ACLP
Consultation-Liaison Psychiatry 2024

Promoting Whole Health Through Innovative and Integrative Approaches to C-L Psychiatry

Medication Safety: Best Practices and Insights Regarding the use of Antipsychotics

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Disclosure

Kinza Tareen, MD

With respect to the following presentation, in the 24 months prior to this declaration there has been no financial relationship of any kind between the party listed above and any ACCME-defined ineligible company which could be considered a conflict of interest.

Objectives

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Promoting Whole Health Through Innovative and Integrative Approaches to C-L Psychiatry

Recognize and apply principles of safe prescribing practices with a focus on antipsychotics

Develop an understanding of role of first and second generation antipsychotics in CL practice

- Mechanisms of action
- Indications
- Formulations

Recognize common adverse effects in the CL context

Differentiate extrapyramidal symptoms and utilize acute management strategies

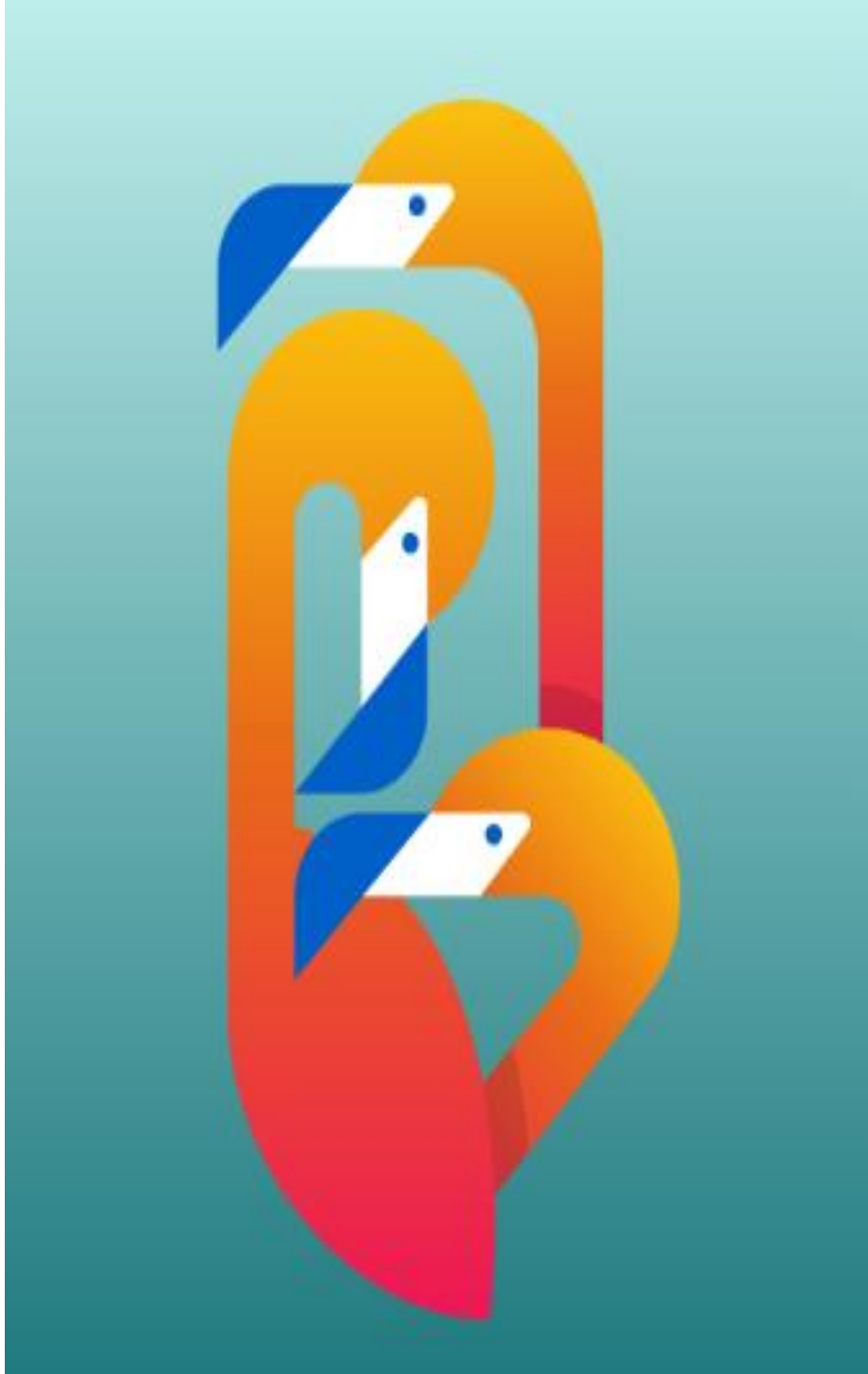
Identify early signs and symptoms psychiatric emergencies related to antipsychotics

- NMS
- Catatonia spectrum

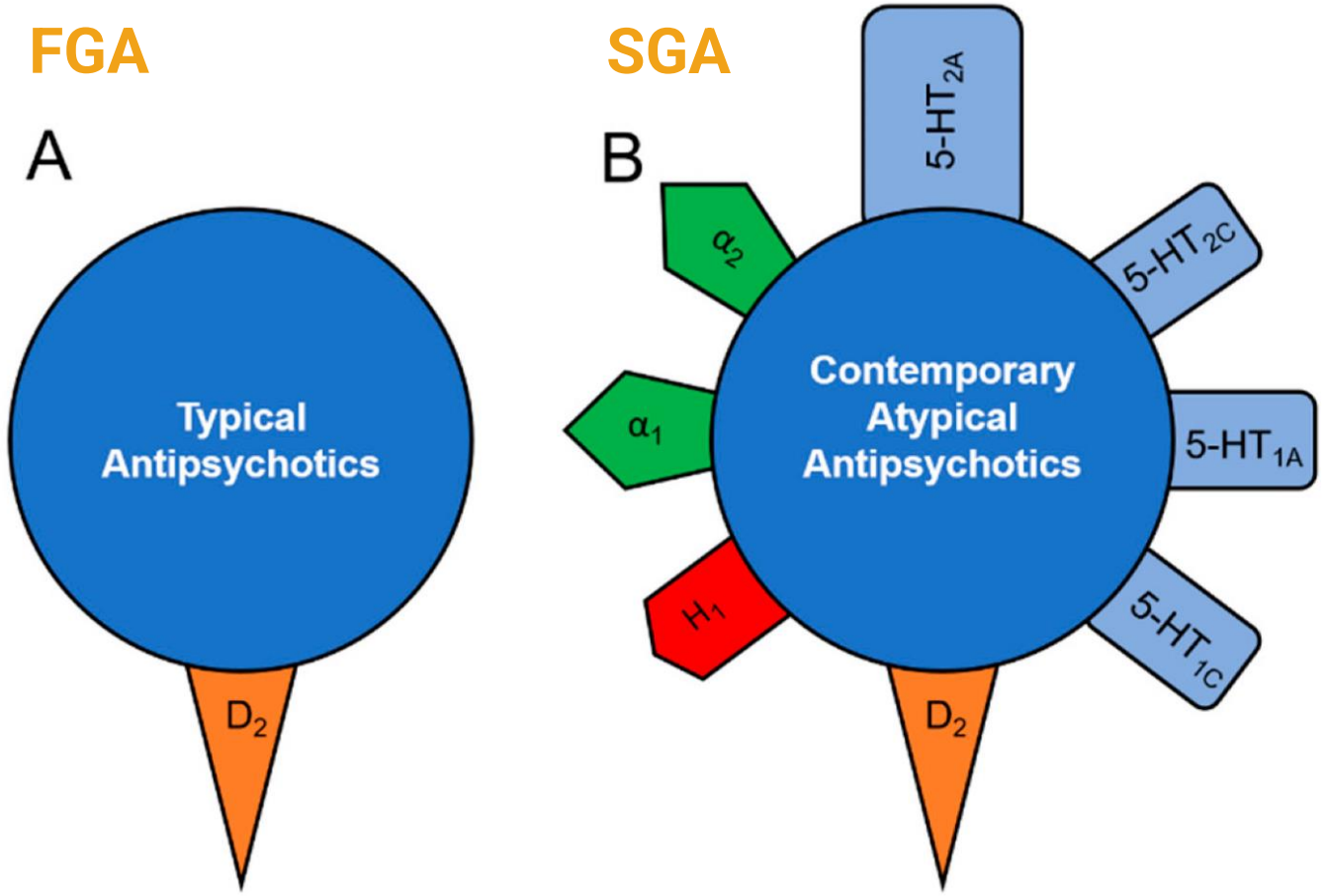
Evaluate the risk of serious cardiac events with exposure to antipsychotics

- QT prolongation relative risks
- Strategies to calculate QTc and stratify risk

First vs Second Generation Antipsychotics



Mechanisms of Action



Adapted from: Grinchii D, Dremencov E. Mechanism of Action of Atypical Antipsychotic Drugs in Mood Disorders. *International Journal of Molecular Sciences*. 2020; 21(24):9532. https://doi.org/10.3390/ijms21249532

Antipsychotics use in inpatient CL practice is ubiquitous, "on and off label"

- Psychosis
  - Primary psychopathology (decompensated schizophrenia) vs otherwise (ie., SLE, medication induced)
- Hyperactive delirium
  - Agitation
  - Psychotic features of delirium
- Withdrawal agitation management
- Anxiety in setting of dyspnea
- Sleep management (insomnia, reset sleep/wake cycle)
- ICU light sedation
- Nausea/vomiting
- Intractable hiccups

Formulation Matters

Clinical context and availability of parenteral dosing often influences the choice of antipsychotic

Medication	Route	Formulation	Bioavailability	Time to maximum plasma concentration (Tmax)
Aripiprazole	Oral	Tablet	87%	3–5 hours
	Oral	Oro-dispersible	87%	3–5 hours
	Oral	Liquid	87%	3–5 hours
	IM	Injection	100%	1 hour
Droperidol	Oral	Tablet	75%	1–2 hours
	IM	Injection	100%	⩽30 minutes
	IV	Injection	100%	seconds/minutes
Haloperidol	Oral	Tablet	60–70%	2–6 hours
	Oral	Liquid	60–70%	2–6 hours
	IM	Injection	100%	20–40 minutes
	IV	Injection	100%	seconds/minutes
Olanzapine	Oral	Tablet	Undetermined	5–8 hours
	Oral	Oro-dispersible	Undetermined	5–8 hours
	IM	Injection	Undetermined	15–45 minutes
	IV	Injection	100%	seconds/minutes
Quetiapine	Oral	Tablet	Unknown	1.5 hours
Risperidone	Oral	Tablet	67%	1–2 hours
	Oral	Oro-dispersible	67%	1–2 hours
	Oral	Liquid	70%	1–2 hours

Patel et al. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation. J Psychopharmacol. 2018 Jun;32(6):601-640.

CL Relevant Adverse Effects

Anticholinergic Effects

Antipsychotic-induced anticholinergic result from a blockade of muscarinic receptors (M_1–M_5) in the brain and periphery

Common effects:

- dry mouth
- blurred vision
- constipation
- urinary retention
- cognitive, memory difficulties, confusion
- delirium

Antipsychotic	Clinical anticholinergic effects	Binding affinity[a]
Clozapine	++++	7.5
Thioridazine	++++	10
Chlorpromazine	++++	60
Methotrimeprazine	++++	–
Olanzapine	+++	1.9
Loxapine	++	62.5
Quetiapine	++	120
Fluphenazine	+	2 000
Flupenthixol	+	–
Haloperidol	+	>20 000
Risperidone	+	>10 000

Gardner DM, Teehan MD. Anticholinergic effects. In: *Antipsychotics and Their Side Effects*. Cambridge University Press; 2010:18-23.

Antipsychotics and Sedation

Medication	Relative Potency (mg)	Common Dose Range (mg/d)	Sedation
Atypical antipsychotics			
Clozapine	50	250–500	Marked
Quetiapine	80	300–800	Moderate
Olanzapine	4	15–30	Moderate
Ziprasidone	20	80–160	Mild
Risperidone	1	2–6	Mild
Conventional antipsychotics			
Chlorpromazine	100	100–600	Moderate
Mesoridazine	50	50–150	Moderate
Fluphenazine	1–2	2–20	Mild
Haloperidol	2	5–20	Mild

[a]Data from Jibson and Tandon.[6]

Sedating properties of antipsychotics can limit tolerance - but also be employed as a ‘useful’ side effect

Quetiapine is commonly used for insomnia
- limited evidence of efficacy in primary insomnia (1 small RCT)

Systematic review of the use of SGA for insomnia suggest lack of evidence for efficacy

Thompson W, Quay TAW, Rojas-Fernandez C, Farrell B, Bjerre LM. Atypical antipsychotics for insomnia: a systematic review. Sleep Med. 2016 Jun;22:13-17.
Miller DD. Atypical antipsychotics: sleep, sedation, and efficacy. Prim Care Companion J Clin Psychiatry. 2004;6(Suppl 2):3-7.

Metabolic Syndrome

Associated with SGAs and characterized by:

- increased waist circumference
- dyslipidemia
- fasting hyperglycemia
- elevated blood pressure

MetS in SMI reduces life expectancy and limits adherence (weight gain in particular)

Risk of T2D is not strictly weight gain dependent

- Insulin resistance due to hyperglycemia can occur within first 6 months

	Weight Gain	Diabetes (T2D)	Dyslipidemia
Clozapine	+++	+++	+++
Olanzapine	+++	+++	+++
Quetiapine	++	++	++
Risperidone	++	++	++
Amisulpride	++	++	++
Asenapine	+	+	+
Lurasidone	+	+	+
Ziprasidone	+	+	+
Aripiprazole	+	+	+

Adapted from: Carli M et al. Atypical Antipsychotics and Metabolic Syndrome: From Molecular Mechanisms to Clinical Differences. Pharmaceuticals (Basel). 2021 Mar 8;14(3):238.

Autonomic and Cardiovascular Effects

- Autonomic side effects result from cholinergic and alpha1-adrenergic blockade
- Propensity to cause hypotension (from greatest risk to least risk):
  - clozapine > iloperidone > quetiapine > risperidone > aripiprazole, asenapine, lurasidone, olanzapine, ziprasidone
- Clozapine and quetiapine have been reported to cause tachycardia in 25% and 7% of cases, respectively
- In 2017, an FDA warning was added to all antipsychotics regarding falls and fall-related injuries resulting from somnolence, orthostasis, and motor instability

James Owen, Ericka Crouse, Cynthia Kirkwood, & James Levenson. (2024). Psychopharmacology. The American Psychiatric Association Publishing Textbook of Psychosomatic Medicine and Consultation-Liaison Psychiatry.

Antipsychotics in the Elderly

- A Swedish registry study identified haloperidol, risperidone, olanzapine, and quetiapine as the antipsychotics associated with the highest **risk of sudden cardiac death** (Danielsson et al. 2016)

- A large cohort study (statewide Medicaid prescription data) found that antipsychotic use was associated with a 2x risk of sudden cardiac death
  - 1 extra death for every 666 persons treated for 1 year with antipsychotic (Ray et al. 2009)

- Due to concern that the risk of death associated with antipsychotics is substantially higher —> FDA boxed warning against the use of antipsychotics in elderly patients with dementia

James Owen, Ericka Crouse, Cynthia Kirkwood, & James Levenson. (2024). Psychopharmacology. The American Psychiatric Association Publishing Textbook of Psychosomatic Medicine and Consultation-Liaison Psychiatry.

Hematological Side Effects

- Transient leukopenia and leukocytosis can present in the first few weeks of therapy and are usually not clinically significant

- Agranulocytosis is the most common serious hematological side effect with clozapine, low-potency FGAs (< 0.1%), and olanzapine

- Most cases of agranulocytosis occur during the first 6 months of therapy, with the highest risk during the first 6–18 weeks

James Owen, Ericka Crouse, Cynthia Kirkwood, & James Levenson. (2024). Psychopharmacology. The American Psychiatric Association Publishing Textbook of Psychosomatic Medicine and Consultation-Liaison Psychiatry.

Antipsychotics and Seizures

- Most antipsychotics lower the seizure threshold and increase seizure risk
- There are no controlled comparative studies of relative seizure risk among antipsychotics, but generally thought to be associated with a dose-dependent effect
- Clozapine carries the highest risk (1% at 300 mg/day, increasing to 4.4% at > 600 mg/day)

High risk (>1.0%)	Intermediate risk (0.5–1.0%)	Low risk (<0.5%)
Chlorpromazine (≥1000 mg/day)	Chlorpromazine (<1000 mg/day)	Aripiprazole
Clozapine (≥300 mg/day)	Clozapine (<300 mg/day)	Fluphenazine
	Olanzapine	Haloperidol
	Quetiapine	Molindone
	Thioridazine	Pimozide
		Risperidone
		Trifluoperazine
		Ziprasidone

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Hepatic and Pancreatic Effects

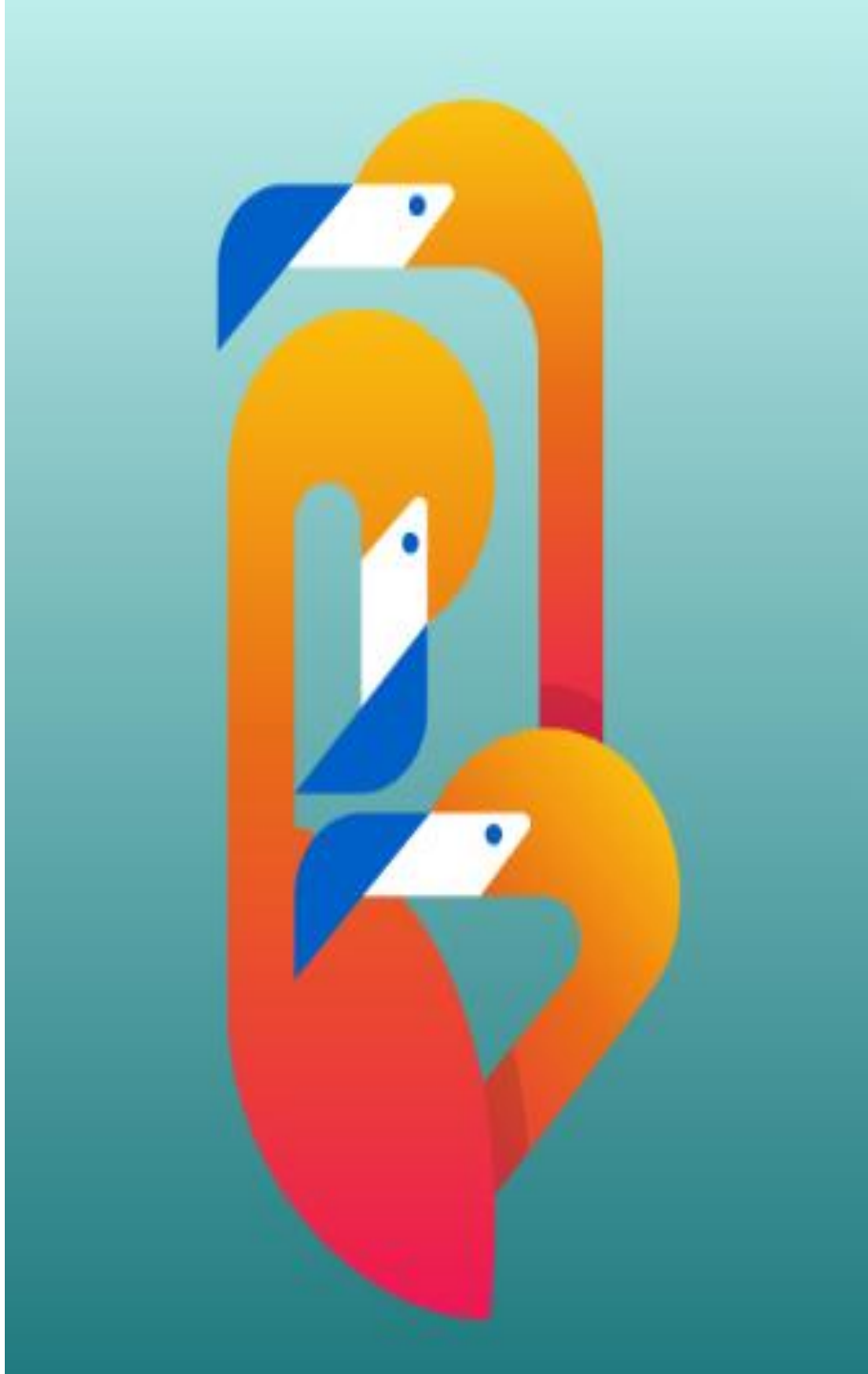
- Mild to moderate elevations in liver aminotransferases and alkaline phosphatase usually occur early in treatment and are unlikely to result in hepatic impairment

- Patients with significant antipsychotic-induced weight gain should be monitored for steatohepatitis

- Antipsychotic-induced pancreatitis has been reported with:
  - clozapine
  - olanzapine
  - risperidone
  - aripiprazole
  - ziprasidone

James Owen, Ericka Crouse, Cynthia Kirkwood, & James Levenson. (2024). Psychopharmacology. The American Psychiatric Association Publishing Textbook of Psychosomatic Medicine and Consultation-Liaison Psychiatry

Extrapyramidal Symptoms



Extrapyramidal Symptoms

Clinical presentations:

- Acute dystonias
- Parkinsonism
- Akathisia
- Tardive dyskinesia*

Most common with high dose, high potency FGAs

- Among SGA, risperidone with greatest risk

Monitor with Abnormal Involuntary Movement Scale (AIMS)

*Some consider tardive dyskinesia a distinct complication and not EPS

Facial and Oral Movements					
1. Muscles of Facial Expression e.g., movements of forehead, eyebrows, periorbital area, cheeks; Include frowning, blinking, smiling, grimacing	0	1	2	3	4
2. Lips and Perioral Area e.g., puckering, pouting, smacking	0	1	2	3	4
3. Jaw e.g., biting, clenching, chewing, mouth opening, lateral movement	0	1	2	3	4
4. Tongue Rate only increases in movement both in and out of mouth, NOT inability to sustain movement	0	1	2	3	4
Extremity Movements					
5. Upper (arms, wrists, hands, fingers) Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous); athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT include tremor (i.e., repetitive, regular, rhythmic).	0	1	2	3	4
6. Lower (legs, knees, ankles, toes) e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0	1	2	3	4
Trunk Movements					
7. Neck, shoulders, hips e.g., rocking, twisting, squirming, pelvic gyrations	0	1	2	3	4
Global Judgments					
8. Severity of abnormal movements	0	1	2	3	4
9. Incapacitation due to abnormal movements	0	1	2	3	4
10. Patient's awareness of abnormal movements (rate only patient's report) 0 = not aware; 1 = aware, no distress; 2 = aware, mild distress; 3 = aware, moderate distress; 4 = aware, severe distress	0	1	2	3	4
Dental Status					
11. Current problems with teeth and/or dentures?	No	Yes			

Gharabawi, G. et al. Abnormal Involuntary Movement Scale (AIMS) and Extrapyramidal Symptom Rating Scale (ESRS): Cross-scale comparison in assessing tardive dyskinesia. *Schizophrenia Research, 77*(2-3), 119–128.

Dystonic Reactions

Clinical Presentation

- Involuntary tonic contractions of skeletal muscle (typically head and face)
- Typically seen within 24-96 hours of initiation
- More common in younger males

Management

- Benztropine 1-2 mg IM
- Diphenhydramine 25-50 mg IM

Parkinsonism

Clinical Presentation

- D2 antagonists or partial agonists can interfere with dopamine transmission via the nigrostriatal tract → producing parkinsonian symptoms
  - Akinesia
  - Bradykinesia
  - Mask facies
  - Pill-rolling tremor at rest,
  - Cogwheel rigidity
  - Shuffling gait
- 90% of cases seen within first 3 months
- More common in older women

Management

Antiparkinsonian Agents

- Benztropine 1-6 mg/day, diphenhydramine 50-200 mg/day, trihexyphenidyl 2-15 mg/day (divided TID)

2nd line or if concern for memory impairment: amantadine

- Typical Duration: 2-3 months then taper

Akathisia

Clinical Presentation

- Inability to sit still; feeling of “inner restlessness”
- Prevalence ~35%
- Most common in middle-aged women
- Dose-dependent
- Seen within weeks of initiation or months later

Management

- Rarely responsive to anticholinergics
- Propranolol 20-160 mg/day in 2-3 divided doses and/or Lorazepam 0.5-5 mg/day in divided doses
- May monitor with Barnes Akathisia Rating Scale

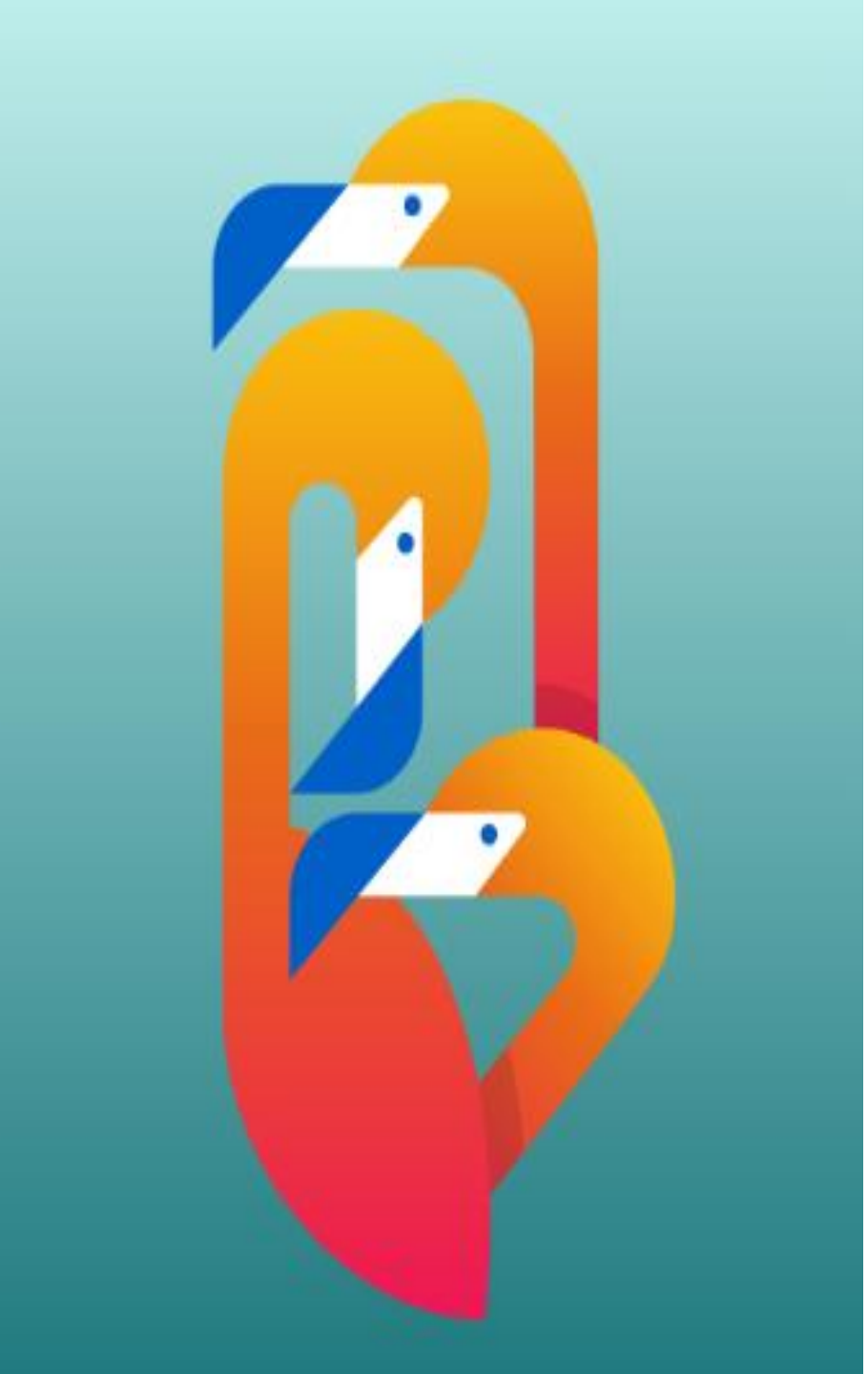
Tardive Dyskinesia

Clinical Presentation

- Stereotypical, involuntary movements of orofacial area or choreiform movements of extremities
- Onset is months-years; often irreversible
- Incidence 4% per year of antipsychotic exposure for at least the first 5-6 yrs
- Usually appears with dose reduction or discontinuation

Management

- Consider switch to clozapine
- Valbenazine (Ingrezza) 40-80 mg daily
- Monitor AIMS every 6 mths (q 3 mths if high risk)



Psychiatric Emergencies Related to Antipsychotics

Neuroleptic Malignant Syndrome

Most often seen with high-potency FGAs - but SGAs and antiemetics have also been implicated
Not a dose-dependent, but higher doses are a risk factor

Symptoms usually develop during the first two weeks, but can be idiosyncratic

Typical symptoms — typically evolves over one to three days

- Mental status change is the initial symptom
  - Catatonic signs can present –
- Generalized muscular rigidity
  - "Lead-pipe rigidity" or stable resistance through all ranges of movement
  - Tremors can also present
- Hyperthermia (> 38°C)
- Autonomic instability
  - Tachycardia
  - Labile or high blood pressure
  - Tachypnea
  - Diaphoresis

Adapted from: Carli M et al. Atypical Antipsychotics and Metabolic Syndrome: From Molecular Mechanisms to Clinical Differences. Pharmaceuticals (Basel). 2021 Mar 8;14(3):238.

Neuroleptic Malignant Syndrome

Differential Considerations

- Serotonin Syndrome:
  - Presents with hyperreflexia, clonus, and gastrointestinal symptoms (n/v), which are less common in NMS
- Malignant Hyperthermia:
  - Triggered by inhalational anesthetics or depolarizing muscle relaxants like succinylcholine. It shares features with NMS but usually has a more rapid onset
- Malignant Catatonia:
  - Presents with fever, rigidity, and altered mental status similar to NMS but responds well to benzodiazepines and ECT
- Central Nervous System Infections:
  - Encephalitis or meningitis can mimic NMS symptoms and can be ruled out through CSF analysis and neuroimaging
- Drug Intoxication or Withdrawal:
  - Intoxication with cocaine, MDMA, or phencyclidine, or withdrawal from alcohol or benzodiazepines can present similarly
- Toxic Encephalopathies:
  - May present with altered mental status and autonomic dysfunction

Management

- Discontinue antipsychotic, supportive care
- Bromocriptine 2.5 mg PO/NG every 6-8 hrs (max 45 mg/day)
- Dantrolene 1-2.5 mg/kg IV, may repeat to max cumulative dose of 10 mg/kg/day, then switch to oral
- Continue treatment for 1-2 weeks after response
- Do not re-challenge with same antipsychotic

Carli M et al. Atypical Antipsychotics and Metabolic Syndrome: From Molecular Mechanisms to Clinical Differences. Pharmaceuticals (Basel). 2021 Mar 8;14(3):238.

NMS - Differential

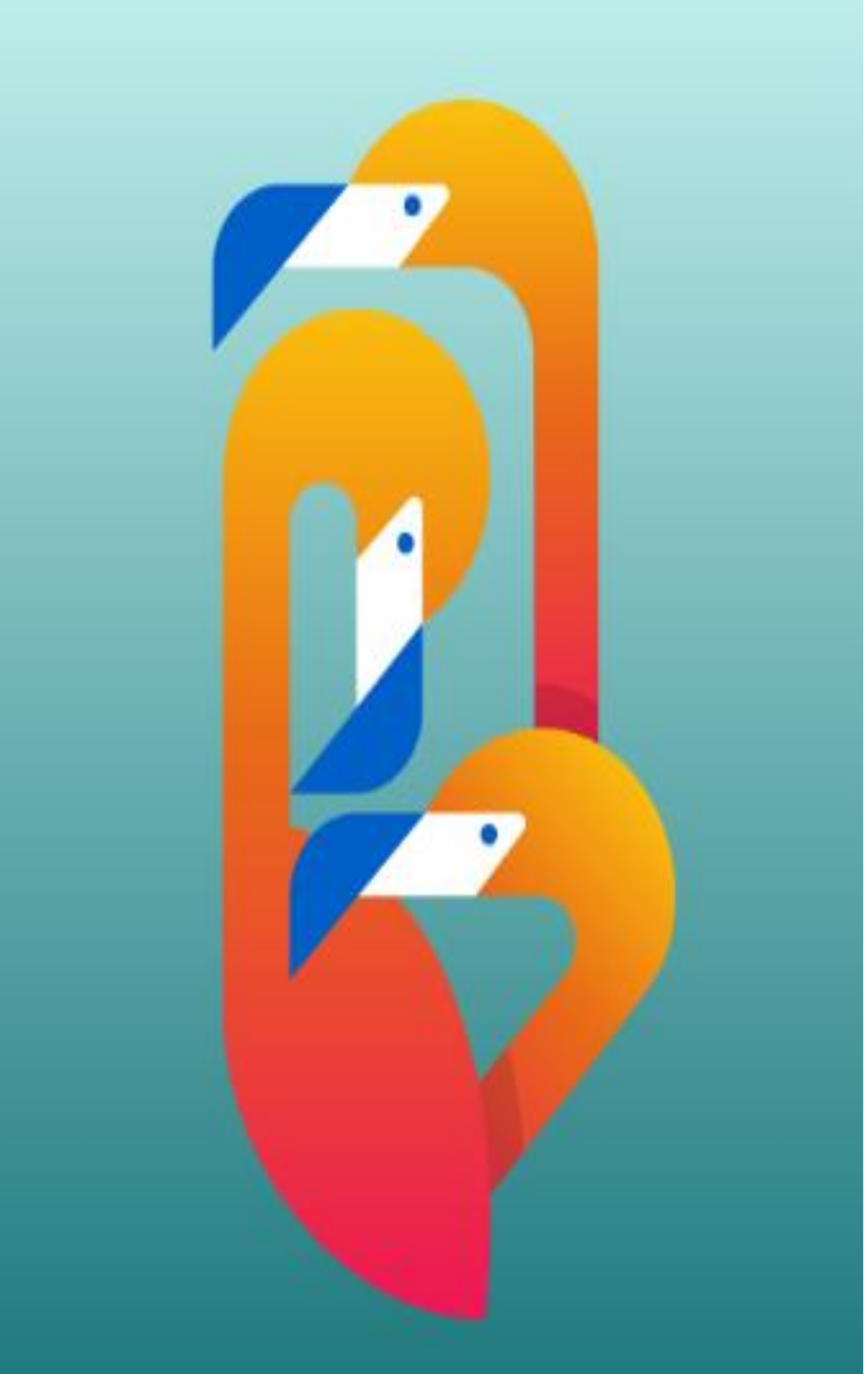
Serotonin Syndrome		Neuroleptic Malignant syndrome
More acute (hours)	**Onset**	More gradual (days-weeks)
SSRIs, SNRIs, MAOIs, tricyclic antidepressants, synthetic opioids, illicit drugs	**Aetiology**	Anti-psychotics, sudden cessation of dopaminergic agents e.g. Levodopa
Tachycardia, raised BP, hyperthermia, diaphoresis, rigidity, altered mental state	**Presentation**	Tachycardia, raised BP, hyperthermia, diaphoresis, rigidity, altered mental state, delirium
Hyperreflexia, clonus, tremor	**Neurological signs**	Hyporeflexia, "lead-pipe" rigidity
Dilated	**Pupils**	Normal
Diarrhoea, increased bowel sounds	**Gastrointestinal features**	Normal
Can be raised but generally more associated with neuroleptic malignant syndrome	**Creatinine kinase (CK)**	Raised; Can cause acute kidney injury
Stop serotonergic drugs IV fluids and cooling Benzodiazepines Cyproheptadine	**Management**	Stop antipsychotics IV fluids Dantrolene Bromocriptine

Figure From Gram Project, online

NMS-Catatonia Spectrum

		Catatonia	NMS
Motor symptoms	hypokinesia/akinesia	bizarre additional symptoms: posturing, automatisms, negativism, rarely hyperkinesia (stereotypies)	only hypokinesia, rigidity, no major behavioral abnormalities
Affective symptoms	anxieties	strong, intense and uncontrollable anxiety	less intense and more controllable anxiety
Onset		slower onset	sudden start of mental changes, motor rigidity, fever, and autonomous dysregulation
Pathophysiology of motor symptoms		right posterior parietal cortical dysfunction	blockade of D-2 receptors in striatum with consecutive dysregulation of subcortical-cortical connections in the "motor loop"
Pathophysiology of affective symptoms		deficits in medial orbitofrontal cortical activity	emotional reaction to akinesia with abnormal subcortical-cortical modulation
Treatment	*first choice*: benzodiazepines (BZP), e.g., Lorazepam 1–2 mg up to 20 mg/day *second choice* in case of nonresponding to BZPs or in case of fever more than 39 °C: ECT	*third choice* – if comorbid with schizophrenia: neuroleptics, predominantly atypical neuroleptics while maintaining BZPs – if comorbid with affective disorders: no neuroleptics	no neuroleptics

Häßler F et al. A case of catatonia in a 14-year-old girl with schizophrenia treated with electroconvulsive therapy. Z Kinder Jugendpsychiatr Psychother. 2013 Jan;41(1):69-74.



QT Considerations with Antipsychotics

QTc and Torsades

Prolongation of the heart rate–corrected QT-interval (QTc) is a risk factor for Torsades de Pointes, a rare but life threatening ventricular arrhythmia

- QTc is prolonged if…
  - > 440 ms in men
  - > 460 ms in women
- QTc > 500 ms is associated with increased risk of TdP

QTc	Formula
Bazett	$QTc = QT / \sqrt{RR}$
Fridericia	$QTc = QT / RR^{1/3}$
Hodges	$QTc = QT + 0.00175 * (HR - 60)$
Framingham	$QTc = QT + 0.154 * (1 - RR)$
Rautaharju	$QTc = QT * (120 + HR) / 180$

QTc is more than a number, shift focus to context and risk stratification

Psychiatric medications are not always the culprit ....

Rege, S. (2024, April 22). QTc prolongation and psychotropics- management of prolonged qtc interval in psychiatry. Psych Scene Hub.

QT Risk

Minimal Risk
• Aripiprazole and lurasidone

Moderate Risk
• Haloperidol, droperidol (5-10mg), chlorpromazine,olanzapine, risperidone, and quetiapine

Highest Risk
• Ziprasidone, iloperidone, thioridazine

Risk Stratification

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Non-modifiable risk factors	Modifiable risk factors
• Female sex • Advanced age • Congenital long QT syndrome (LQTS) • Personal history of drug-induced QTc interval prolongation • Personal history of structural or functional cardiac disease (e.g., heart failure with reduced ejection fraction) • Metabolizer status	• Concurrent use of more than one QTc interval prolonging drug • Pharmacokinetic drug-drug interactions • Drug toxicity • Rapid intravenous infusion of QTc interval prolonging drugs • Severe acute illness • Bradycardia • Starvation • Inadequate dose adjustment of hepatically-metabolized drugs in patients with hepatic cirrhosis • Inadequate dose adjustment of renally-eliminated drugs in patients with acute kidney injury or chronic kidney disease • Risk or presence of hypokalemia, hypomagnesemia, or hypocalcemia

Funk MC et al. QTc Prolongation and Psychotropic Medications. Am J Psychiatry. 2020 Mar 1;177(3):273-274.

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Thank you.

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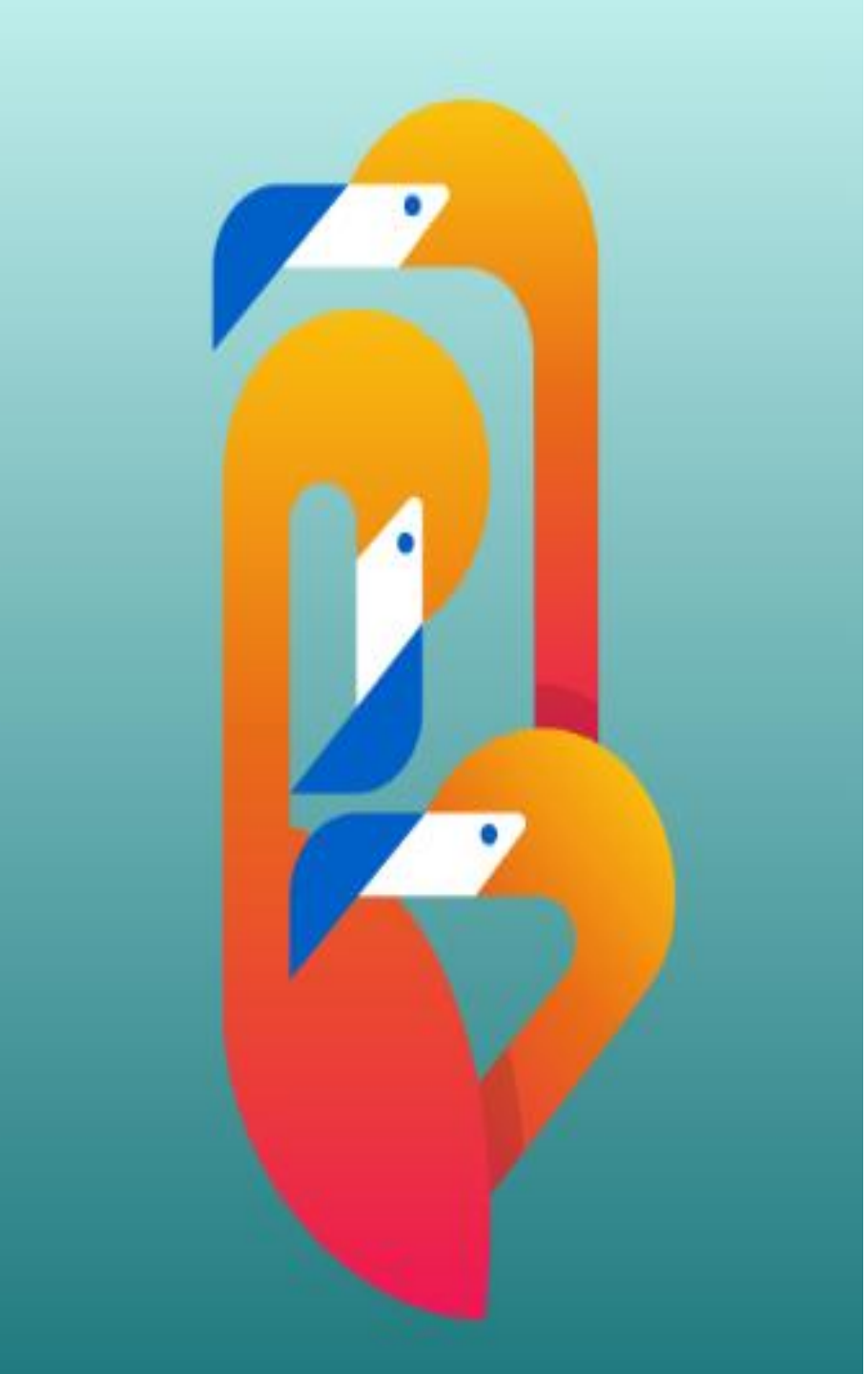

Interactive Case Discussion

Moderators:

Kristin Beizai, MD, FACLP, DFAPA

Matthew McWeeny, MSN, APRN-CNP, PMHNP-BC

Additional ACLP Resources

How To Guide: Medication Syndromes

How To Guide: QT Prolongation

Table 1: Clinical Presentation of Major Toxidromes

	Neuroleptic Malignant Syndrome	Serotonin Syndrome	Anticholinergic Toxicity
Precipitated by	Dopamine antagonists	Serotonergic agents	Anticholinergic agents
Onset	Variable (1-3 days)	Variable (<1d)	< 12 hours
Vital signs	Hypertension, tachycardia, tachypnea	Hypertension, tachycardia, and tachypnea	Hypertension, tachycardia, tachypnea
Temperature	Hyperthermia	Hyperthermia	Hyperthermia (<38.8)
Mucosa	Sialorrhea	Sialorrhea	Dry
Skin	Diaphoresis	Diaphoresis	Hot/red
Mental Status	Delirium	Delirium	Delirium
Muscles	"Lead pipe" rigidity	Increased tone	Normal
Reflexes	Hyporeflexia	Hyperreflexia, clonus	Normal
Pupils	Normal	Dilated	Dilated
Bowel sounds/movements	Normal or decreased	Hyperactive, diarrhea	Decreased or absent, constipation

Hunter Serotonin Toxicity Criteria (may miss mild cases): Serotonergic agent in past 5 weeks + ANY of the following symptoms: 1) tremor and hyperreflexia; 2) spontaneous clonus; 3) Muscle rigidity, temperature >38C, and either ocular or inducible clonus; 4) ocular clonus and agitation or diaphoresis; 5) inducible clonus and agitation or diaphoresis

Sternbach Criteria (Non-specific and overlap with other toxidromes): 1) Recent addition or increase in known serotonergic agent; 2) Absence of other possible etiologies; 3) No recent addition or increase of a neuroleptic agent; 4) ≥3 of the following symptoms: mental status change, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, fever

QTc	Formula
Bazett	$QTc = QT / \sqrt{RR}$
Fridericia	$QTc = QT / RR^{1/3}$
Hodges	$QTc = QT + 0.00175 * (HR - 60)$
Framingham	$QTc = QT + 0.154 * (1 - RR)$
Rautaharju	$QTc = QT * (120 + HR) / 180$