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Beyond psychosis: Use and Monitoring of Antipsychotics Across Mental Health Conditions

Disclosure

- Own and operate Bernard Wellness Initiative, LLC
- No financial disclosures
- I will discuss off-label uses of medications, but these are explicitly identified.

Audience Polling Question #1

What is an FDA-approved indication for aripiprazole?

- A. Autism-related irritability in 6- to 17-year-old patients
- B. Behavioral disturbances in 6- to 17-year-old patients
- C. Post-traumatic stress disorder
- D. Bipolar depression

Audience Polling Question #2

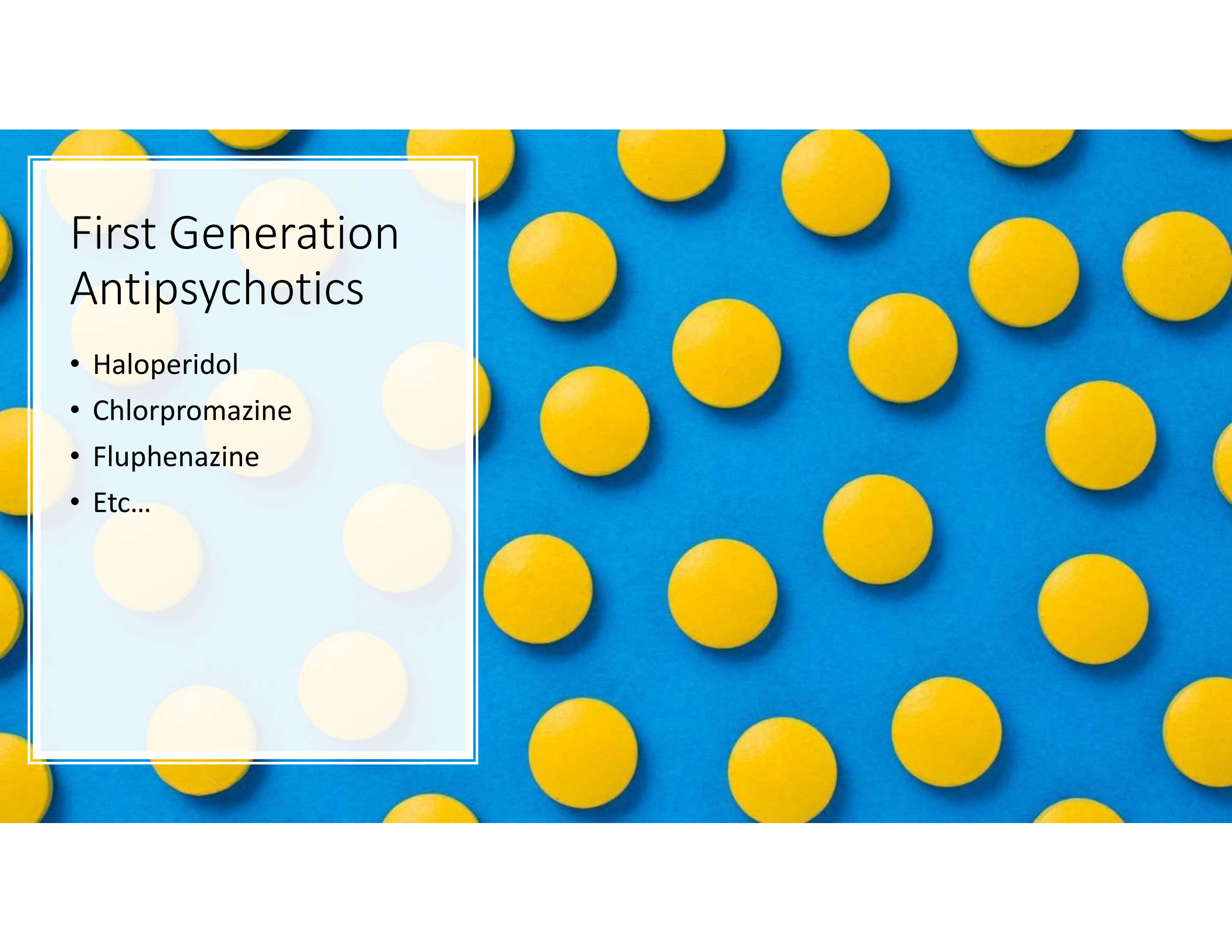
What is a considered a negative symptom of schizophrenia?

- A. Delusions
- B. Hallucinations
- C. Disorganized speech
- D. Reduced speech

Audience Polling Question

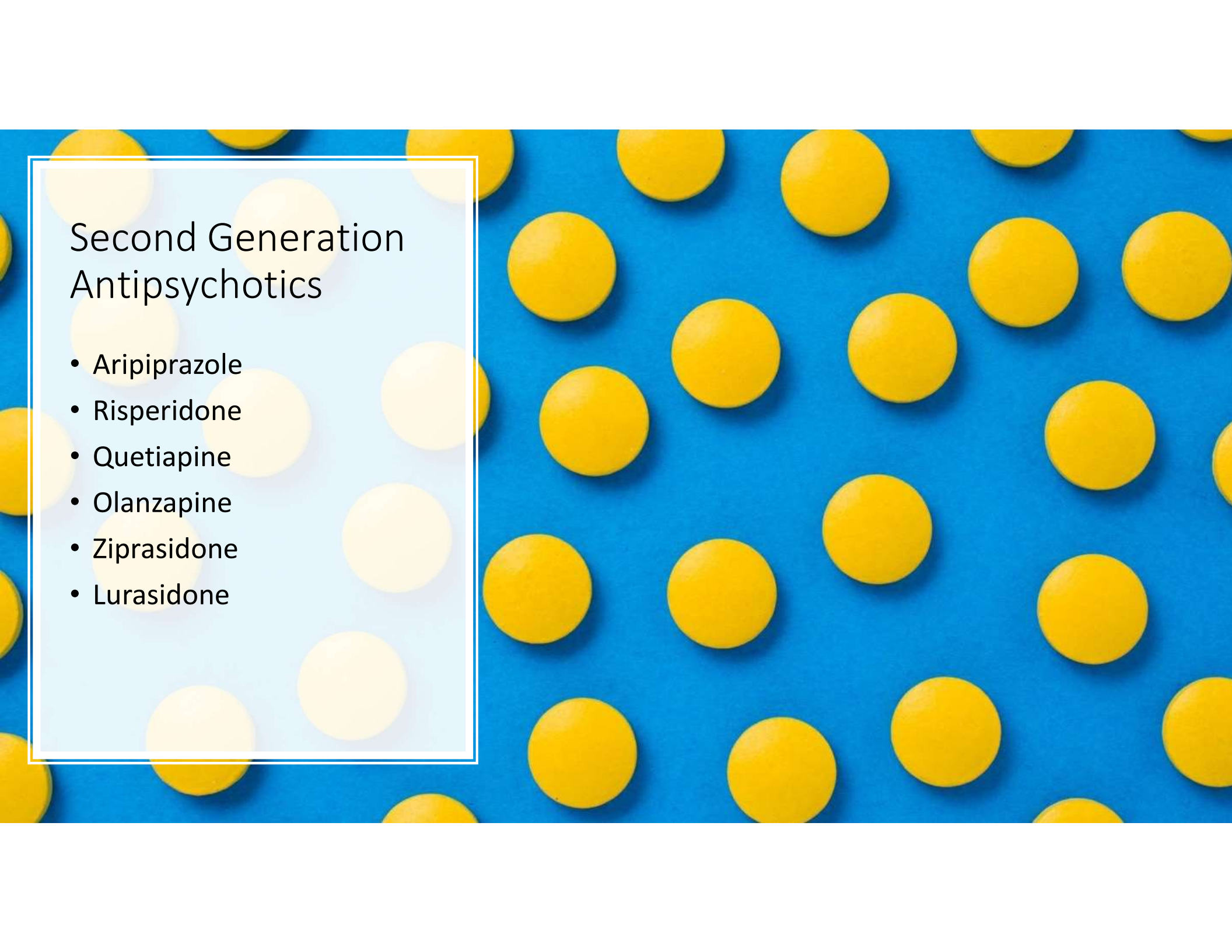
When should a patient who is taking olanzapine be started on metformin to address weight gain?

- A. After the patient has gained greater than 5% of his/her body weight
- B. After the patient has gained any amount of weight
- C. Before weight gain occurs
- D. After a 10% or greater increase in his/her triglycerides



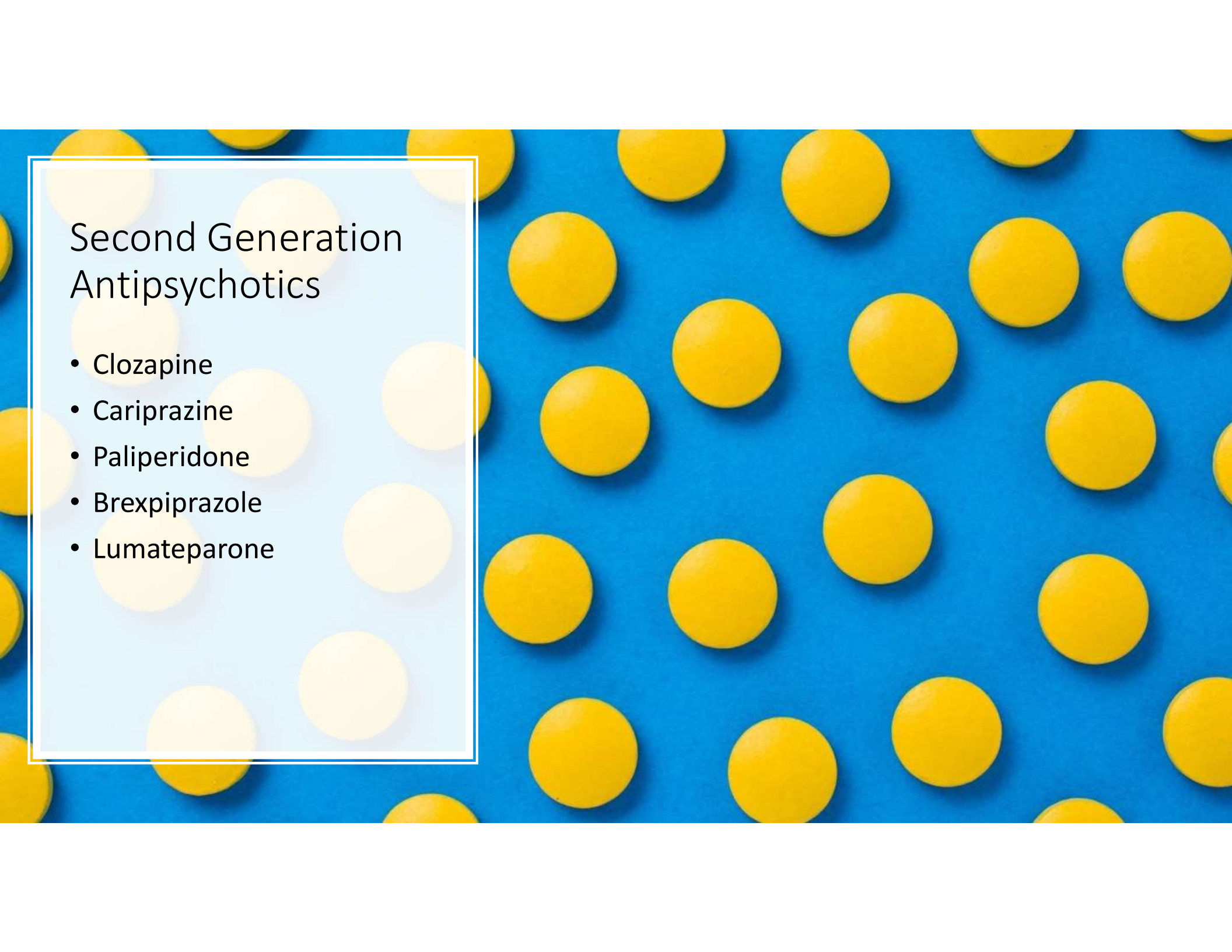
First Generation Antipsychotics

- Haloperidol
- Chlorpromazine
- Fluphenazine
- Etc...

The background of the slide is a top-down view of numerous yellow, circular pills scattered across a bright blue surface. The pills are arranged in a somewhat regular but not perfectly grid-like pattern, creating a textured, polka-dot effect. The lighting is even, highlighting the smooth, slightly reflective surface of the pills.

Second Generation Antipsychotics

- Aripiprazole
- Risperidone
- Quetiapine
- Olanzapine
- Ziprasidone
- Lurasidone



Second Generation Antipsychotics

- Clozapine
- Cariprazine
- Paliperidone
- Brexpiprazole
- Lumateparone

My average Tuesday:



9:00 am

- Diagnosis: Treatment-resistant unipolar depression, multiple suicide attempts
- Medications: aripiprazole, lamotrigine, escitalopram



10:00 am

- Diagnosis: Autism spectrum disorder, GAD, history of homicidal ideation
- Medications: aripiprazole, propranolol



11:00 am

- Diagnosis: Bipolar disorder II, ADHD
- Medications: lurasidone, methylphenidate XR, guanfacine XR

Will you see patients on antipsychotics?



Youth

- 10% of children with an exacerbation of a mental health condition are seen in a primary care setting



Adults

- 73% of depressed patients are treated in primary care
- <25% of adults will see a mental health professional in a given year



Elderly

- 20% of nursing home residents are treated with an antipsychotic

Duong, M. T. et al. (2021). Analysis. *Administration and Policy in Mental Health and Mental Health Services Research*, 48(3); Kroenke, K., & Unutzer, J. (2017). *Journal of General Internal Medicine*, 32(4); Cioltan, H. et al. (2017). *BMC Geriatrics*, 17(1)

FDA- Approved Conditions

- Schizophreniform disorders
- Bipolar disorder
 - Mania – acute or mixed
 - Agitation associated with acute mania
 - Bipolar maintenance or adjunct
 - Bipolar depression
- Major depression
 - Treatment resistant
- Autism-related irritability
- Tourette's disorder

Off-Label Uses

- Behavioral disturbances
 - Children and adolescents
 - Dementia
 - Parkinson's Disease
 - Lewy Body Dementia
- Impulse control problems
- PTSD
- OCD (adjunct to SSRIs)
- Severe treatment resistant anxiety
- Borderline personality disorder
- Other psychotic disorders

Real World Antipsychotic Prescribing



Youth

- Dx: ADHD, ODD, **disruptive behavior do**, bipolar do, depression, anxiety



Adults

- Dx: depression, bipolar do, schizophrenia



Elderly

- Dx: behavioral symptoms of dementia

Olfson, M. et al. (2012). *Archives of General Psychiatry*, 69(12)

Cioltan, H. et al. (2017). *BMC Geriatrics*, 17(1)



Antipsychotics in Children

- Highest in:
 - Medicaid vs. Private insurance
 - Foster care populations
- Often prescribed off label
 - 6% children and 12.9% adolescent visits were consistent with FDA indications
 - Most common – disruptive behavior disorder
- Most common additional psychotropic:
 - Stimulant
 - Antidepressant

Olfson, M. et al. (2012). *Archives of General Psychiatry*, 69(12)



Antipsychotics in Pregnancy

- Approximately 50% of pregnant women with bipolar disorder remain on antipsychotics during pregnancy
- Most commonly prescribed medications during pregnancy: aripiprazole and quetiapine

Park, Y. et al. (2017). *Psychiatric Services*, 68(11)

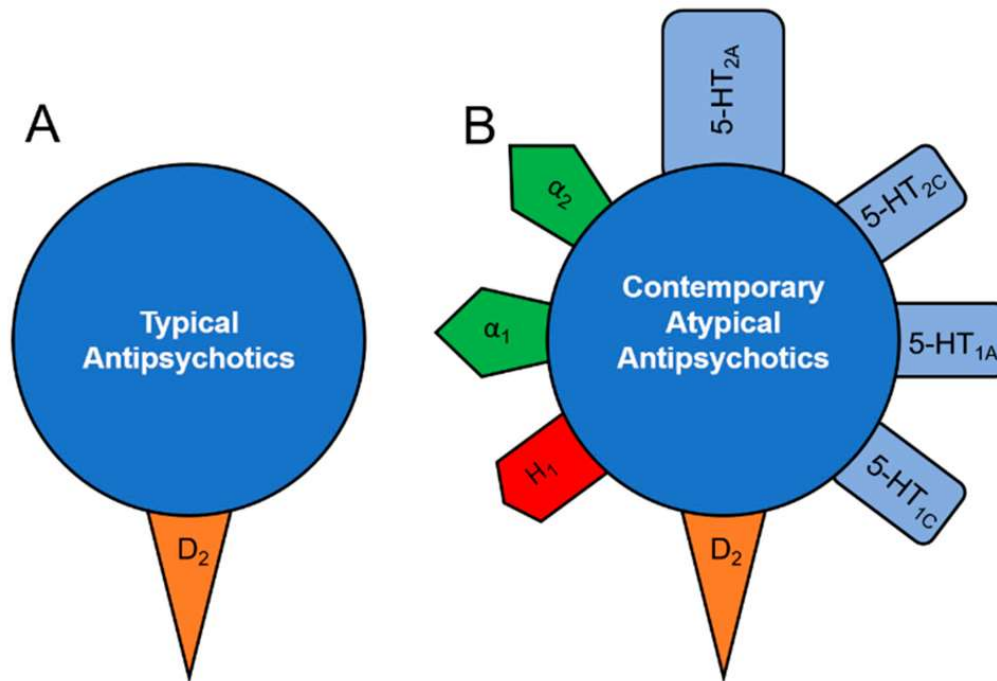


Antipsychotics in the Elderly

- FDA Black Box Warning on all Antipsychotics
 - Increased risk of mortality in elderly patients with dementia-related psychosis treated with antipsychotics
- Commonly given for agitation and aggression associated with dementia

Cioltan, H. et al. (2017). *BMC Geriatrics*, 17(1)
Rubino, A. et al. (2020). *JAMA Network Open*, 3(4)

Pharmacology



Symptoms of Schizophrenia

Positive:



Delusions



Hallucinations



Disorganized speech

Negative:



Flattened affect



Reduced speech



Lack of initiative



Mania may have positive symptoms

- Grandiosity or inflated sense of esteem
- Flight of ideas or racing thoughts
- Overtalkativeness or pressured speech
- Psychosis





Depression may have negative symptoms

- Flat affect or psychomotor retardation
- Reduced motivation or marked diminished interest or pleasure in daily activities
- Social isolation

FDA Indications for Aripiprazole

- Schizophrenia (> 13 yrs old)
- Mania – acute or mixed (> 10 yrs old)
- Acute agitation associated with schizophrenia or bipolar d/o (IM)
- Bipolar maintenance and adjunct
- Depression adjunct
- Autism-related irritability (6-17 yrs old)
- Tourette's disorder (6-18 yrs old)

FDA Indications for Risperidone

- Schizophrenia (> 13 yrs old)
- Other psychotic disorders
- Mania – acute or mixed (> 10 yrs old)
- Autism-related irritability (5-16 yrs old)
- Bipolar maintenance and adjunct

FDA Indications for Quetiapine

- Schizophrenia (> 13 yrs old)
- Acute mania (10-17 yrs old and adults) – monotherapy and adjunct to lithium or valproate
- Bipolar maintenance
- **Bipolar depression**
- Depression

FDA Indications for Olanzapine

- Schizophrenia (> 13 yrs old)
- Mania – acute or mixed (> 13 yrs old) monotherapy or as adjunct to lithium or valproate
- Acute agitation associated with schizophrenia or bipolar I mania (IM)
- Bipolar maintenance
- Bipolar depression (with fluoxetine)
- Treatment resistant depression (with fluoxetine)

FDA Indications for Ziprasidone

- Schizophrenia
- Acute agitation in schizophrenia
- Mania – acute or mixed
- Bipolar maintenance

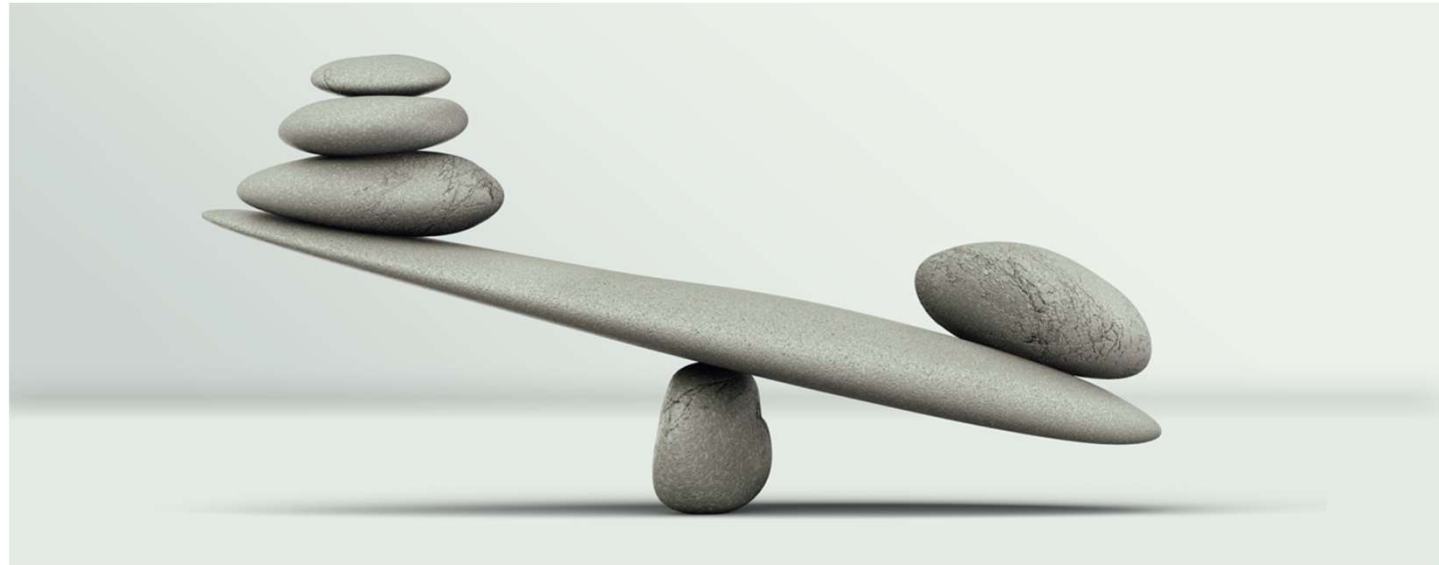
FDA Indications for Lurasidone

- Schizophrenia (> 13 yrs old)
- Bipolar depression (> 10 yrs old as monotherapy; adults as adjunct)

FDA Indications for Clozapine

- Treatment resistant schizophrenia
- Reduction in risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder
- Clozapine REMS Program Certification:
 - Review Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers
 - Successfully complete the Clozapine REMS Knowledge Assessment for Healthcare Providers

Balancing Efficacy with Tolerability



- Monitor for common adverse effects
- Prevention is more effective than trying to treat adverse effects
- Goal is safety, efficacy and compliance



Why patients quit taking:

- Weight gain
- Cardiometabolic disturbance
- Movement disorders
- Somnolence
- Sexual dysfunction

Number Needed to Harm Benefit vs Risk of Agents Approved for Bipolar Depression

NNH by Agent Calculated Using Rates of the Outcomes Provided in Product Labeling

Effect Size

- NNH < 10 (higher risk)
- NNH: 10 to 19 (intermediate risk)
- NNH > 20 (low risk*)

	Olanzapine/ fluoxetine 6/25, 6/50 12/50 mg/d	Quetiapine IR/ER 300 or 600 mg/d	Lurasidone 20-60 mg/d	Lurasidone 80-120 mg/d	Cariprazine 1.5 mg/d	Cariprazine 3.0 mg/d
Weight gain ≥ 7%	6	16	29	5550	50	50
EPS	NA	NA	40	16	50	25
Somnolence	13	3	130	14	34	50
Akathisia	NA	NA	18	12	36	13
Nausea	NA	NA	39	11	29	21
Discontinued due to AEs	-37	10	642	-151	298	31

AE, adverse event; EPS, extrapyramidal symptoms; NA, not available; NNH, number needed to harm.

*A negative value for NNH occurs when the rate of harm is lower for drug than placebo.

Citrome L, et al. Presented at: 33rd Annual Psych Congress Virtual Meeting; September 10-13, 2020; Poster 112. <https://www.hmpglobelearningnetwork.com/site/pcn/posters/assessing-benefit-risk-ratio-approved-treatments-bipolar-depression-using-likelihood-be>



Cardiometabolic Effects

- Weight gain
- Dyslipidemia
- Increased risk of diabetes mellitus

Risk of Weight Gain Among Antipsychotics



LOW

amisulpride
aripiprazole
brexpiprazole
cariprazine
lumateperone
lurasidone
pimavanserin
ziprasidone

MODERATE

asenapine
iloperidone
paliperidone
quetiapine
risperidone

HIGH

clozapine
olanzapine

Stahl SM et al. Acta Psychiatr Scand 2020;10.1111/acps.13266;
Citrome L et al. CNS Spectr 2018;23(3):228-38;
Pillinger T et al. Lancet Psychiatry 2020;7(1):64-77.



Predictors of Significant Long Term Weight Gain on Antipsychotics

Immediate elevation
of triglycerides
(suggestive of insulin
resistance)

Rapid weight gain
($> 5\%$ of body weight)
in first month

Children are
especially susceptible



Monitoring for Antipsychotic-Induced Weight Gain

- Fasting glucose
- Hemoglobin A1C
- Fasting lipids
- Weight
- Waist circumference

Prevention and Treatment of Weight Gain

Prevention

- Choose antipsychotics with less risk (aripiprazole, lurasidone)
- Metformin – start before weight gain occurs (olanzapine, clozapine)

Treatment of Weight Gain

- Olanzapine/samidorphan combination tablet
- Naltrexone/bupropion (more studies needed)
- Topiramate
- Amantadine

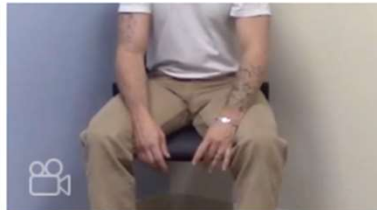


Movement Disorders

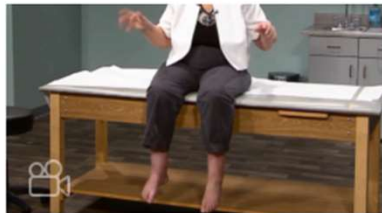
- Tardive dyskinesia
- Akathisia
- Drug-induced Parkinsonism



UNCONTROLLABLE TONGUE MOVEMENTS



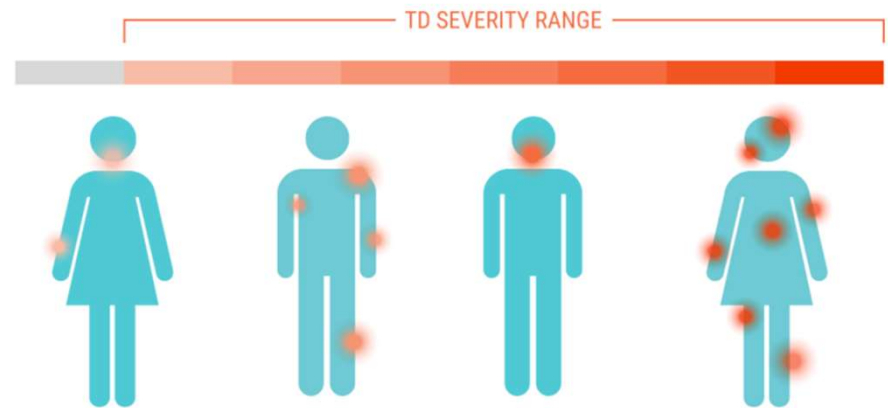
UNCONTROLLABLE FINGER TAPPING



UNINTENTIONAL ARM AND LEG MOVEMENTS



INVOLUNTARY FACIAL GRIMACING



Tardive Dyskinesia

- Hyperkinetic movement
- Involuntary and continuous
- Often irreversible

Abnormal Involuntary Movement Scale (AIMS) to Identify Tardive Dyskinesia



- 12 items
 - Facial, oral, extremity, and trunk movements (1-7)
 - Overall severity (8-10)
 - Dental care (11-12)
- 5-point severity scale (0 to 4)
- Takes 10 minutes to administer
- Positive test:
 - Score of 2 (mild) in 2 or more movements
 - Score of 3 (moderate) or 4 (severe) in a single movement

Treat Tardive Dyskinesia

- Lowering the dose or safely discontinuing the offending agent
- Cross-taper to another antipsychotic with lower risk of TD if continued treatment is required:
 - Clozapine (significant side effect profile)
 - Quetiapine
- Symptomatic treatment:
 - Benzodiazepines for mild symptoms
 - Vesicular monoamine transporter type 2 (VMAT2) inhibitors (tetrabenazine, valbenazine, deutetrabenazine) for moderate to severe TD

Risk of Akathisia/DIP Among Antipsychotics



LOW
clozapine
iloperidone
lumateperone
pimavanserin
quetiapine

MODERATE
amisulpride
aripiprazole
asenapine
brexpiprazole
cariprazine
lurasidone
olanzapine
ziprasidone

HIGH
paliperidone
risperidone

NOTE: Treatment-emergent akathisia is generally higher with typical than atypical antipsychotics

Stahl SM et al. Acta Psychiatr Scand 2020;10.1111/acps.13266;
Abbas A, Roth BL. Expert Opin Pharmacother 2008;9(18):3251-9;
Huhn M et al. Lancet 2019;394(10202):939-51.



Akathisia

Treatment

- Reduce dose of antipsychotic
- Change to another antipsychotic with less risk for akathisia
- Beta blocker
- Benzodiazepine



Akathisia's
a movement disorder
characterized by
feeling of inner restlessness
and inability to stay
still.
Often people feel
like they want to
crawl out of their
own skin.

Parkinsonism Symptoms



Slow movements
(bradykinesia)



Parkinsonian
gait



Rigidity



Face
masking



Tremors



Slowed reaction
time



Frequent
falls

Drug-Induced Parkinsonism Treatment

- Bzotropine (anticholinergic)
- Reduce dose of antipsychotic
- Change to another antipsychotic with less risk for DIP

Unique Side Effect Profiles

Clozapine

- Agranulocytosis, seizures, myocarditis

Risperidone

- Hyperprolactinemia & movement disorders

Aripiprazole

- Moderate risk of akathisia or insomnia earlier on

Lurasidone

- Akathisia

Quetiapine

- Cataracts

Ziprasidone

- QTc prolongation

Summary

Patients commonly seek care for mental health conditions in primary care.

Antipsychotics are prescribed to patients in all stages of life and for various common mental health conditions.

Common adverse effects are weight gain, cardiometabolic disturbances, and movement disorders.

Monitoring for side effects will improve safety, tolerability, and efficacy.