Antipsychotic Comparison: Advanced Clinical Reference

💊 First-Generation Antipsychotics (FGAs) vs Second Generation Antipsychotics (SGAs)

This comprehensive reference provides detailed comparisons between antipsychotic classes for psychiatric prescribers, with evidence-based clinical pearls and monitoring recommendations.

🧠 Receptor Binding Profiles

RECEPTOR	FGAs	SGAs	CLINICAL SIGNIFICANCE
🔵 D_2	High affinity, tight binding	Lower affinity, fast dissociation	FGAs: ↑ EPS, hyperprolactinemia SGAs: ↓ EPS risk, "hit and run" binding
🟣 5-HT_2A	Minimal to moderate	High (5-HT_2A/D_2 ratio >1)	SGAs: ↓ EPS, possible ↑ efficacy for negative symptoms
🟠 α_1	Variable to high	Moderate	Orthostatic hypotension, dizziness, reflex tachycardia
🟢 H_1	Variable to high	Moderate	Sedation, weight gain
🔴 M_{1-4}	High	Variable	Anticholinergic effects, cognitive impairment

Efficacy

NexGen Psychiatry Starter Kit

⚖️ Comparative

DOMAIN	FGAs	SGAs	EVIDENCE QUALITY
🎯 Positive symptoms	Effective	Effective	High
😐 Negative symptoms	Limited	Modest	Moderate
🧠 Cognitive symptoms	Limited/	Modest	Moderate
🛡️ Treatment-resistant	Limited	Clozapine	High
🔄 Relapse prevention	Effective	Effective	Moderate
✨ Quality of life	Moderate	Modest	Moderate

advantage

advantage

advantage

superior

(possibly superior)

advantage

⚠️ Side Effect Profiles: Comparative Risk Assessment - Extrapyramidal Symptoms

SIDE EFFECT	HIGH RISK FGAs	HIGH RISK SGAs	MONITORING
☐ Acute dystonia	Haloperidol, fluphenazine	Rare with SGAs	Onset: Hours to days	AIMS, SAS, BARS
☐ Parkinsonism	All FGAs	Risperidone, paliperidone	Onset: Days to weeks	(dose-dependent)	Assess gait, rigidity, tremor
☐ Akathisia	All FGAs	Aripiprazole, lurasidone	Onset: Days to weeks	BARS scale
☐ Tardive dyskinesia	All FGAs	SGAs	AIMS q3-6 months	(4-5% annual risk)	(0.5-1% annual risk)	VMAT2 inhibitors	if detected

Side Effect Profiles: Comparative Risk Assessment - Metabolic Effects

SIDE EFFECT	HIGH RISK FGAs	HIGH RISK SGAs	MONITORING
☐ Weight gain	Low	Clozapine, olanzapine > quetiapine, risperidone > others	BMI, waist circumference Baseline, 4 weeks, q3 months
☐ Diabetes risk	Low-moderate	Clozapine, olanzapine > quetiapine, risperidone > others	FPG/HbA1c: Baseline, 3 months, annually Monitor polyuria, polydipsia
☐ Dyslipidemia	Low-moderate	Clozapine, olanzapine > quetiapine, risperidone > others	Lipid panel: Baseline, 3 months, annually

Side Effect Profiles: Comparative Risk Assessment - Cardiovascular Effects

SIDE EFFECT	HIGH RISK FGAs	HIGH RISK SGAs	MONITORING
☐ QTc prolongation	Thioridazine, pimozide iloperidone	Ziprasidone, dose changes Avoid if QTc >500ms	ECG: Baseline, or ↑ >60ms
☐ Orthostatic hypotension	Chlorpromazine, thioridazine	Clozapine, quetiapine,	Orthostatic vitals Titrate slowly in iloperidone elderly
☐ Myocarditis/ cardiomyopathy (0.1-1%)	Rare	Clozapine	Troponin, CRP, BNP if suspected Highest risk: first 2 months

Side Effect Profiles: Comparative Risk Assessment - Other Effects

SIDE EFFECT	HIGH RISK FGAs	HIGH RISK SGAs	MONITORING

Hyperprolactinemia	All FGAs	Risperidone, paliperidone >	Assess menstrual irregularities, others
Anticholinergic	Chlorpromazine, thioridazine	Clozapine, olanzapine	Monitor cognition, constipation, urinary retention
Sedation	Chlorpromazine, olanzapine, quetiapine	Clozapine, somnolence, dose at bedtime if sedating	Assess daytime
Seizure risk	Low-moderate (dose-dependent)	Clozapine seizures	EEG if history of Consider prophylaxis if >600mg clozapine
Neutropenia/ agranulocytosis (0.8% agranulocytosis)	Rare	Clozapine	ANC monitoring per REMS protocol

Pharmacokinetic Considerations

PARAMETER	CLINICAL IMPLICATIONS	HIGH-RISK AGENTS
CYP450 Metabolism		
1A2 substrates	↑ levels with	Clozapine, olanzapine, fluvoxamine, ciprofloxacin, caffeine
2D6 substrates	↑ levels with	Risperidone, aripiprazole, iloperidone, paroxetine, fluoxetine, bupropion
3A4 substrates	↑ levels with	Quetiapine, lurasidone, clarithromycin, ketoconazole, grapefruit, pimozide

Protein Binding		
High (>90%)	Displacement	Haloperidol, lurasidone, interactions, free fraction changes
Half-life		
Short (<12h)	More frequent dosing,	Quetiapine IR, ziprasidone, rapid washout
Long (>24h)	Once daily dosing,	Aripiprazole, cariprazine, extended withdrawal

Active Metabolites | | | Present | Extended effect, | Risperidone → paliperidone | | | altered side effect | Aripiprazole → | | | profile | dehydroaripiprazole |

Special Populations: Comparative Safety

POPULATION	PREFERRED AGENTS	AGENTS TO AVOID	SPECIAL CONSIDERATIONS
Elderly	Quetiapine	FGAs (↑ EPS,	Start low, go			(low dose)	falls)	slow			Aripiprazole	Clozapine,	↓ dose by 30-50%			Brexpiprazole	olanzapine	Monitor				(↑ anticholinergic)| orthostasis
Pregnancy	Haloperidol	Clozapine	Category C:			Risperidone	(agranulocytosis)	risk/benefit			Quetiapine	Newer agents	Monitor neonatal				(limited data)	EPS
			Avoid polypharmacy
Hepatic	Paliperidone	Clozapine	↓ dose by 50% in		impairment	Asenapine	Olanzapine	moderate				impairment				Monitor LFTs
Renal	Olanzapine	Paliperidone	↓ dose for CrCl		impairment	Quetiapine	Amisulpride	<50 mL/min				Monitor for ↑					side effects
Seizure	Haloperidol	Clozapine	Lower threshold:

| disorder | Risperidone | Chlorpromazine | clozapine > | | | | olanzapine > FGAs | | | | > risperidone |

Clinical Pearls

Cross-titration strategies:

• FGA → SGA: Overlap for 1-2 weeks, gradually ↓ FGA while ↑ SGA		• High anticholinergic → Low anticholinergic: Slow taper to avoid withdrawal		cholinergic rebound		• Clozapine initiation: Consider inpatient for first 2 weeks to monitor for		agranulocytosis, seizures, myocarditis

Antipsychotic equivalencies (approximate):

| 100mg chlorpromazine ≈ 2mg haloperidol ≈ 2mg risperidone ≈ 5mg olanzapine | | ≈ 75mg quetiapine ≈ 60mg ziprasidone ≈ 7.5mg aripiprazole |

Clozapine optimization:

| • Therapeutic plasma levels: 350-450 ng/mL | | • Consider divided dosing to minimize sedation and seizure risk | | • Manage constipation aggressively (can be fatal) | | • Smoking cessation requires dose reduction (↓ 1A2 induction) |

Treatment resistance considerations:

| • True resistance: Inadequate response to 2+ antipsychotics (1 SGA) at | | adequate dose/duration | | • Before clozapine: Confirm adherence (consider LAI), rule out substance use, | | optimize psychosocial interventions | | • Augmentation strategies: Evidence strongest for clozapine + ECT |

Long-acting injectable (LAI) selection factors:

| • Oral tolerability established first | | • Half-life considerations: Risperidone microspheres (2 weeks) vs. | | paliperidone palmitate (1-3 months) | | • Injection site reactions: Deltoid vs. gluteal (absorption differences) | | • Missed dose protocols vary by agent |

Antipsychotic discontinuation:

| • Supersensitivity psychosis risk with abrupt D_2 antagonist discontinuation | | • Taper over 3+ months when possible | | • Withdrawal dyskinesia may be temporary | | • Monitor for rebound insomnia, anxiety, psychosis, autonomic symptoms |

Cardiometabolic monitoring:

• American Diabetes Association/American Psychiatric Association consensus:		Baseline, 4 weeks, 8 weeks, 12 weeks, quarterly, then annually		• Consider metformin for antipsychotic-induced weight gain (especially | | olanzapine)		• Switching strategies for metabolic issues: Consider aripiprazole,		brexpiprazole, lurasidone, ziprasidone, cariprazine

References

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