Therapy of Schizophrenia

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A 19-year-old male student is brought into the clinic by his mother who has been concerned about her son's erratic behavior and strange beliefs. He destroyed a TV because he felt the TV was sending harassing messages to him. In addition, he reports hearing voices telling him that family members are trying to poison his food. As a result, he is not eating. After a diagnosis is made, haloperidol is prescribed at a gradually increasing dose on an outpatient basis. The drug improves the patient's positive symptoms but ultimately causes intolerable adverse effects including severe akathisia. Lurasidone is then prescribed, which, over the course of several weeks of treatment, improves his symptoms and is tolerated by the patient.

In the treatment of schizophrenia, what benefits do the second-generation antipsychotic drugs offer over the traditional agents such as haloperidol?

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- **Schizophrenia represents a heterogeneous syndrome of disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect, and impaired psychosocial functioning.**
- **Multiple neurotransmitter dysfunctions are involved in schizophrenia.**
- **The etiology is more likely mediated by multiple subcellular processes that are influenced by different genetic polymorphisms.**

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- **Antipsychotics are similar regarding the beneficial effect.**
- **Therefore, adverse effect profiles are important for appropriate selection of an antipsychotic drug for an individual patient.**
- **Pharmacotherapy guidelines emphasize antipsychotics monotherapies with adequate benefit/risk ratios.**
- **Combination regimens should only be used in the most treatment-resistant patients.**

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- **Long-term maintenance antipsychotic treatment is needed for the vast majority of patients in order to prevent relapse.**
- **Psychosocial rehabilitation programs should be used in combination with antipsychotic treatment to be effective.**
- **Most deterioration in psychosocial functioning occurs during the first 5 years after the initial psychotic episode, and treatment should be particularly used during this period.**

Drug-Induced Psychosis

1. Cannabis, Marijuana
2. Cocaine
3. Amphetamines: ecstasy (MDMA), methamphetamine, methylphenidate
4. LSD
5. Phencyclidine and ketamine
6. Alcohol

- **Patients with schizophrenia who continue to abuse alcohol or drugs usually have a poor response to medications and a poor prognosis.**

- Opioids
- Drugs for Parkinsonism
- NSAIDs
- Digitalis
- Beta-blockers
- Corticosteroids
- Antihistamines
- Sedatives, benzodiazepines
- Mushrooms poisoning
- Others

Medical Causes of Psychosis

- HIV (AIDS)
- Malaria
- Syphilis
- Alzheimer's disease
- Parkinson's disease
- Hypoglycaemia
- SLE
- Multiple sclerosis

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Desired Outcome:

1. **Avoiding unwanted adverse effects of therapy.**
2. **Integrating the patient back into the community.**
3. **Increasing adaptive functioning.**
4. **Preventing relapse.**

TABLE 29–1 Antipsychotic drugs: Relation of chemical structure to potency and toxicities.

Chemical Class	Drug	D_2/5-HT_{2A} Ratio[1]	Clinical Potency	Extrapyramidal Toxicity	Sedative Action	Hypotensive Actions
Phenothiazines						
Aliphatic	Chlorpromazine	High	Low	Medium	High	High
Piperazine	Fluphenazine	High	High	High	Low	Very low
Thioxanthene	Thiothixene	Very high	High	Medium	Medium	Medium
Butyrophenone	Haloperidol	Medium	High	Very high	Low	Very low
Dibenzodiazepine	Clozapine	Very low	Medium	Very low	Low	Medium
Benzisoxazole	Risperidone	Very low	High	Low[2]	Low	Low
Thienobenzodiazepine	Olanzapine	Low	High	Very low	Medium	Low
Dibenzothiazepine	Quetiapine	Low	Low	Very low	Medium	Low to medium
Dihydroindolone	Ziprasidone	Low	Medium	Very low	Low	Very low
Dihydrocarbostyril	Aripiprazole	Medium	High	Very low	Very low	Low

[1] Ratio of affinity for D_2 receptors to affinity for 5-HT_{2A} receptors.

[2] At dosages below 8 mg/d.

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Some Antipsychotics:

1. **First-Generation Antipsychotics (FGAs): Chlorpromazine, Haloperidol, Thiothixine, Loxapine.**

- **Mechanism: They block dopaminergic neurotransmission mainly. They also have noradrenergic, cholinergic, and histaminergic blocking action.**

2. **Second-Generation Antipsychotics (SGAs): Aripiprazole, Clozapine, Olanzapine, Quetiapine, Risperidone, Ziprasidone.**

- **Mechanism: blocking D_2 dopamine receptors as well as 5-HT_{2A} serotonin receptor.**

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Pharmacologic Therapy:

- **Exclude general medical or substance-induced causes of psychosis.**
- **Use a drug that produce antipsychotic response with few or no acutely occurring extrapyramidal adverse effects (EPS).**
- **The major advantage of SGAs is their lower risk of neurologic adverse effects, particularly motor effects.**
- **However, some SGAs have increased risk of metabolic adverse effects, such as, weight gain, hyperlipidemias, and diabetes mellitus.**

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A. Initial Treatment of an Acute Psychotic Episode:

- **The goals during the first 7 days of treatment should be reduction of symptoms (agitation, hostility, combativeness, anxiety, tension, and aggression) and normalization of sleep and eating patterns.**
- **In first-episode psychotic patients, typical dosing ranges are ~ 50% of the doses used in chronically ill individuals, because of increased susceptibility to EPS. (aripiprazole, risperidone or ziprasidone).**

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- **Previously treated patients: use any antipsychotic except clozapine and antipsychotics that were not effective or poorly tolerated by the patient.**
- **Patients who were not responsive with 2 antipsychotic trials, and patients who were severely suicidal, clozapine monotherapy may be attempted.**

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B. Stabilization Therapy:

- **If the patient begins to show adequate response at a particular dose, then the patient should continue at this dose.**
- **Improvement is usually a slow but steady process over 6 - 12 weeks or longer:**

a) **Increased socialization and improvement in self-care habits and mood take 2-3 weeks to occur.**

b) **Improvement in formal thought disorder can take an additional 6 - 8 weeks to occur.**

c) **Chronically ill patients may need 3-6 months to improve.**

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- **Before changing medications in a poorly responding patient, the following should be considered:**

1. **Confirm the diagnosis of schizophrenia, or exclude a different diagnosis, a long-standing behavioral problem, a substance abuse disorder, or a general medical condition.**
2. **Check weather the patient has a treatment-resistant schizophrenia.**

- **Medications are effective at decreasing the symptoms of schizophrenia (palliative), but they are not curative. Some symptoms may remain.**

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C. Maintenance Treatment:

- **Maintenance drug therapy prevents relapse.**
- **After treatment of the first psychotic episode, medication should be continued for 1 - 5 years after remission.**
- **In chronically ill individuals, continuous or lifetime pharmacotherapy is necessary in the majority of patients to prevent relapse, using the lowest effective - tolerable dose of the antipsychotic.**

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- **Antipsychotics should be tapered slowly over at least 1 - 2 weeks while the second antipsychotic is initiated and the dose titrated up.**
- **Antipsychotic tapering needs to occur more slowly with clozapine.**
- **Abrupt discontinuation, especially for clozapine, can result in withdrawal symptoms: Insomnia, nightmares, headaches, GI symptoms (abdominal cramps, stomach pain, nausea, vomiting, and diarrhea), restlessness, increased salivation, and sweating.**

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Long-Acting Injectable (LAI) Antipsychotics:

- **Used for patients who are unreliable in taking oral medication on a daily basis.**
- **It may be offered as a treatment option earlier in treatment before patients become non-adherent to therapy.**
- **Before declaring a patient non-adherent, the cause should be identified.**

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- **If medication nonadherence is due to adverse effects, an alternative medication with a more favorable adverse effect profile should be considered before a long-acting injectable antipsychotic is given.**
- **Paliperidone palmitate is a long-acting injectable antipsychotic (once-monthly IM injection).**
- **Aripiprazole is available as once monthly injection that requires 2 - 3 weeks of oral antipsychotic overlap.**

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- **Olanzapine can be used as LAI administered every 2 - 4 weeks.**
- **It may be associated with a post-injection delirium/sedation syndrome in 2% of patients.**
- **The injection must be administered in a healthcare facility, and the patient must be observed for at least 3 hours after administration and must not drive or operate machinery for that day.**

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Management of Treatment-Resistant Schizophrenia:

- **“Treatment Resistant” describes a patient who has had inadequate response from multiple antipsychotic trials.**
- **In patients failing ≥ 2 pharmacotherapy trials, reexamine diagnosis, exclude substance abuse, medication non-adherence, and psychosocial stressors.**
- **Targeted cognitive behavioral therapy or psychosocial augmentation strategies should be considered.**

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- **Clozapine may be effective in the management of treatment-resistant schizophrenia.**
- **Symptomatic improvement occurs slowly (over 6 months).**
- **It has been effective in patients with severe suicidality, aggressive behavior, or those who cannot tolerate neurologic adverse effects of even low doses of other antipsychotics.**
- **Its use requires Absolute Neutrophil Count (ANC) monitoring.**

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- **Because of the risk of orthostatic hypotension, clozapine is usually titrated more slowly than other antipsychotics, particularly on an outpatient basis.**
- **Clozapine dose: should not exceed 900 mg daily.**
- **Initial dose: 12.5 mg orally once or twice a day**
  Titration and Maintenance dose: May increase total daily dose in increments of 25 - 50 mg per day to a target dose of 300 - 450 mg per day (administered in divided doses) by the end of week 2.

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Clozapine Monitoring:

- **A therapeutic window of 0.35 - 0.5 mg/L is suggested.**
- **Plasma levels greater than 0.6 mg/L are related to an increased risk of convulsions.**
- **Levels of around 0.6-0.8 mg/L have been proposed as the upper therapeutic limit.**
- **There is a clearer link between seizures and plasma levels over 1.0 mg/L and other types of toxicity with levels over 0.75 mg/L.**
- **For levels >1mg/L, consider cautious dose reduction and LFT (Liver Function Test) measurement.**
- **The norclozapine level under normal circumstances is expected to be around two thirds of the clozapine level.**
- **The plasma trough clozapine: norclozapine ratio (clozapine metabolic ratio) provides a simple measure of clozapine metabolism in individuals.**

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Pharmacokinetics:

- Antipsychotics are highly lipophilic and highly bound to membranes and plasma proteins, and have large volumes of distribution.
- Most antipsychotics are largely metabolized by CYPs.
- For those metabolized by CYP2D6, metabolism is polymorphic as patients may be poor, intermediate, rapid , or ultrarapid metabolizers.

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- **That is especially important for dosing and monitoring of antipsychotics.**
- **Most antipsychotics have long elimination half-lives ≥ 24 hours, with the exception of quetiapine and ziprasidone, which have shorter half-lives (2-10 hours).**

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Adverse Effects:

Endocrine System:

1. **Hyperprolactinemia due to dopamine blockade in the tuberoinfundibular system. It is associated with gynecomastia, galactorrhea, menstrual irregularities, decreased libido, and sexual dysfunction.**
2. **Weight gain: it has been associated with antihistaminic effects, antimuscarinic effects, and blockade of 5-HT_{2C} receptors.**

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Cardiovascular System:

1. **Orthostatic Hypotension (α-adrenergic blockade).**
2. **Sudden cardiac death.**
3. **Elevation of serum triglycerides and cholesterol.**
4. **Sinus tachycardia from anticholinergic effects.**
5. **Reflex tachycardia from α-adrenergic blockade.**
6. **Prolongation of QTc, which may be associated with polymorphic ventricular arrhythmias, including torsade de pointes syndrome. Most common with thioridazine and ziprasidone, but can be caused by other antipsychotics.**

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Anticholinergic Adverse Effects:

- **Dry mouth, constipation, tachycardia, blurred vision, impairment of erection, urinary retention, or impaired memory.**
- **Paralytic ileus and necrotizing enterocolitis can also occur.**

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Central Nervous System:

A. Extrapyramidal Symptoms:

- They are movement disorders due to excess dopamine blockade in the nigrostriatal pathway.

1. Dystonia:

- **Prolonged tonic contractions**, usually within 1-4 days of initiating or increasing the dose of an antipsychotic.
- They can be life-threatening, as in the case of pharyngeal–laryngeal dystonias

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- They can contribute to patient nonadherance.
- They include trismus, glossospasm, tongue protrusion, pharyngeal– laryngeal dystonia, blepharospasm, oculogyric crisis (spasmodic movements of the eyeballs into a fixed position, usually upwards), torticollis, and retrocollis.
- The risk of dystonia is greatly reduced with SGAs.
- Dystonia may be treated with Intramuscular or IV anticholinergics or benzodiazepines.

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2. Akathisia:

- **Defined as the inability to sit still associated with functional motor restlessness (pacing, shifting, shuffling, or tapping feet).**
- **Akathisia is common with some FGAs, frequently accompanied by dysphoria.**
- **May be associated with insomnia, increased suicidality and development of tardive dyskinesia.**
- **Quetiapine and clozapine appear to have the lowest risk of producing akathisia.**

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- **Benzodiazepines may be used, but not in the case of substance abuse.**
- **The β-blockers (propranolol, nadolol, and metoprolol) may be effective.**
- **5-HT_2 receptor antagonist (cyproheptadine, mirtazapine, and trazodone) may be protective against akathisia and may be used for its management.**

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3. Pseudoparkinsonism:

- Due to D_2 blockade in the nigrostriatum.
- More common with FGAs.
- The onset is typically 1 - 2 weeks after initiation or a dose increase.
- Can be treated with anticholinergic drugs (trihexyphenidyl, benztropine, orphenadrine), but may produce euphoria.
- Amantadine may be effective, but have less effect on memory function.

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- **Rotigotine, a dopamine agonist, may be effective.**
- **The risk of pseudoparkinsonism with SGAs is low, but may occur with risperidone at relatively large doses.**
- **Quetiapine, aripiprazole, and clozapine are reasonable alternatives in a patient experiencing EPS with other SGAs.**

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4. Tardive Dyskinesia (TD):

- **It is a syndrome characterized by abnormal involuntary movements buccal–lingual–masticatory, or orofacial.**
- **The onset is usually insidious, and appears late after initiation.**
- **The first detectable signs of tardive dyskinesia are mild forward, backward, or lateral movements of the tongue.**

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- Associated with higher overall morbidity and mortality.
- More prevalent with FGAs (20 - 50%).
- Short-term treatment of TD with either clonazepam or ginkgo biloba may be effective.
- Clozapine decreases abnormal involuntary movements.

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B. Sedation:

- **Chlorpromazine, thioridazine, clozapine, olanzapine, and quetiapine are the most sedating antipsychotics.**
- **Administration of most or all of the daily dosage at bedtime can decrease daytime sedation.**
- **Sedation occurs early in treatment and can decrease over time.**

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C. Seizures:

- **Antipsychotics decrease the seizure threshold.**
- **Seizures have been reported with most antipsychotics, but the highest risk is with clozapine or chlorpromazine.**
- **Lowest potential for seizures is with risperidone, thioridazine, haloperidol, pimozide, trifluoperazine, and fluphenazine.**

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D. Neuroleptic Malignant Syndrome (NMS):

- (NMS) occurs in 0.5% - 1% of patients receiving FGAs.
- Less common with SGAs, including clozapine.
- It develops rapidly, over the course of 24 - 72 hours.
- NMS can occur after antipsychotic discontinuation, especially when depot agents are used.
- Possible mechanisms include disruption of the central thermoregulatory process or excess production of heat secondary to skeletal muscle contractions.

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- **Signs and symptoms: temperature > 38°C, loss of consciousness, autonomic dysfunction (tachycardia, labile blood pressure, diaphoresis, tachypnea, or urinary or fecal incontinence), and muscle rigidity.**
- **Associated with leukocytosis and increased creatine kinase (CK), AST, ALT, LDH, and myoglobinuria.**
- **Treatment should begin with antipsychotic discontinuation and supportive care. Bromocriptine, amantadine, dantrolene (skeletal muscle relaxant).**

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Ophthalmologic Effects:

- **Exacerbation of narrow-angle (angle-closure) glaucoma (anticholinergic effect).**
- **Opaque deposits in the cornea and lens (chlorpromazine).**
- **Cataract (risperidone and quetiapine).**
- **Retinitis pigmentosa (thioridazine doses > 800 mg daily), due to melanin deposits and can result in permanent visual impairment or blindness.**

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Genitourinary System:

1. **Urinary hesitancy and retention secondary to anticholinergic effects (FGAs and clozapine).**
2. **Urinary incontinence due to α-blockade (clozapine).**
3. **Sexual dysfunction (dopaminergic blockade, hyperprolactinemia, histaminergic blockade, anticholinergic effects, and α-adrenergic blockade). Manifested by decreased libido, erectile dysfunction, difficulty achieving orgasm, and ejaculatory abnormalities.**
4. **Priapism (unprovoked sustained and painful erection). May be due to α_1-adrenergic receptor blockade, leading to intracavernosal blood stasis).**

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Hematologic System:

- **Agranulocytosis (clozapine (0.8%), chlorpromazine, and olanzapine).**
- **The onset is usually within the first 8 weeks of therapy.**
- **If the absolute neutrophil count (ANC) is < 500/µL, the antipsychotic should be discontinued and the ANC monitored closely until it returns to normal and also monitored closely for the development of infections.**

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- **The baseline ANC must be at least 1,500/µL in order to start clozapine.**
- **Weekly ANC monitoring for the first 6 months of therapy is required. Then every 2 weeks for the next 6 months.**
- **After this, monitoring can be decreased to monthly if all ANCs remains greater than 1,500/µL.**
- **If at any time the ANC drops to less than 500/µL, clozapine must be discontinued.**

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Skin:

- **Contact dermatitis**
- **Skin reaction with Eosinophilia (ziprasidone).**
- **Photosensitivity (all, especially chloropromazine).**
- **Blue-gray or purplish skin coloration in areas exposed to sunlight (chlorpromazine), concurrent with corneal or lens pigmentation.**
- **Exposure to sunlight should be limited (blocking sunscreen, hats, protective clothing, and sunglasses).**

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Miscellaneous Adverse Effects:

- **Sialorrhea (drooling) in 54% of patients (Clozapine).**
- **May be due to antagonistic effect on both α_1- and α_2-adrenergic receptors at the salivary glands leading to vasodilation and increased blood flow.**
- **Anticholinergics such as benztropine and atropine, and α_2-agonists such as clonidine have been used to treat clozapine-related sialorrhea.**

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Use in Pregnancy and Lactation:

- **There is a slightly increased risk of birth defects with FGAs.**
- **Haloperidol is the best studied of all antipsychotics, and no relationship between its use and teratogenicity has been found.**
- **Elevated risk of preterm birth in patients taking FGAs.**
- **Increased risk of cardiovascular defects with FGAs.**

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Postnatal and gestational complications:

1. **Weight gain (olanzapine and clozapine).**
2. **Increased risk of gestational diabetes (olanzapine and clozapine).**
3. **Risk of neonatal EPS (FGAs), with effects lasting for 3 - 12 months after birth.**
4. **Increased risk of hypertension as well as venous thromboembolism.**
5. **The FDA issued a safety announcement that the pregnancy risk applies for the entire antipsychotic class, highlighting the potential risk for EPS and withdrawal symptoms in newborns whose mothers were treated with antipsychotics during their third trimester.**

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Use During Lactation:

- **Antipsychotics appear in breast milk with milk-to-plasma ratios of 0.5:1.**
- **1 week after delivery, clozapine milk concentrations may reach 3X the plasma concentrations.**
- **Clozapine use during breast-feeding is NOT recommended due to the risk of bone marrow suppression.**
- **Aripiprazole and quetiapine are generally considered safe during breastfeeding.**

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- **Infants exposed to chlorpromazine through breast milk may become drowsy and lethargic.**
- **The co-administration of chlorpromazine and haloperidol may result in developmental delays at 12 - 18 months of age.**
- **The lowest effective dose of antipsychotics should be used in the mother, and the infant carefully monitored for antipsychotic adverse effects such as EPS, sedation, seizures and developmental delays.**

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Pharmacodynamic Drug Interactions:

1. **Excess sedation when antipsychotics are used with other sedative.**
2. **Additive antimuscarinic effects with other antimuscarinic drugs.**
3. **Both combined sedative and anticholinergic effects from multiple medications can result in impaired cognition, particularly in the elderly.**
4. **More orthostatic hypotension when used with other drugs that cause orthostasis.**

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5. **Metoclopramide lead to more akathisia and other EPS if it is used concomitantly with antipsychotics.**
6. **Careful monitoring is required when drugs that prolong the QTc interval are coadministered with antipsychotics having the same effect or with diuretics that produce hypokalemia.**

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7. **SSRIs can interact with antipsychotics:**

a) **5-HT_2 receptors are present on the presynaptic dopaminergic neuron, and their activation leads to decreased DA release from the presynaptic terminal.**

b) **Increased availability of 5-HT through SSRI effect can, thus, decrease DA release and add to the dopaminolytic effects of antipsychotics.**

c) **SSRIs can precipitate akathisia or EPS when added to a patient stabilized on an antipsychotic.**

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Pharmacokinetic Drug Interactions:

- **Antipsychotic drugs are metabolized by CYP2D6, CYP3A4 and CYP1A2.**
- **More than one of these isoenzymes may also metabolize a particular antipsychotic agent.**
- **Knowledge of common substrates, inducers and inhibitors of CYPs is necessary to predict the kind of interaction, when antipsychotics are co-administered with other drugs.**