ighly motivated** to remain abstinent, **have good judgment,** and not be **impulsive**

Disulfiram. (2023). In Merative Micromedex [Electronic version].Merative US L.P.

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AUD Treatment: Disulfiram (Antabuse®)

- Dosed once daily
- Rapid onset: Up to 12 hours for full effect
- **Contraindications:**
  - Psychoses, use of ethanol or metronidazole, severe myocardial disease
- **Warnings/Precautions:**
  - **MUST be alcohol free for 12 hours, or have a 0% BAC prior to starting, and for at least 14 days after stopping**
  - **AVOID oral and topical alcohol containing products** (mouthwash, OTCs liquid medications, hand sanitizers, etc.)

Common ADEs	Serious ADEs
Abnormal taste (metallic/garlic) Fatigue, drowsiness	Hepatotoxicity

Disulfiram. (2023). In Merative Micromedex [Electronic version].Merative US L.P.

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Audience Question 3

A patient with active AUD and OUD (in remission) is seeking treatment for the first time. Which of the following treatment options would be most appropriate for this patient?

Current Medications:

- Atorvastatin 40 mg po daily
- Gabapentin 300 mg po TID
- Methadone 80 mg po daily

A. Oral naltrexone
B. Long-acting injectable naltrexone
C. Oral acamprosate
D. Long-acting injectable acamprosate

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Recap

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First- and Second-Line Treatment

	Schizophrenia	Bipolar Disorder: Mania/Hypomania	Bipolar Disorder: Depression	OUD	AUD
First-line	FGA* SGA*	Lithium Valproic acid SGA* *Combination treatment*	Lithium Lamotrigine Quetiapine Lurasidone Olanzapine/ fluoxetine Other SGA*	Methadone Buprenorphine +/- naloxone*	Naltrexone* Acamprosate
Second-line	Alternative FGA or SGA*	Alternative first-line CBZ Haloperidol*	Alternative first-line *Combination treatment*	Naltrexone*	Disulfiram

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Guideline-Driven Treatment of Mental Illnesses and Substance Use Disorders

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University of Connecticut
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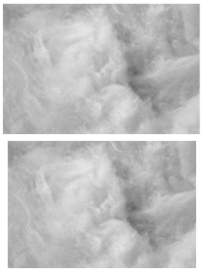

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