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Pharmacology of Antipsychotics

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Disclosures

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- The presenter has no conflicts to disclose.

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Learning Objectives

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- Review mechanisms behind antipsychotic medications
- Classify antipsychotic medications based on pharmacology
- Consider common side effects of antipsychotic medications

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Epidemiology

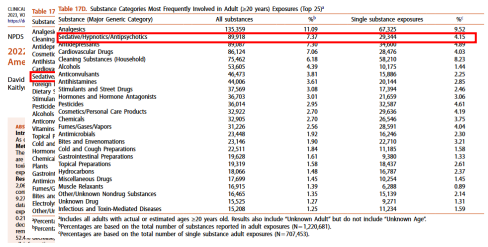

Table 17D. Substance Categories Most Frequently Involved in Adult (≥20 years) Exposures (Top 25)[a]

Substance (Major Generic Category)	All substances	%[b]	Single substance exposures	%[c]
Analgesics	135,359	11.09	67,335	9.52
Sedative/Hypnotics/Antipsychotics	89,918	7.37	29,344	4.15
Antidepressants	89,087	7.30	29,009	4.09
Cardiovascular Drugs	86,124	7.06	28,476	4.03
Cleaning Substances (Household)	75,462	6.18	58,210	8.23
Alcohols	53,605	4.39	10,175	1.44
Anticonvulsants	46,473	3.81	15,886	2.25
Antihistamines	44,006	3.61	20,144	2.85
Stimulants and Street Drugs	37,569	3.08	17,394	2.46
Hormones and Hormone Antagonists	36,703	3.01	21,659	3.06
Pesticides	36,014	2.95	32,587	4.61
Cosmetics/Personal Care Products	32,922	2.70	29,636	4.19
Chemicals	32,905	2.70	26,546	3.75
Fumes/Gases/Vapors	31,226	2.56	28,591	4.04
Antimicrobials	23,448	1.92	16,246	2.30
Bites and Envenomations	23,196	1.90	22,710	3.21
Cold and Cough Preparations	22,511	1.84	11,185	1.58
Gastrointestinal Preparations	19,628	1.61	9,380	1.33
Topical Preparations	19,319	1.58	18,437	2.61
Hydrocarbons	18,066	1.48	16,787	2.37
Miscellaneous Drugs	17,699	1.45	10,254	1.45
Muscle Relaxants	16,915	1.39	6,288	0.89
Other/Unknown Nondrug Substances	16,465	1.35	15,139	2.14
Unknown Drug	15,525	1.27	9,271	1.31
Infectious and Toxin-Mediated Diseases	15,208	1.25	11,234	1.59

[a]Includes all adults with actual or estimated ages ≥20 years old. Results also include "Unknown Adult" but do not include "Unknown Age".
[b]Percentages are based on the total number of substances reported in adult exposures (N = 1,220,681).
[c]Percentages are based on the total number of single substance adult exposures (N = 707,453).

Gummin DD, Mowry JB, Beuhler MC, et al. 2022 annual report of the national poison data system ® (NPDS) from america's poison centers ®: 40th annual report. *Clinical Toxicology*. 2023;61(10):717-939.

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Schizophrenia: Presentation

- **Positive symptoms:**
  - Hallucinations, excitability, delusions, thought disorders
- **Negative symptoms:**
  - Flat affect, anhedonia, lack of motivation, asociality
- **Cognitive dysfunction:**
  - Attention, memory, executive functioning
- **Affective symptoms**
  - Depression, anxiety

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Schizophrenia: Mechanisms

- Presynaptic **dopaminergic** overactivity is associated with psychosis symptoms
- Descending **glutamate** pathways from the prefrontal cortex are associated with both the positive and negative symptoms
- **Serotonergic** (5HT2A) pathways may be involved in cognition, mood, response to stressors

Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. Ingelfinger JR, ed. *N Engl J Med*. 2015;373(2):163-172.

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Dopamine Pathways

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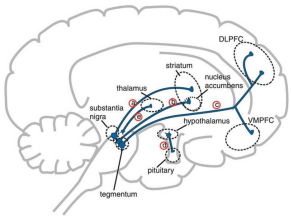
Dopamine Pathways and Key Brain Regions



- (a) Nigrostriatal Pathway
  - Motor function, movement
- (b) Mesolimbic Pathway
  - Pleasure, reward, psychosis
- (c) Mesocortical Pathway
  - Cognitive and affective symptoms
- (d) Tuberoinfundibular Pathway
  - Suppressing lactation
- (e) Thalamic Pathway
  - Sleep and arousal

Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application*. 4th ed. Cambridge University Press; 2013.

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Antipsychotic Medications

"Typical" Antipsychotics

"Atypical" Antipsychotics

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"Typical" Antipsychotics

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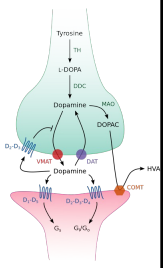
Dopamine Antagonists

- Earliest antipsychotics
- Positive symptoms are associated with excessive presynaptic dopamine release
- D_2 receptors are primarily post-synaptic
  - Inhibiting will improve symptoms in ~2/3 of patients



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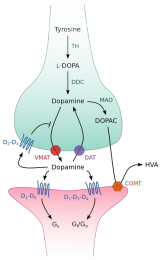
DA Antagonists: Adverse Effects

- Parkinsonism
- Akathisia
- Tardive dyskinesia
- Dystonia

Extrapyramidal Symptoms

- Prolactin elevation
- Glycemic control



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DA Antagonists: Adverse Effects

- **Parkinsonism**
- Akathisia
- Tardive dyskinesia
- Dystonia
- Prolactin elevation

Image: American Parkinson's Disease Association

- Tremor
- Rigidity
- Bradykinesia
- Vocal symptoms
- Postural instability
- Gait difficulties
- Cognitive changes
- Depression/anxiety

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DA Antagonists: Adverse Effects

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- Parkinsonism
- **Akathisia**
- Tardive dyskinesia
- Dystonia
- Prolactin elevation

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DA Antagonists: Adverse Effects

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- Parkinsonism
- Akathisia
- **Tardive dyskinesia**
- Dystonia
- Prolactin elevation

Amitriptyline induced tardive dyskinesia in a patient with cirrhotic Parkinsonism. *Indian Journal of Medical Specialities*. 2017;8(2):86-88.

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DA Antagonists: Adverse Effects

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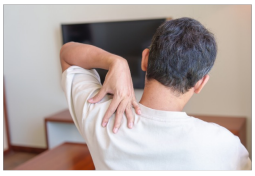
- Parkinsonism
- Akathisia
- Tardive dyskinesia
- **Dystonia**
- Prolactin elevation



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DA Antagonists: Adverse Effects

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TABLE 67–4 The Extrapyramidal Syndromes

Disorder	*Time of Maximal Risk*	*Features*	*Postulated Mechanism*	*Suggested Treatments*
Akathisia	Hours to days	Restlessness and general unease; inability to sit still	Mesocortical D_2 antagonism	Dose reduction, trial of alternate drug, propranolol, benzodiazepines, anticholinergics
Dystonia	Hours to days	Sustained, involuntary muscle contraction, including torticollis, blepharospasm, oculogyric crisis	Imbalance of dopaminergic or cholinergic transmission	Anticholinergics, benzodiazepines
Neuroleptic malignant syndrome	2–10 days	Many (Table 67–5): altered mental status, motor symptoms, hyperthermia, autonomic instability, catatonia, mutism	D_2 antagonism in striatum, hypothalamus, and mesocortex	Cooling, benzodiazepines, supportive care, bromocriptine, amantadine, or other direct-acting dopamine agonist
Parkinsonism	Weeks	Bradykinesia, rigidity, shuffling gait, masklike facies, resting tremor	Postsynaptic striatal D_2 antagonism	Dose reduction, anticholinergics, dopamine agonists
Tardive dyskinesia	3 months to years	Late-onset involuntary choreiform movements, buccolinguomasticatory movements	Excess dopaminergic activity	Recognize early and stop offending drug; addition of other antipsychotic; cholinergics

Nelson LS, Howland M, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. eds. *Goldfrank's Toxicologic Emergencies, 11e*. McGraw-Hill Education; 2019.

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DA Antagonists: Adverse Effects

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- Parkinsonism
- Akathisia
- Tardive dyskinesia
- Dystonia
- **Prolactin elevation**

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Drug Receptor Binding

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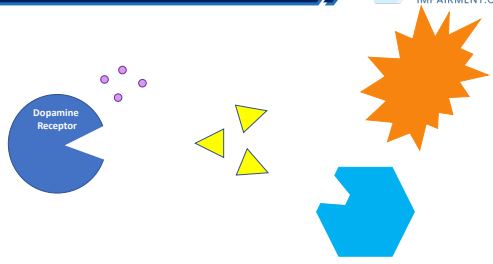

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Typical Antipsychotics

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Table 2 Potency and side-effects of traditional neuroleptics

Potency	Sedation	Hypotension	Anticholinergic effects	Extrapyramidal side-effects
High				
Haloperidol	Low	Low	Low	High
Fluphenazine	Medium	Low	Low	High
Intermediate				
Perphenazine	Low	Low	Low	High
Trifluoperazine	Medium	Low	Low	High
Thiothixene	Low	Low	Low	High
Loxapine	Medium	Medium	Medium	High
Low				
Chlorpromazine	High	High	Medium	Low
Thioridazine	High	High	High	Low

Bouman WP and Pinner G (2002) The Use of Atypical Antipsychotic Drugs in Old Age Psychiatry. Advances in Psychiatric Treatment, 8, 49-58.

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Typical Antipsychotics

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TABLE 67–2 Clinical and Toxicologic Manifestations of Selected Antipsychotics

	α_1-Adrenergic Antagonism	Muscarinic Antagonism	Fast Sodium Channel (I_{Na}) Blockade	Delayed Rectifier (I_K) Blockade
Clinical effect	Hypotension	Central and peripheral anticholinergic effects	QRS complex widening; myocardial depression	QT interval prolongation; torsade de pointes
Typical				
Chlorpromazine	+++	++	++	++
Fluphenazine	–	–	+	+
Haloperidol	–	–	+	++
Loxapine	+++	++	++	+
Mesoridazine	+++	+++	+++	++
Perphenazine	+	–	+	++
Pimozide	+	–	+	++
Thioridazine	+++	+++	+++	+++
Trifluoperazine	+	–	+	++

Nelson LS, Howland M, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. eds. *Goldfrank's Toxicologic Emergencies, 11e*. McGraw-Hill Education; 2019.

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Interactions and Metabolism

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TABLE 67–1 Classification of Commonly Used Antipsychotics

Classification	Antipsychotic	Usual Daily Adult Dose (mg)	Volume of Distribution (L/kg)	Half-Life (Range, h)	Protein Binding (%)	Active Metabolite
Typicals						
Butyrophenones	Droperidol	1.25–30	2–3	2–10	85–90	N
	Haloperidol	1–20	18–30	14–41	90	Y
Diphenylbutylpiperidines	Pimozide	1–20	11–62	28–214	99	Y
Phenothiazines						
Aliphatic	Chlorpromazine	100–800	10–35	18–30	98	Y
	Methotrimeprazine	2–50	23–42	17–78	NR	Y
	Promazine	50–1,000	30–40	8–12	98	N
	Promethazine	25–150	9–25	9–16	93	Y
Piperazine	Fluphenazine	0.5–20	220	13–59[a]	99	NR
	Perphenazine	8–64	10–35	8–12	>90	NR
	Prochlorperazine	10–150	13–32	17–27	>90	NR
	Trifluoperazine	4–50	NR	7–18	>90	Y
Piperidine	Mesoridazine	100–400	3–6	2–9	98	Y
	Thioridazine	200–800	18	26–36	96	Y
	Pipotiazine	25–250 (monthly IM depot)	7.5	3–11	NR	N

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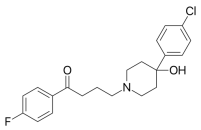
Haloperidol

- Most commonly used typical antipsychotic
- Dose range: 1-20 mg per day
- T ½: ~14-41 hours
- Decanoate version:
  - Dosed every 2-4 weeks



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Antipsychotic Medications

"Typical" Antipsychotics

"Atypical" Antipsychotics

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"Atypical" Antipsychotics

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Atypical Antipsychotics

Drug	D_2 Antag	D_2 PA	D_3	$5HT_{1A}$	$5HT_{2A}$	$5HT_{2C}$	$5HT_7$	α_1	M_1	M_3	H_1
Aripiprazole		+++	+++	+++	++	++	+++	++			++
Asenapine	+++		+++	++	++++	++++	++++	+++	+		+++
Clozapine	+		+	+	++	++	++	+++	+++	++	+++
Iloperidone	+++		++	++	+++	+	++	+++			++
Lurasidone	+++		?	+++	++	+	++++	++			
Olanzapine	++		++		+++	++	+	++	++	++	+++
Paliperidone	+++		+++	+	++++	++	+++	+++			++
Quetiapine	+		+	+*	++*	+*	++*	+++	++*	++*	+++*
Risperidone	+++		+++	+	++++	++	+++	+++			++
Ziprasidone	+++		+++	++	++++	++	+++	++			++
Therapeutic Effects	Reduced positive symptoms	Reduced positive symptoms	Reduced positive symptoms; Reduced negative symptoms; Procognitive; Antidepressant	Reduced EPS; Reduced hyperprolactinemia; Antidepressant; Anxiolytic	Reduced EPS; Reduced hyperprolactinemia	Antidepressant	Reduced circadian rhythm dysfunction; Reduced negative symptoms; Procognitive	Reduced nightmares	Reduced EPS	Reduced EPS	Hypnotic
Side Effects	EPS; Hyperprolactinemia; Increased negative symptoms; Increased negative symptoms; Increased cognitive deficits; Sedation	Relatively lower risk of EPS	Unknown	Unknown	Cardiometabolic	Cardiometabolic	Unknown	Dizziness; Sedation; Hypotension	Constipation; Sedation; Dry mouth; Blurred vision	Cardiometabolic; Constipation; Sedation; Dry mouth; Blurred vision	Cardiometabolic; Sedation

+ weak binding affinity (100>Ki<1000)
++ moderate binding affinity (10>Ki<100)
+++ strong binding affinity (1>Ki<10)
++++ very strong binding affinity (Ki<1)
? No data yet available
* Binding property due primarily to the metabolite norquetiapine

National Institutes of Mental Health Psychoactive Drug Screening Program. Cited 2012 Aug. Available from: http://pdsp.med.unc.edu/indexR.html. Stahl SM. Stahl's essential psychopharmacology. 3rd ed. New York, NY: Cambridge University Press; 2008

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Atypical Antipsychotics

- The major downsides are their metabolic effects:
  - Weight gain (sometimes extreme)
  - Drug induced diabetes mellitus
  - Cholesterol
- Many are anticholinergic and some can be sedating

Medication (brand)	Recommended dose range (mg/day)*	Half-life (hours)	Drug interactions*
Aripiprazole (*Abilify*)	10–30	75	Half dose with strong CYP3A4 or CYP2D6 inhibitors Double dose with CYP3A4 inducers
Asenapine (*Saphris*)	10–20	13–39	Cautiously approach coadministration with fluvoxamine and paroxetine; sublingual administration without food or drink for 10 minutes after administration
Clozapine (*Clozaril*)	150–600 (FDA max 900 mg)	12	Cautiously approach coadministration with drugs that involve CYP1A2, CYP2D6, and CYP3A4
Iloperidone (*Fanapt*)	12–24	18–33	Half dose with strong CYP2D6 and CYP3A4 inhibitors Half dose in poor metabolizers of CYP2D6
Lurasidone (*Latuda*)	40–160	18–31	Not recommended with strong CYP3A4 inhibitors or inducers Reduce dose with moderate CYP3A4 inhibitors; give after ≥350 calorie snack or meal
Olanzapine (*Zyprexa*)	10–30* *some settings allow 40 mg or more for difficult cases	33	Dose adjustment may be required with carbamazepine, fluvoxamine, fluoxetine, omeprazole, and rifampin
Paliperidone ER (*Invega*)	3–12	23	Dose adjustment may be required with carbamazepine and divalproex sodium
Quetiapine (*Seroquel, SeroquelXR*)	300–750* *some settings allow 1200 mg or more for difficult cases	6	A decrease in dose may be required with CYP3A and CYP2D6 inhibitors An increase in dose may be required with hepatic enzyme inducers such as carbamazepine, phenytoin, barbiturates, rifampicin, sulphonylureas, griseofulvin, and excess alcohol
Risperidone (*Risperdal*)	2–8	24	Dose adjustment may be required with cimetidine, ranitidine, clozapine, fluoxetine, paroxetine, carbamazepine, and other known enzyme inducers
Ziprasidone (*Geodon*)	80–160* *some settings allow up to 320 mg for difficult cases	7	Dose adjustment may be required with CYP3A4 inhibitors and inducers; give after ≥500 calorie snack or meal

Stahl SM, Morrissette DA, Citrome L, et al. "Meta-guidelines" for the management of patients with schizophrenia. *CNS Spectr*. 2013;18(3):150-162.

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Clozapine

- The first "atypical" antipsychotic
- D2, 5HT2A receptor antagonist
- Very anticholinergic. Uniquely does not cause EPS.
- Can be useful in refractory patients who failed to respond to other therapies called "awakeners"
- Side effects:
  - Hypersalivation
  - Extreme weight gain
  - Hyperglycemia
  - Agranulocytosis
- Requires extensive and frequent blood monitoring

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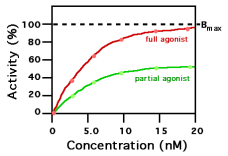
"Third Generation"

- Aripiprazole, brexpiprazole, cariprazine
- In general, fewer metabolic side effects
- D2 partial agonists



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Long-acting injectables

- Several of the atypicals are available as long-acting injectables:
  - Aripiprazole
  - Paliperidone
  - Risperidone
  - Olanzapine
- Dosed infrequently, improves adherence
- Downsides: cannot be easily reversed

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