Update on Antipsychotic-Induced Movement Disorders

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Learning Objectives

1. Describe antipsychotic-induced movement disorders.
2. Know potential management for movement disorders.
3. Understand the risk of movement disorders with first-generation and second-generation antipsychotics

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Antipsychotic-Induced Movement Disorders

Types:

- Akathisia
- Acute Dystonia
- Pseudoparkinsonism
- Tardive Dyskinesia

- Also known as extrapyramidal symptoms (EPS)

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Movement Disorders

Other causes:

- Lithium
- SSRIs
- Valproate (Depakote®)
- Metoclopramide (Reglan®)
- Promethazine (Phenergan®)
- Prochlorperazine (Compazine®)

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Introduction

- Expanding indications for antipsychotics
  - Schizophrenia
  - Bipolar disorder
  - Depression
  - Others?

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Introduction

- Antipsychotics may cause adverse effects
- Movement disorders are one of the most distressing

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Introduction

Other considerations in selection of an antipsychotic:

- Weight gain
- Metabolic side effects
- Sedation
- Prolactin
- QTc prolongation

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Introduction

- Movement disorders can result in:
  - decreased quality of life
  - decreased adherence to medications
  - increased use of health care resources
- Potentially overlooked in patients taking second-generation antipsychotics because risk is less

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Development of Antipsychotics

First Generation Antipsychotics

1952	1960s	1970s
Chlorpromazine	Haloperidol	Molindone
	Fluphenazine	Pimozide
	Thioridazine	
	Loxapine	
	Perphenazine	
	Trifluoperazine	
	Thiothixene	

Tandon R. *J Clin Psychiatry* 2011;72(Suppl 1):4-8.

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Practice Question

The first-generation antipsychotics bind primarily to which type of receptors?

A. Serotonin
B. Dopamine
C. Histamine

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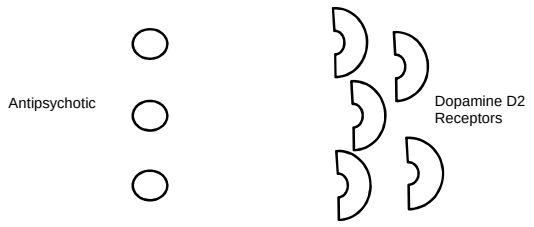
First-generation Antipsychotics: Efficacy



Block ~60% of these receptors for antipsychotic effect

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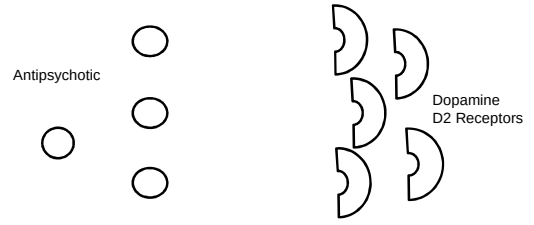
First-generation Antipsychotics: EPS



Blocking ~80% of these receptors leads to EPS

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Development of Antipsychotics

Second Generation Antipsychotics

1980s	1990s	2000s
⬇	⬇	⬇
Clozapine	Risperidone	Aripiprazole
	Olanzapine	Paliperidone
	Quetiapine	Iloperidone
	Ziprasidone	Asenapine
		Lurasidone

Tandon R. *J Clin Psychiatry* 2011;72(suppl 1):4-8.

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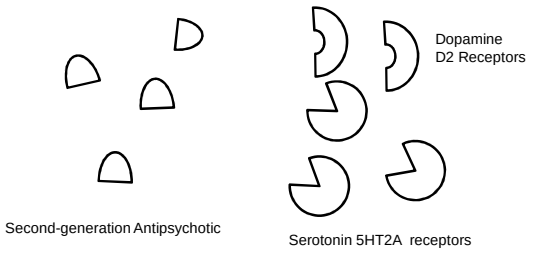
Second-generation antipsychotics



Antipsychotic effect due to blocking D2 and 5HT2A receptors

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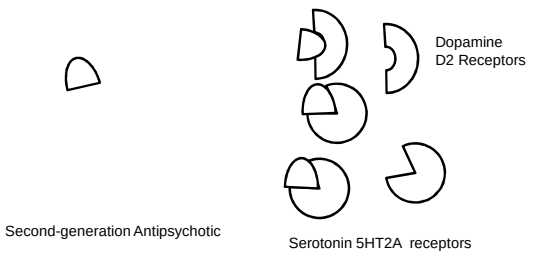
What's different about second-generation antipsychotics?



Loose binding and fast dissociation from D2 receptors

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D2 Effects of Antipsychotics

Antagonistic D2 effect	First-Generation Antipsychotic	Second-generation antipsychotics
Low	Chlorpromazine Thioridazine	Clozapine Quetiapine
Intermediate	Trifluoperazine Perphenazine	Olanzapine
High	Haloperidol Fluphenazine	Risperidone Ziprasidone Aripiprazole

Divac N., et al. *BioMed Res Int* 2014;1-6.

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First-Generation Antipsychotics:	**EPS Risk**
Chlorpromazine (Thorazine®)	Moderately high
Fluphenazine (Prolixin®)	High
Haloperidol (Haldol®)	High
Perphenazine (Trilafon®)	High
Thioridazine (Mellaril®)	Moderately high
Thiothixene (Navane®)	High
Second-Generation Antipsychotics:	**EPS Risk**
Aripiprazole (Abilify®)	Low
Clozapine (Clozaril®)	Low
Olanzapine (Zyprexa®)	Moderate
Quetiapine (Seroquel®)	Low
Risperidone (Risperdal®)	Moderate
Ziprasidone (Geodon®)	Moderate

Crismon ML, et al. Schizophrenia. Pharmacotherapy: A Pathophysiological Approach, 2011.

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Practice Scenario:

Michael is a 18-year-old diagnosed with bipolar disorder. You have noticed that Michael is often pacing since he started taking lurasidone (Latuda®). He also complains of feeling restless. Which of the following movement disorders is Michael likely experiencing?

A. Dystonia
B. Akathisia
C. Pseudoparkinsonism

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Akathisia

Symptoms:

- An inability to sit still
- Shuffling, pacing, tapping feet
- Feeling of inner restlessness

Onset:

- Usually occurs within first three months of starting antipsychotic

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Conditions with similar symptoms:

- Agitation due to psychotic symptoms or affective disorder
- Anxiety
- Delirium
- Head injury
- Parkinson's disease
- Huntington's disease
- Restless legs syndrome

Kane JM, et al. *J Clin Psychiatry* 2009; 70 (5): 627-643.

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Akathisia

Monitoring:

- Barnes Akathisia Rating Scale (BARS)

Barnes TRE. *Br J Psychiatry* 1989:154:672-6.

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Akathisia: Management

- Discontinue or reduce dose
- Switch to a second-generation antipsychotic
  - Quetiapine and clozapine – least likely to cause akathisia

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Practice Question

Which of the following medications is usually not helpful in treating akathisia?

A. Beta-blocker such as propranolol (Inderal)

B. Anticholingergic such as diphenhydramine (Benadryl)

C. Benzodiazepine such as lorazepam (Ativan)

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Akathisia: Management

Beta-blocker (off-label)

- First choice of treatment
- Examples: propranolol, metoprolol
- Side effects: bradycardia, hypotension, depression, dizziness, drowsiness

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Akathisia: Management

Benzodiazepines (off-label)

- Example: Lorazepam (Ativan)
- Used with caution due to high prevalence of substance abuse
- Side effects: drowsiness, confusion, dizziness

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Akathisia: Management

Anticholingergics

- Examples: benztropine (Cogentin®), diphenhydramine (Benadryl®)
- Generally not helpful

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Adverse Effects of Anticholinergics

Blind as a bat
Mad as a hatter
Red as a beet
Hot as a hare
Dry as a bone
The bowel and bladder loose their tone
And the heart runs alone

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Practice Scenario:

Greg is a 21-year-old male diagnosed with schizophrenia. He started taking haloperidol (Haldol) two days ago. He is experiencing a sustained muscle contraction of the neck. Which of the following movement disorders is Greg likely experiencing?

A. Acute Dystonia
B. Akathisia
C. Pseudoparkinsonism

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Acute Dystonia

- Symptoms:
  - Sustained muscle contractions or spasms
  - Abnormal postures, twisting, repetitive movements
  - Involuntary
  - May affect neck, extremities, larynx, trunk, jaw
  - Potentially life-threatening

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Acute Dystonia

Onset:
- Rapid (within 2-5 days of initiation/dose increase)

Risk Factors:
- Younger men
- Use of first-generation antipsychotics
  - Especially high-potency

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Acute Dystonia: Treatment

- Anticholinergics
  - Benztropine (Cogentin®)
  - Diphenhydramine (Benadryl®)
- Benzodiazepines (off-label)
  - Lorazepam (Ativan®)

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Practice Scenario:

William is an 76-year-old male diagnosed with schizophrenia. You notice that he has a tremor, difficulty initiating movement, and a masklike facial expression. Which of the following movement disorders is he likely experiencing?

A. Acute Dystonia
B. Akathisia
C. Pseudoparkinsonism

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Pseudoparkinsonism

- Imbalance of dopamine and acetylcholine
- Resembles Parkinson's disease

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Pseudoparkinsonism

Symptoms:

- Akinesia, bradykinesia, or decreased motor activity
  - difficulty initiating movement, slowed speech, mask-like facial expression, micrographia, decreased arm swing
- Tremor
- Cogwheel rigidity
- Postural abnormalities

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Pseudoparkinsonism

- Onset: 1-2 weeks after initiation or dose increase
- Risk factors:
  - Elderly
- Monitoring:
  - Simpson-Angus Scale

Simpson G, Angus J. *Acta Psychiatr Scand* 1970:212 (Suppl 44):11-9.

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Pseudoparkinsonism: Management

- Benztropine (Cogentin®)
- Trihexyphenidyl (Artane®)
- Diphenhydramine (Benadryl®)
- Amantadine (Symmetrel®)
  - Side effects: dizziness, anxiety, impaired concentration, insomnia

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Practice Question

TRUE OR FALSE

Patients may be unaware of unusual movements such as chewing or sticking out their tongue.

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Tardive Dyskinesia

Symptoms:

- Involuntary movements of face, neck, back, trunk, extremities
- Orofacial movements
  - Typically first detectable sign
  - Tongue thrusting, rolling
  - Interferes with chewing, swallowing, speaking

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Tardive Dyskinesia

Symptoms:

- Sometimes irreversible
- Not painful, but cause embarrassment and disability
- Disappear during sleep

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Tardive Dyskinesia

Onset:
- Late in onset in relation to initiation of therapy (after at least one month)
- Within the first 5 years of treatment

Complications:
- Oral ulcerations
- Inability to wear dentures
- Eating difficulties
- Weight loss
- Respiratory difficulties

Chen J. *Ment Health Clin* 2012;1(7):17.

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Tardive Dyskinesia

Risk Factors:
- Increased age
  - Elderly 5 times more likely to develop
- Long treatment duration

Screening & Monitoring
- Abnormal Involuntary Movement Scale (AIMS)
- Dyskinesia Identification System Condensed User Scale (DISCUS)

Jeste D. *J Clin Psychiatry* 2004;65 (Suppl 9):21-4.
Guy W. AIMS ECDUE Assessment Manual for Psychopharmacology.1976:534-7.
Sprague R, et al. *Psychopharmacol Bull* 1991;27(1):51-8.

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AIMS

- Uses a 5-point rating scale
- Facial and oral movements
  - Muscles of facial expression
  - Lips and Perioral area
  - Jaw
  - Tongue
- Extremity Movements
  - Upper
  - Lower

Guy W. AIMS ECDUE Assessment Manual for Psychopharmacology. 1976:534-7.

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AIMS

- Trunk Movements
- Severity of Movements
- Patient's awareness
- Dental Status

Guy W. AIMS ECDUE Assessment Manual for Psychopharmacology. 1976:534-7.

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Practice Question

Which of the following antipsychotics is the least likely to cause tardive dyskinesia?

A. Risperidone
B. Haloperidol
C. Clozapine

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Tardive Dyskinesia: Management

- Early detection is key because the longer the duration of TD, the less likely that remission will occur.
- Occasionally TD may occur when an antipsychotic is withdrawn. This usually improves within 3 months.

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Tardive Dyskinesia: Management

- Discontinuing or reducing dose
  - May consider a switch to a second-generation antipsychotic
- Discontinuing anticholinergic medications
- Treatment has limited efficacy
  - Vitamin E (off-label)
  - Others

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Practice Scenario:

Matt is an 62-year-old male diagnosed with schizophrenia. His doctor recently increased the dose of his risperidone (Risperdal®) because he continued to have hallucinations. He is complaining that he has trouble sitting still. Which of the following movement disorders is Greg likely experiencing?

A. Acute Dystonia
B. Akathisia
C. Pseudoparkinsonism

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Consequences of EPS

- Worse negative symptoms
- Worse cognition
- Worse depression/suicidality
- Increased risk of tardive dyskinesia

Tandon R. *Ann Clin Psychiatry* 2002;14:123-9.

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FGAs vs SGAs

- Most studies comparing FGAs and SGAs focused on efficacy
- EPS is less frequent than several decades ago

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Comparing Haloperidol to Second Generation Antipsychotics

- 7 randomized controlled trials showed that haloperidol increased rates of EPS compared to a second-generation antipsychotics
- In 2009, meta-analysis also showed that haloperidol had increased rates of EPS

Pakpoor J et al. *Psychiatr Danub* 2014; 26 (Suppl 1):273-84.
Leucht S et al. *Lancet* 2009;373: 31-41.

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CATIE study

- 3-phase, 18-month, randomized controlled trial
- 2 FGAs (perphenazine and fluphenazine)
- 5 SGAs (clozapine, olanzapine, quetiapine, risperidone, ziprasidone)

Lieberman J et al. *N Engl J Med* 2005:353:1209-23.

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CATIE Outcome Measures

Outcome Measure	FGA	SGAs			
	Perphenazine (Trilafon®)	Olanzapine (Zyprexa®)	Quetiapine (Seroquel®)	Risperidone (Risperdal®)	Ziprasidone (Geodon®)
AIMS global severity score>=2	17%	14%	13%	16%	14%
Barnes Akathisia Rating Scale Global score >=3	7%	5%	5%	7%	9%
Simpson-Angus Extrapyramidal Signs Scale mean score>=1	6%	8%	4%	8%	4%

Lieberman J et al. *N Engl J Med* 2005:353:1209-23.

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CUtLASS

- Cost Utility of the Latest Antipsychotics in Schizophrenia Study
- Randomized controlled trial
- No difference in Parkinsonism between FGAs and SGAs

Peluso MJ et al. *Br J Psychiatry* 2012;200:387-92.

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2009 Meta-analysis

- Meta-analysis of randomized controlled trials to compare SGAs and FGAs
- Multiple outcomes including EPS
- SGAs fewer EPS than haloperidol
- SGAs (except clozapine, olanzapine, and risperidone) not better than low potency FGAs

Leucht S et al. *Lancet* 2009;373: 31-41.

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2013 Meta-analysis

- Meta-analysis of randomized controlled trials
- 15 antipsychotics (only 2 FGAs)
- Multiple secondary outcomes including EPS
- Clozapine fewer EPS than all others
- Haloperidol more EPS except for chlorpromazine and zotepine

Leucht S, et al. Lancet 2013;382:951-62.

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Tardive Dyskinesia Study

- Objective: Incidence of TD with SGAs compared to FGAs
- Prospective Cohort of 350 outpatients
- Rate-ratio=0.68 (95%CI 0.29-1.64)

Woods S, et al. *J Clin Psychiatry* 2010;71(4):463-74.

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Discrepancies

- In earlier studies, difference between FGA and SGAs may have been exaggerated
  - high-dose haloperidol
- CATIE minimized difference by selecting a study population at unusually low risk of EPS

Tandon R. *Curr Psychiatry* 2006;5(11):35-45.

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Tips for Antipsychotic Use

- GOAL – minimize EPS
- Focus on antipsychotic dosing to achieve an antipsychotic effect without EPS
- Select an antipsychotic and dosage with consideration of the individual's vulnerabilities

Tandon R. *Curr Psychiatry* 2006;5(11):35-45.

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Tips for Antipsychotic Use

- Avoiding EPS without anticholinergics is key
  - Better cognition
  - Less negative symptoms
  - Less dysphoria
  - Lower risk of tardive dyskinesia

Tandon R. *Curr Psychiatry* 2006;5(11):35-45.

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Conclusion

- EPS can greatly impact quality of life
- Importance of screening for both FGAs and SGAs
- Individualize treatment with consideration of patient's goals

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Questions?

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