Schizophrenia

Schizophrenia is one of the most complex and challenging of psychiatric disorders. It represents a heterogeneous syndrome of disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect, and impaired psychosocial functioning.

Clinical presentation:

Symptoms of the acute episode may include the following:

- being out of touch with reality;
- hallucinations (especially hearing voices);
- delusions (fixed false beliefs);
- ideas of influence (actions controlled by external influences);
- disconnected thought processes (loose associations);
- ambivalence (contradictory thoughts);
- flat, inappropriate, or labile affect;
- autism (withdrawn and inwardly directed thinking);
- uncooperativeness, hostility, and verbal or physical aggression;
- impaired self-care skills; and
- disturbed sleep and appetite.

After the acute psychotic episode has resolved, the patient typically has residual features (e.g., anxiety, suspiciousness, lack of volition, lack of motivation, poor insight, impaired judgment, social withdrawal, difficulty in learning from experience, and poor self-care skills). Patients often have comorbid substance abuse and are nonadherent with medications.

Factors affecting diagnosis and prognosis

There is a reluctance to classify people as suffering schizophrenia on the basis of one acute psychotic illness, but there are a number of features which aid prediction of whether an acute illness will become chronic. These features include:

- Age of onset, which, typically for schizophrenia, is late teenage to 30 years.
• Reports of a childhood which indicate the individual did not mix or was a rather shy and withdrawn personality
• A poor work record
• A desire for social isolation
• Being single and not seeming to have sexual relationships
• A gradual onset of the illness and deterioration from the previous level of functioning
• Grossly disorganised behaviour

Causes of schizophrenia:
Although the cause of schizophrenia remains unknown, there are many theories and models.

Vulnerability model:
The vulnerability model postulates that the persistent characteristic of schizophrenia is not the schizophrenic episode itself but the vulnerability to the development of such episodes of the disorder. The episodes of the illness are time limited but the vulnerability remains, awaiting the trigger of some stress.

Developmental model
The developmental model postulates that there are critical periods in the development of neuronal cells which, if adversely affected, may result in schizophrenia. Two such critical periods are postulated to occur when migrant neural cells do not reach their goal in fetal development and when supernumerary neural cells slough off at adolescence. This model is supported by neuroimaging studies which show structural brain abnormalities in patients with schizophrenia.

Ecological model
The ecological model postulates that external factors involving social, cultural and physical forces in the environment, such as population density, individual space, socio-economic status and racial status, influence the development of the disorder. The evidence in support of such a model remains weak.
Genetic model
There is undoubtably a genetic component to schizophrenia, with a higher incidence in the siblings of schizophrenics. However, even in monozygotic twins there are many cases where only one sibling has developed schizophrenia.

Transmitter abnormality model
The suggestion that schizophrenia is caused primarily by an abnormality of dopamine receptors and, in particular, D2 receptors, has largely emerged from research into the effect of antipsychotic drugs. Such a theory is increasingly being questioned.

Other factors
Numerous other factors have been implicated in the development and cause of schizophrenia. These include migration, socio-economic factors, perinatal insult, infections, season of birth, viruses, toxins and family environment.

Diagnosis
✓ Persistent dysfunction lasting longer than 6 months
✓ Two or more symptoms (present for at least 1 month), including hallucinations, delusions, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms
✓ Significantly impaired functioning (work, interpersonal, or self-care)

The Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision, classifies symptoms as positive or negative.

Positive symptoms (the ones most affected by antipsychotic drugs) include delusions, disorganized speech (association disturbance), hallucinations, behavior disturbance (disorganized or catatonic), and illusions.

Negative symptoms include alogia (poverty of speech), avolition, affective flattening, anhedonia, and social isolation.
Cognitive dysfunction is another symptom category that includes impaired attention, working memory, and executive function.
Goals of treatment:
The goals of treatment include the following:
- alleviation of target symptoms,
- avoidance of side effects,
- improvement in psychosocial functioning and productivity,
- compliance with the prescribed regimen, and involvement of the patient in treatment planning.

Treatment:
A thorough mental status examination, physical and neurologic examination, a complete family and social history, vital signs and laboratory workup (complete blood count, electrolytes, hepatic function, renal function, electrocardiogram [ECG], fasting serum glucose, serum lipids, thyroid function, and urine drug screen) should be performed prior to treatment.

Nonpharmacologic therapy
Psychosocial rehabilitation programs oriented toward improving patients’ adaptive functioning are the mainstay of nondrug treatment for schizophrenia. These programs may include basic living skills, social skills training, basic education, work programs, and supported housing.

Comprehensive Care Elements in the Treatment of Schizophrenia
- Medication treatment
- Individual supportive therapy
- Cognitive and psychosocial therapies
- Family psychoeducation and support
- Social support
- Case management
- Housing
- Financial support
- Vocational support

Second-generation antipsychotics (SGAs) (also known as atypical antipsychotics), except clozapine, are the agents of first choice in treatment of schizophrenia. Growing, but still controversial, evidence supports that the SGAs (e.g., clozapine, olanzapine,
risperidone, quetiapine, ziprasidone, and aripiprazole) have superior efficacy for
treatment of negative symptoms, cognition, and mood.

SGAs cause few or no acutely occurring extrapyramidal side effects. Other attributes
ascribed include minimal or no propensity to cause tardive dyskinesia (TD) and less
effect on serum prolactin than the FGAs. Clozapine is the only SGA that fulfills all
these criteria.

The Clinical Antipsychotic Trials of Intervention Effectiveness study showed that
olanzapine, compared with quetiapine, risperidone, ziprasidone, and perphenazine, has
modest superiority in persistence of maintenance therapy, but olanzapine had more
metabolic side effects.

**Selection of an antipsychotic should be based on**

1. The need to avoid certain side effects,
2. Concurrent medical or psychiatric disorders, and
3. Patient or family history of response.

Predictors of good antipsychotic response include a prior good response to the drug
selected, absence of alcohol or drug abuse, acute onset and short duration of illness,
acute stressors or precipitating factors, later age of onset, affective symptoms, family
history of affective illness, compliance with the prescribed regimen, and good
premorbid adjustment. Negative symptoms are generally less responsive to
antipsychotic therapy.

If partial or poor adherence is an issue, a long-acting or depot injectable antipsychotic
should be considered (e.g., risperidone microspheres, haloperidol decanoate,
fluphenazine decanoate).

**Initial therapy:**

The goals during the first 7 days are decreased agitation, hostility, anxiety, and
aggression and normalization of sleep and eating patterns. In general, titrate over the
first few days to an average effective dose. After 1 week at a stable dose, a modest
dosage increase may be considered. If there is no improvement within 3 to 4 weeks at
therapeutic doses, then an alternative antipsychotic should be considered.

In partial responders who are tolerating the antipsychotic well, it may be reasonable to
titrated above the usual dose range.
In general, rapid titration of antipsychotic dose is not recommended. IM antipsychotic administration (e.g., ziprasidone 10 to 20 mg, olanzapine 2.5 to 10 mg, or haloperidol 2 to 5 mg) can be used to calm agitated patients. However, this approach does not improve the extent of response, time to remission, or length of hospitalization.

Intramuscular (IM) lorazepam, 2 mg, as needed in combination with the maintenance antipsychotic may actually be more effective in controlling agitation than using additional doses of the antipsychotic.

**Stabilization therapy:**
During weeks 2 and 3, the goals should be to improve socialization, self-care habits, and mood. Improvement in formal thought disorder may require an additional 6 to 8 weeks. If symptom improvement is not satisfactory after 8 to 12 weeks, a different strategy should be tried.

**Maintenance therapy:**
Medication should be continued for at least 12 months after remission of the first psychotic episode. Continuous treatment is necessary in most patients at the lowest effective dose.

Antipsychotics (especially FGAs and clozapine) should be tapered slowly before discontinuation to avoid rebound cholinergic withdrawal symptoms.

In general, when switching from one antipsychotic to another, the first should be tapered and discontinued over 1 to 2 weeks after the second antipsychotic is initiated.

- **Risperidone Consta** is the first SGA to be available as a long-acting injectable. The recommended starting dose is 25 mg. Usual dosing range is 25 to 50 mg deep IM every 2 weeks. Significant risperidone serum concentrations are measurable about 3 weeks after single-dose administration. Thus oral medication must be administered for at least 3 weeks after beginning injections. Dose adjustments should be made no more often than every 4 weeks.

- For fluphenazine decanoate, which uses 1.2 times the oral daily dose for stabilized patients, rounding up to the nearest 12.5-mg interval, administered IM in weekly doses for the first 4 to 6 weeks (1.6 times the oral daily dose for
patients who are more acutely ill). Subsequently, fluphenazine decanoate may be administered once every 2 to 3 weeks. Oral fluphenazine may be overlapped for 1 week.

- For haloperidol decanoate, an esterified formulation in sesame seed oil, a factor of 10 to 15 times the oral daily dose is commonly recommended, rounding up to the nearest 50-mg interval, administered IM in a once monthly dose with oral haloperidol overlap for 1 month.

- Haloperidol and fluphenazine decanoate should be administered by a deep, “Z-track” IM method. Long-acting risperidone is injected by deep IM injection in the gluteus maximus, but Z-tracking is not necessary.

- In patients previously unexposed to the drug, an oral test dose of the medication is recommended before long-acting antipsychotics are given.

**Management of treatment-resistant schizophrenia:**

Only clozapine has shown superiority over other antipsychotics in randomized clinical trials for the management of treatment-resistant schizophrenia. Symptomatic improvement with clozapine often occurs slowly in resistant patients, and as many as 60% of patients may improve if clozapine is used for up to 6 months.

Because of the risk of orthostatic hypotension, clozapine is usually titrated more slowly than other antipsychotics. If a 12.5-mg test dose does not produce hypotension, then 25 mg of clozapine at bedtime is recommended, increased to 25 mg twice daily after 3 days, and then increased in 25- to 50- mg/day increments every 3 days until a dose of at least 300 mg/day is reached.

Augmentation therapy involves the addition of a non-antipsychotic drug to an antipsychotic in a poorly responsive patient, while combination treatment involves using two antipsychotics simultaneously.
Responders to augmentation therapy usually improve rapidly. If there is no improvement, the augmenting agent should be discontinued.

Mood stabilizers (e.g., lithium, valproic acid, and carbamazepine) used as augmentation agents may improve labile affect and agitated behavior.

Selective serotonin reuptake inhibitors have been used with FGAs with improvement of negative symptoms. Selective serotonin reuptake inhibitors have been used for obsessive-compulsive symptoms that worsen or arise during clozapine treatment.

Propranolol, pindolol, and nadolol have been used for antiaggressive effects, especially in organic aggressive syndrome. If propranolol is used, a 20-mg test dose should be given to assess tolerability. If well tolerated, it can be initiated at 20 mg three times daily. Increments can then be 60 mg/day every 3 days. Six to 8 weeks may be needed to evaluate response.

Combining an FGA and an SGA and combining different SGAs have been suggested, but no data exist to support or refute these strategies. If a series of antipsychotic monotherapies fails, a time-limited combination trial may be attempted. If there is no improvement within 6 to 12 weeks, one of the drugs should be tapered and discontinued.

Adverse effects:
Side-Effect Incidence of commonly used antipsychotics (Sedation, extrapyramidal side effects EPS, Anticholinergic, orthostasis, weight gain and Prolactin)

Autonomic Nervous System: Anticholinergic (ACh) side effects include impaired memory, dry mouth, constipation, tachycardia, blurred vision, inhibition of ejaculation, and urinary retention. Elderly patients are especially sensitive to these side effects. Low potency FGAs, clozapine, and olanzapine are most likely to cause ACh effects.

Dry mouth can be managed with increased intake of fluids, oral lubricants, ice chips, or use of sugarless chewing gum or hard candy.
Constipation can be treated with increases in exercise, fluid, and dietary fiber intake.
Central Nervous System:
Extrapyramidal System

Dystonia
Dystonias are prolonged tonic muscle contractions, with rapid onset (usually within 24 to 96 hours of dosage initiation or dosage increase); they may be life threatening (e.g., pharyngeal-laryngeal dystonias). Dystonic reactions occur primarily with FGAs. Risk factors include younger patients (especially males), use of high-potency agents, and high dose.

Treatment includes IM or IV AChs or benzodiazepines. Benztropine mesylate, 2 mg, or diphenhydramine, 50 mg, may be given IM or IV, or diazepam, 5 to 10 mg slow IV push, or lorazepam, 1 to 2 mg IM, may be given. Relief usually occurs within 15 to 20 minutes of IM injection or within 5 minutes of IV administration. The dose should be repeated if no response is seen within 15 minutes of IV injection or 30 minutes of IM injection.

Prophylactic ACh medications (but not amantadine) are reasonable when using high-potency FGAs (e.g., haloperidol, fluphenazine), in young men, and in patients with a history of dystonia.

Dystonias can be minimized through the use of lower initial doses of FGAs and by using SGAs instead of FGAs.

Akathisia
Symptoms include subjective complaints (feelings of inner restlessness) and/or objective symptoms (pacing, shuffling, or tapping feet).

Treatment with AChs is disappointing, and reduction in antipsychotic dose may be the best intervention. Another alternative is to switch to an SGA, although akathisia occasionally occurs with the SGAs. Quetiapine and clozapine appear to have the lowest risk for causing akathisia.

Diazepam may be used (5 mg three times daily), but efficacy data are conflicting.
Propranolol (up to 160 mg/day) and metoprolol (up to 100 mg/day) are reported to be effective.
Pseudoparkinsonism
Patients with pseudoparkinsonism may have any of four cardinal symptoms:
(1) akinesia, bradykinesia, or decreased motor activity, including mask-like facial expression, micrographia, slowed speech, and decreased arm swing;
(2) tremor (predominantly at rest and decreasing with movement);
(3) rigidity, which may present as stiffness; cogwheel rigidity is seen as the patient’s limbs yield in jerky, ratchet-like fashion when moved passively by the examiner; and
(4) postural abnormalities, including stooped, unstable posture and slow, shuffling, or festinating gait.

Risk factors are FGAs (especially in high dose), increasing age, and possibly female gender.
The onset of symptoms is usually 1 to 2 weeks after initiation of antipsychotic therapy or dose increase. The risk of pseudoparkinsonism with SGAs is low except in the case of risperidone in doses greater than 6 mg/day.

AChs are an effective treatment. Benztropine has a half life that allows once-to twice-daily dosing. Trihexyphenidyl, diphenhydramine, and biperiden usually require three-times-daily dosing. Diphenhydramine produces more sedation, but all of the AChs have been abused for euphoriant effects.
Amantadine is as efficacious as AChs and has less effect on memory.
An attempt should be made to taper and discontinue these agents 6 weeks to 3 months after symptoms resolve.

Tardive Dyskinesia:
TD is sometimes irreversible and is characterized by abnormal involuntary movements occurring with chronic antipsychotic therapy.

Risk factors for TD include duration of antipsychotic therapy, higher dose, possibly cumulative dose, increasing age, occurrence of acute extrapyramidal symptoms, poor antipsychotic response, diagnosis of organic mental disorder, diabetes mellitus, mood disorders, and possibly female gender.
To date, there are no reports of TD with clozapine monotherapy. Switching the patient with TD to clozapine is a first-line strategy, especially in patients with moderate to severe dyskinesias.

Sedation and Cognition:
Administration of most or all of the daily dose at bedtime can decrease daytime sedation and may eliminate the need for hypnotics.
The SGAs as first-line treatment have been shown to improve cognition over a 9-month period.

Seizures:
There is an increased risk of drug-induced seizures in all patients treated with antipsychotics. The highest risk for antipsychotic-induced seizures is with the use of (Chlorpromazine) CPZ or clozapine. Seizures are more likely with initiation of treatment and with the use of higher doses and rapid dose increases.

When an isolated seizure occurs, a dosage decrease is recommended, and anticonvulsant therapy is usually not recommended.
If a change in antipsychotic therapy is required, risperidone, molindone, thioridazine, haloperidol, pimozide, trifluoperazine, and fluphenazine may be considered.

Thermoregulation:
In temperature extremes, patients taking antipsychotics may experience their body temperature adjusting to ambient temperature. Hypothermia is also a risk, particularly in elderly patients. These problems are more common with the use of low-potency FGAs.

Neuroleptic Malignant Syndrome:
Neuroleptic malignant syndrome occurs in 0.5% to 1% of patients taking FGAs. It may be more frequent with high-potency FGAs, injectable, or depot antipsychotics; in dehydrated patients; or in those with organic mental disorders. It has been reported with the SGAs, including clozapine, but is less frequent than with the FGAs.
Symptoms develop rapidly over 24 to 72 hours and include body temperature exceeding 38°C (100.4°F), altered level of consciousness, autonomic dysfunction (tachycardia,
labile blood pressure, diaphoresis, tachypnea, urinary or fecal incontinence), and rigidity.

Laboratory evaluation frequently shows leukocytosis, increases in creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and myoglobinuria.

Treatment should begin with antipsychotic discontinuation and supportive care.

**Endocrine System:**

Antipsychotic-induced elevations in prolactin levels with associated galactorrhea and menstrual irregularities are common. These effects may be dose related and are more common with the use of FGAs and risperidone.

Possible management strategies for galactorrhea include switching to an SGA (e.g., olanzapine, quetiapine, aripiprazole, or ziprasidone).

Weight gain is frequent with antipsychotic therapy including SGAs, especially olanzapine and clozapine. Weight gain may also occur with risperidone and quetiapine, but ziprasidone and aripiprazole are associated with minimal weight gain.

Schizophrenics have a higher prevalence of type 2 diabetes than nonschizophrenics. Antipsychotics may adversely affect glucose levels in diabetic patients.

**Cardiovascular System:**

The incidence of orthostatic hypotension is greatest with low-potency FGAs, especially with IM or IV administration. Diabetics with cardiovascular disease and the elderly are predisposed.

Tolerance to this effect usually occurs within 2 to 3 months. Reducing the dose or changing to an antipsychotic with less α-adrenergic blockade may also help.

Low-potency piperidine phenothiazines (e.g., thioridazine), clozapine, and ziprasidone are more likely to cause ECG changes.

**Lipid Effects:**

Some SGAs and phenothiazines cause elevations in serum triglycerides and cholesterol. The risk for this effect may be less with risperidone, ziprasidone, and aripiprazole.
**Ophthalmologic Effects**

Impairment in visual accommodation results from paresis of ciliary muscles. Photophobia may also result. If severe, pilocarpine ophthalmic solution may be necessary.

**Hepatic System:**

Liver function test abnormalities are common. If aminotransferases are greater than three times the upper limit of normal, the antipsychotic should be changed to a chemically unrelated antipsychotic. These changes are less common with the SGAs but are reported with risperidone and clozapine.

**Genitourinary System:**

Urinary hesitancy and retention are commonly reported, especially with low-potency FGAs and clozapine, and men with benign prostatic hypertrophy are especially prone.

Urinary incontinence is especially problematic with clozapine.

Risperidone produces at least as much sexual dysfunction as FGAs, but other SGAs (which have a weaker effect of prolactin) are less likely to have this effect.

**Hematologic System:**

Transient leukopenia may occur with antipsychotic therapy, but it typically does not progress to clinically significant parameters.

If the white blood cell (WBC) count is less than 3,000/mm^3^ or the absolute neutrophil count (ANC) is less than 1,000/mm^3^, the antipsychotic should be discontinued, and the WBC count monitored closely until it returns to normal.

**Dermatologic System**

Allergic reactions are rare and usually occur within 8 weeks of initiating therapy. They manifest as maculopapular, erythematous, or pruritic rashes. Drug discontinuation and topical steroids are recommended when they occur.

Both FGAs and SGAs can cause photosensitivity. Erythema and severe sunburns can occur. Patients should be educated to use maximal blocking sunscreens, hats, protective clothing, and sunglasses when in the sun.
Blue-gray or purplish discoloration of skin exposed to sunlight may occur with higher doses of low-potency phenothiazines (especially CPZ) long term.

**Use in pregnancy and lactation:**
There is a slightly increased risk of birth defects with low-potency FGAs. There is no relationship between haloperidol use and teratogenicity. Concern has been expressed over the use of SGAs in pregnancy because of the risk for weight gain and potential risk for gestational diabetes.

Antipsychotics appear in breast milk with milk-to-plasma ratios of 0.5 to 1, however, 1-week post-delivery. Use of clozapine during breast-feeding is not recommended. Antipsychotic pharmacokinetics can be significantly affected by concomitantly administered enzyme inducers or inhibitors. Smoking is a potent inducer of hepatic enzymes and may increase antipsychotic clearance by as much as 50%.

**Evaluation of therapeutic outcomes:**
Weight should be monitored monthly for 3 months, then quarterly. Body mass index, waist circumference, blood pressure, fasting plasma glucose, and fasting lipid profile should be monitored at the end of 3 months, then annually. The use of patient self assessments is encouraged.