

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) |

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|---------------------------|---------------------------------|----------|
| 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> | |

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|--|--|--|--|
| 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

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