

Schizophrenia

Clinical Background

Schizophrenia is a mental illness that severely impairs social and mental functioning.

Epidemiology

- Incidence – 2-4/1000
 - Lifetime prevalence of 1%
- Age – onset in 20s, younger age for men
- Sex – M>F

Risk Factors

- Family history is strongly correlated
- Other less-correlated factors
 - Cannabis use
 - CNS infection in childhood
 - Maternal obstetrical complications

Pathophysiology

- Neurotransmitter is likely involved in dopamine transmission
 - Drugs that induce states similar to schizophrenia increase dopaminergic transmission
 - Drugs that treat schizophrenia decrease dopaminergic transmission

Clinical Presentation

- Hallucinations, delusions
- Disorganized speech
- Disorganized behavior
- Signs and symptoms must be present >30 days in the absence of treatment

Treatment

- Antipsychotic drugs are the mainstay of therapy
- Dopamine D2 antagonists – chlorpromazine, clozapine, fluphenazine, fluphenazine decanoate, haloperidol, haloperidol decanoate, loxapine, molindone, perphenazine, thioridazine, thiothixene, trifluoperazine
- Atypical mixed neuroreceptor antagonists (low affinity D2 antagonists, high-affinity 5-HT_{2A} antagonists) – aripiprazole, chlorpromazine, clozapine, olanzapine, quetiapine, risperidone, thioridazine, ziprasidone
- Hepatic phase 1 oxidation is catalyzed by cytochrome P450 (CYP)
 - Inheritance of clinically significant CYP2D6 variants alter drug metabolism

Diagnosis

- Based on clinical presentation plus psychiatric evaluation

Differential Diagnosis

- Brief psychotic episode
- Delirium
- Acute or chronic medical illness
- Substance abuse
- Schizophreniform disorders

- Medication-induced disorder
- Pervasive developmental disorder

Monitoring

- Important to be aware of drug interactions (see CYPs with Major Roles in the In-Vivo Clearance of Antipsychotic Agents table below)
 - Hepatic phase 1 oxidation is catalyzed by cytochrome P450 (CYP)
 - Inheritance of clinically significant CYP2D6 variants alter drug metabolism
- Pharmacogenetic testing may guide drug and dose selection
- Periodic drug monitoring is useful to assure compliance, identify drug-drug interactions or other reasons to adjust dosing, and may establish optimal therapeutic ranges for an individual patient
- Suggested therapeutic ranges and toxic thresholds are available for some but not all commonly used antipsychotic drugs (see Pharmacokinetics of Antischizophrenic Therapeutics table below)
- Additional clinical testing (such as complete blood count, liver enzyme testing) is required for some drugs to detect toxicity

CYPs with Major Roles in the In-Vivo Clearance of Antipsychotic Agents				
CYP	Antipsychotic drug	Inhibitors	Inducers	Number of allelic variants
1A2	Clozapine Haloperidol Olanzapine	Amiodarone Cimetidine Ciprofloxacin	Omeprazole	24 plus wild-type (also 9 predicted haplotypes)
2C19	R-mephobarbital	Cimetidine Fluoxetine Lansoprazole Omeprazole Topiramate	Carbamazepine	
2D6	Aripiprazole Chlorpromazine Haloperidol Risperidone Thioridazine	Celecoxib Cimetidine Diphenhydramine Fluoxetine Methadone Paroxetine Ranitidine	Dexamethasone	94 plus wild-type
3A4/5/7	Aripiprazole Haloperidol Quetiapine Risperidone Ziprasidone	Cimetidine Clarithromycin Diltiazem Erythromycin HIV antivirals Norfloxacin Verapamil	Carbamazepine Dexamethasone Phenytoin Rifampicin	38 plus wild-type

P450 Drug Interactions: Abbreviated Clinically Relevant Table [↗](#)
 Cytochrome P450 drug interaction table [↗](#)

Pharmacokinetics of Antischizophrenic Therapeutics	
Aripiprazole	
Rapid Metabolizers	
Aripiprazole	De hydro-aripiprazole

Time to peak plasma level	3-5 hours (PO) 1-3 hours (IM)	
Half-life	75 hours	94 hours
Therapeutic range	No published data	
Poor Metabolizers		
	Aripiprazole	De hydro-aripiprazole
Time to peak plasma level	60% higher exposure to drugs	
Half-life		
Chlorpromazine		
Rapid Metabolizers		
	Chlorpromazine	7 hydroxy chlorpromazine
Time to peak plasma level	30 minutes-8 hours (highly variable)	
Half-life	23-37 hours	10-40 hours
Therapeutic range		
Clozapine		
Rapid Metabolizers		
	Clozaril	
Time to peak plasma level	1-6 hours	
Half-life	4-12 hours	
Therapeutic range	350-500 ng/mL	
Toxic threshold (when available)		
Fluphenazine		
Rapid Metabolizers		
	Fluphenazine	
Time to peak plasma level	1-8 hours (but peak plasma with steady state may be 3 months)	
Half-life		
Therapeutic range	0.2-2.0 ng/mL (from LTD)	
Haloperidol		
Rapid Metabolizers		
	Haloperidol	Hydroxyperidol
Time to peak plasma level	2-6 hours (PO) 10-20 (IM)	
Half-life	24 hours (PO) 21 hours (IM)	
Therapeutic range	2.0-15.0 ng/mL (from LTD)	
Loxapine		
Rapid Metabolizers		
	Loxapine	
Time to peak plasma level	1.5-3 hours (PO)	

	20-30 minutes (IM)	
Half-life	4 hours (PO) 12 hours (IM)	
Therapeutic range		
Molindone		
Rapid Metabolizers		
	Molindone	
Time to peak plasma level	1.5 hours	
Half-life	24-36 hours	
Therapeutic range	Not established	
Olanzapine		
Rapid Metabolizers		
	Olanzapine	
Time to peak plasma level	6 hours (PO) 15-45 minutes (IM)	
Half-life	21-54 hours	
Therapeutic range	5-75 ng/ml (from LTD)	
Perphenazine		
Rapid Metabolizers		
	Perphenazine	
Time to peak plasma level	4-8 hours (PO) 30-60 minutes (IM)	
Half-life	9 hours	
Therapeutic range	0.8-2.4 ng/mL (from LTD)	
Quetiapine		
Rapid Metabolizers		
	Quetiapine	N-des alkyl quetiapine
Time to peak plasma level	1.5 hours (IR) 6 hours (ER)	
Half-life	7 hours	9-12 hours
Therapeutic range	Suggested range 70-170 ng/mL	
Risperidone		
Rapid Metabolizers		
	Risperidone	9-hydroxyrisperidone
Time to peak plasma level	1-2 hours (steady state = 1 day)	(steady state = 5-6 days)
Half-life	3 hours	20 hours
Therapeutic range		
Poor Metabolizers		
	Risperidone	9-hydroxyrisperidone
Time to peak plasma level	1 hour (steady state = 1 day)	17 hours (steady state = 6-8 hours)

Half-life	20 hours	30 hours
Therapeutic range		
Thioridazine		
Rapid Metabolizers		
	Thioridazine	
Time to peak plasma level		
Half-life		
Therapeutic range		
Thiothixene		
Rapid Metabolizers		
	Thiothixene	
Time to peak plasma level	1-3 hours	
Half-life	3-34 hours	
Therapeutic range	1.0-12.0 ng/mL (from LTD)	
Trifluoperazine		
Rapid Metabolizers		
	Trifluoperazine	
Time to peak plasma level	No information available	
Half-life		
Therapeutic range		
Ziprasidone		
Rapid Metabolizers		
	Ziprasidone	
Time to peak plasma level	6-8 hours (IM) 1-3 days (PO)	
Half-life	2-7 hours	
Therapeutic range	Not established	

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Chlorpromazine 0090870 Method: High Performance Liquid Chromatography	Monitoring chlorpromazine Evaluate compliance		

<p>Clozapine 0098930</p> <p>Method: High Performance Liquid Chromatography</p>	<p>Use along with white blood cell and absolute neutrophil counts test for monitoring clozapine</p> <p>Evaluate compliance</p>		
<p>Haloperidol 0099640</p> <p>Method: High Performance Liquid Chromatography</p>	<p>Monitoring haloperidol</p> <p>Evaluate compliance</p>	<p>The therapeutic range relates to the management of psychoses; lower concentrations may be therapeutic for Tourette syndrome and mania</p> <p>The toxic range is not well established. Some patients experience toxicity within the therapeutic range</p>	
<p>Loxapine, Urine 0091499</p> <p>Method: High Performance Liquid Chromatography</p>	<p>Evaluate compliance</p>	<p>Serum or plasma are preferred for therapeutic monitoring</p>	
<p>Loxapine, Serum or Plasma 0091295</p> <p>Method: High Performance Liquid Chromatography</p>	<p>Monitoring loxapine</p> <p>Evaluate compliance</p>		
<p>Molindone (Moban®), Serum or Plasma 0091451</p> <p>Method: High Performance Liquid Chromatography/Mass Spectrometry</p>	<p>Monitoring molindone</p> <p>Evaluate compliance</p>		
<p>Molindone (Moban®), Urine 0091450</p> <p>Method: High Performance Liquid Chromatography/Mass Spectrometry</p>	<p>Evaluate compliance</p>	<p>Serum or plasma are preferred for therapeutic monitoring</p>	
<p>Olanzapine 0098833</p> <p>Method: High Performance Liquid Chromatography</p>	<p>Monitoring olanzapine</p> <p>Evaluate compliance</p>		

<p>Risperidone 0092055</p> <p>Method: Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS)</p>	<p>Use with the measurement of 9-hydroxyrisperidone when monitoring and evaluating metabolism of risperidone</p>		
<p>Seroquel®, Serum or Plasma 0091532</p> <p>Method: Gas Chromatography</p>	<p>Monitoring quetiapine Evaluate compliance</p>		
<p>Thiothixene 0099904</p> <p>Method: High Performance Liquid Chromatography</p>	<p>Monitoring thiothixene. Evaluate compliance</p>		
<p>Ziprasidone (Geodon®), Serum or Plasma 0091519</p> <p>Method: Liquid Chromatography/Mass Spectrometry</p>	<p>Use when monitoring the antischizophrenic therapy of ziprasidone Evaluate compliance</p>		
<p>Cytochrome P450 2D6 (CYP2D6) 14 Mutations & Gene Duplication 0051232</p> <p>Method: Polymerase Chain Reaction/Primer Extension</p>	<p>Detect variants in genes that code for drug metabolizing enzymes Clinical sensitivity: greater than 95% of the deleterious CYP2D6 mutations are detected in Caucasians; sensitivity is unknown in other ethnicities</p>	<p>Only the targeted CYP2D6 mutations will be detected; mutations in other genes will not be detected Rare diagnostic errors can occur due to primer site mutations</p>	

Cytochrome P450 2C19 by Tag-IT 0051104 Method: Polymerase Chain Reaction/Bead Hybridization	Screening for potential adverse reactions to schizophrenic drugs		
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Additional Tests Available

Test Name and Number	Comments
Lithium, Serum or Plasma 0020038 Method: Reflectance Spectrophotometry	

Additional Information

Additional genetic and drug tests relevant to schizophrenia may be available; contact ARUP Laboratories to discuss.

Guidelines

Tandon R, Belmaker RH, Gattaz WF, Lopez-Ibor JJ Jr, Okasha A, Singh B, Stein DJ, Olie JP, Fleischhacker WW, Moeller HJ. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. *Schizophr Res.* 2008; 100 (1-3) :20-38.

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Caravati EM, Juenke JM, Crouch BI, Anderson KT. Quetiapine cross-reactivity with plasma tricyclic antidepressant immunoassays. *Ann Pharmacother*. 2005; 39 (9) :1446-1449.

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