# SCHIZOPHRENIA

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# Introduction



- Schizophrenia is a devastating, chronically debilitating disorder.
- Manifests with psychotic symptoms commonly, accompanied by cognitive impairment, impaired insight and judgment, and negative symptoms.
- Cognitive impairments and negative symptoms account for much of the poor social and functional outcomes.
- Is associated with substantially lower rates of employment, marriage, and independent living.

# EPIDEMIOLOGY



- Approximately 1% of the world population suffers from schizophrenia.
- Symptoms typically presenting in late adolescence or early adulthood.
- Prevalence is equal in men and women.
- Symptoms appear earlier in men with first hospitalization typically occurring at 15 to 24 years compared to 25 to 34 years.

# ETIOLOGY



The etiology of schizophrenia remains unknown.

A genetic basis is supported by the fact that :

- first-degree relatives of patients with schizophrenia carry a 10% risk, and when both parents have the diagnosis, the risk to their offspring is 40%. For monozygotic twins, the concordance rate is about 50%.
- Some data suggest intrauterine exposure to significant stress, viral or bacterial infections may be a risk factor;

# PATHOPHYSIOLOGY



- The dopamine hypothesis: psychosis is caused by excessive dopamine in the brain.
- Dysregulation hypothesis," hyper dopaminergic and hypo dopaminergic brain regions in schizophrenia.
- Combined dysfunction of the dopamine and glutamate neurotransmitter systems: glutamate, possibly through malfunctioning NMDA receptors, impacts dopaminergic activity in the mesolimbic and mesocortical pathways.

# Clinical Presentation



- People with schizophrenia may appear uncooperative, suspicious, hostile, anxious, or aggressive.
- Psychotic and depressive symptoms may lead to poor hygiene and impaired self care.
- Sleep and appetite are often disturbed.
- Type 2 diabetes and COPD, are prevalent.
- Approximately 60% of people with schizophrenia smoke, and approximately 50% use illicit drugs and alcohol.

# Clinical Presentation of Schizophrenia

## General

Schizophrenia is a chronic disorder of thought and affect, causing significantly impaired vocational and interpersonal function. Onset is usually preceded by gradual social withdrawal, diminished interests, changes in appearance and hygiene, changes in cognition, and bizarre or odd behaviors. The clinical presentation of a person with schizophrenia is extremely varied.

## Symptoms

*Psychotic symptoms (positive symptoms)*:

- Hallucinations (distortions or exaggeration of perception)
  - Most frequently auditory, can also be visual, olfactory, gustatory, and tactile.
  - Can be voices or thoughts that feel distinct from the person's mind.
  - Voices may be threatening or commanding (eg, commanding the person to perform a particular action).
- Delusions (fixed false beliefs)
  - Beliefs despite invalidating evidence
  - May be bizarre in nature
  - Often paranoid in nature which may cause suspiciousness
- Thought disorder (illogical thought and speech)
  - Loosening of associations
  - Tangentiality
  - Thought blocking
  - Concreteness
  - Circumstantiality
  - Perseveration
  - Thinking and speech may be incomprehensible and illogical

*Negative symptoms*:

- Impoverished speech and thinking
- Lack of social drive (avolition)
- Flatness of emotional expression
- Apathy
- May be primary or occur secondarily to medication side effects, mood disorder, environmental understimulation, or demoralization
- The best strategy for differentiating primary from secondary negative symptoms is to observe for their persistence over time despite efforts at resolving the other causes

*Cognitive impairments (diminished function in the following)*:

- Attention
- Processing speed
- Verbal, visual memory, and working memory
- Problem solving
- There is a loss of, on average, one standard deviation of preillness IQ, with the average IQ between 80 and 84.

## Laboratory and Other Diagnostic Assessments

- An initial psychotic work up includes a thorough neurologic, medical and laboratory evaluation to rule out other causes
  - Electrolytes
  - Blood urea nitrogen
  - Serum creatinine
  - Urinalysis
  - Liver and thyroid function profile
  - Syphilis serology
  - Serum pregnancy test
  - Urine toxicology

# DIAGNOSIS



- A diagnosis of schizophrenia is made clinically.
- Patients presenting with odd behaviors, illogical thought processes, fixed false beliefs, and hallucinations should be assessed to rule out other diagnoses or contributing factor.
- Often, people with psychosis are poor historians and the gathering of collateral information is necessary.

**Diagnostic Criteria for Schizophrenia**

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be 1, 2, or 3:
   1. Delusions
   2. Hallucinations
   3. Disorganized speech (eg, frequent derailment or incoherence)
   4. Grossly disorganized or catatonic behavior
   5. Negative symptoms (ie, diminished emotional expression or avolition)

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved before onset (or when onset is in childhood or adolescence, there is a failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meets Criterion A (ie, active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (eg, odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness

E. The disturbance is not attributable to the physiological effects of a substance (eg, drug of abuse or medication) or another medical condition

F. If there is a history of autism spectrum disorder or communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated)

# COURSE AND PROGNOSIS



- Treatment is often associated with poor long term outcomes, however, some people can achieve remission.
- Though many of the more dramatic and acute symptoms may fade with time, severe residual symptoms may persist.
- Life expectancy is shortened .
- Lifetime risk of suicide for people with schizophrenia is 5% to 10%.

# COURSE AND PROGNOSIS…



- Persistent compliance with a tolerable drug regimen improves prognosis.
- while relapse without medication exceeds 50% in the year following noncompliance.
- The onset of schizophrenia can be rapid, or can be insidious.
- Patients may hide symptoms from family and friends.
- Recent data suggest that people treated early in their illness may have a better prognosis.

# TREATMENT



- **Desired Outcomes**
- The goals of treatment are to reduce symptomatology and psychotic relapses and to improve functional and social outcomes.
- Patients should receive comprehensive treatment as early as possible.
- Improvements in negative symptoms, cognitive functioning, social skills, and judgment generally require adjunctive treatments and a longer period to improve.

# General Approach to Treatment



- The cornerstone of treatment is antipsychotic medications.
- Most patients are on lifelong antipsychotic medication because non adherence and discontinuation are associated with high relapse rates.
- Often, adjunctive medications may also be necessary for specific symptoms or comorbid diagnoses.
- If other symptoms are present, such as depression and anxiety, these symptoms should be aggressively treated.
- Psychosocial treatments are also often used concomitantly.

# Antipsychotic Treatment



- Since 1990, the SGAS have been marketed in the US.
- Include: risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, lurasidone, and clozapine.
- Clozapine, the prototype SGA, is reserved as second-line therapy because of its unusual side-effect profile.
- Compared with the FGAS, the SGAS are associated with a lower risk of motor side effects (tremor, stiffness, restlessness, and dyskinesia).

# Antipsychotic Treatment



- The use of FGAs has progressively decreased. This decline occurred because of the advertised better side-effect profile other possible benefits of SGAs in nonpyshcotic domains of the illness.
- However, a large landmark study (the Clinical Antipsychotics Trials of Intervention Effectiveness; CATIE trial; *n* greater than 1400) examined the effectiveness of SGAs relative to a mid potency FGA, perphenazine.
- And revealed that the FGA was equal to the SGAs for the primary endpoint of time to discontinuation of medication.

# Antipsychotic Treatment



- SGAs have historically been much more expensive than the FGAs; however risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and clozapine are now available in generic formulations.
- In conclusion, when selecting an antipsychotic, the risk-to-benefit profile becomes fundamental and the **varying side-effect profiles** must be considered.

# Second-Generation (Atypical) Antipsychotics



- Despite heterogeneous receptor binding, the efficacy among the SGAs is similar.
- Additionally, recent data for SGAs and FGAs (lower doses) document similar overall efficacy with an effect size for acute treatment of 0.30 to 0.60 for most antipsychotics.
- Only clozapine, however, has demonstrated superior efficacy and that is in treatment-resistant patients.

# Second-Generation (Atypical) Antipsychotics



- An important distinction of the SGAs is their lower propensity to cause extrapyramidal symptoms (EPSs) and tardive dyskinesia (TD).
- TD risk with SGAs is 1.5% annually in adults (less than 54 years of age) compared to approximately a 5% annual risk with FGA treatment.
- Many SGAs carry an increased risk for weight gain and for the development of glucose and lipid abnormalities; therefore, careful monitoring is essential.

# Risperidone



- Risperidone, was the initial first-line oral SGA to become available generically.
- It has high binding affinity to both serotonin 2A (5-HT2A) and D2 receptors and binds to α 1 and α2 receptors, with very little blockade of cholinergic receptors.
- Risperidone is also approved for relapse prevention and is associated with significantly lower relapse rates than long-term haloperidol treatment.

# Risperidone



- At doses less than or equal to 6 mg/day, EPSs are low, although higher doses are associated with a greater incidence of EPS.
- Risperidone use causes serum prolactin elevations similar to or greater than FGAs.
- Elevated prolactin levels can but not always , lead to amenorrhea, galactorrhea, gynecomastia, and sexual dysfunction.

# Risperidone



- Mild to moderate weight gain and mild elevations in serum lipids and glucose may occur.
- However, patients chronically treated with other antipsychotics may experience a decline in cholesterol and triglyceride levels when changed to risperidone mono therapy

# Olanzapine



- In the CATIE trial, olanzapine was associated with the longest time to treatment discontinuation, suggesting it may differ from the other SGAs in effectiveness.
- Olanzapine has a low rate of EPS and causes slight, transient prolactin elevations.
- Olanzapine causes significant weight gain across the dosage range, similar to that seen with clozapine and greater than that observed with the other SGAs.

# Olanzapine



- Olanzapine is also associated with hypertriglyceridemia, increased fasting glucose, and new-onset type 2 diabetes (ie, metabolic syndrome).
- Among the first-line SGAs, it is associated with the greatest elevations in these metabolic parameters.

# Quetiapine



- Quetiapine, structurally related to clozapine and olanzapine. may be beneficial for anxiety and depression.
- Motor side effects and prolactin elevations are uncommon.
- Orthostasis occurred in 4% of subjects in clinical trials.
- Sedation is generally transient.
- Mild weight gain and minor elevations in triglycerides can occur.
- Use with agents that can prolong the QTc interval or in patients with prolonged QTc should be avoided.

# Ziprasidone



- It should be taken with food.
- Liability for EPS, weight gain, and lipid elevations is low but does occur.
- causes some prolongation of the QTc interval in adults.
- Use of ziprasidone with agents that can prolong the QTc interval or in patients with existing diseases associated with prolonged QTc should be avoided.

# Ziprasidone



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# Aripiprazole



- Aripiprazole is a dopamine modulator, with both antagonist and agonist activity at the D2 receptor.
- It is the only D2 partial agonist available for the treatment of schizophrenia.
- Sedation, N&V are the most often seen S/Es.
- Elevations in weight, lipids, and glucose are generally negligible, and it doesn't usually cause elevations in serum prolactin.
- In fact, patients switched to aripiprazole from other antipsychotic agents may experience decreases in prolactin

# Paliperidone



- Paliperidone is the 9-hydroxy (9-OH) metabolite of risperidone.
- The efficacy of risperidone and paliperidone are similar.
- Receptor binding affinity is also similar between the two agents, with paliperidone having a greater affinity at 5-HT2A compared with D 2 receptors.

# Paliperidone



- Unlike many other antipsychotic medications, paliperidone is mostly excreted unchanged, a potential advantage in patients with liver impairment.
- Patients should be told to expect to see the shell of the tablet in the stool.
- Side effects of paliperidone are expected to be similar to those of risperidone,

# Iloperidone



- is indicated for acute treatment of adults with schizophrenia.
- Doses must be titrated because of the risk of orthostatic hypotension, and dosing should be reduced by half in CYP2D6 poor metabolizers.
- Common ADR include dizziness, dry mouth, fatigue, orthostatic hypotension, tachycardia, and weight gain.
- Dizziness, tachycardia, and weight gain were twice as common with higher dose (20–24 mg total daily dose) .
- Use of iloperidone with agents that can prolong the QTc interval or in patients with associated diseases should be avoided.

# Asenapine



- Asenapine is approved for the acute treatment of schizophrenia in adults.
- Asenapine tablets must be placed under the tongue and allowed to dissolve completely; tablets should not be chewed or swallowed.
- Patients should not drink or eat for 10 minutes after administration.
- No added benefit was seen with doses above 10 mg twice daily, but adverse effects increase.

# Asenapine



- Common adverse effects include somnolence, dizziness, and akathisia.
- It has shown little effect on metabolic parameters and weight change.
- Labeling for asenapine was modified to address rare occurrence of hypersensitivity reactions, including anaphylaxis and angioedema

# Lurasidone



- Lurasidone antagonizes D2 and 5HT2A receptors.
- Lurasidone should be taken with food.
- Adverse reactions reported in at least 5% of patients (and at least twice the placebo rate) include somnolence, akathisia, nausea, parkinsonism, and agitation.
- Lurasidone has shown only a small effect on body weight and causes minimal changes in other metabolic parameters

**Second-Generation (Atypical) Antipsychotics**

| Second-Generation Antipsychotic | Usual Starting and Target Dose (mg/day) (Schizophrenia) | Maximum Dose Likely to Be Beneficial (mg/day) | Available Dosage Forms |
|---|---|---|---|
| Aripiprazole (Abilify) | Initial: 10–15<br>Target: 15–30 | 30 | • 2-, 5-, 10-, 15-, 20-, and 30-mg tablets<br>• 1-mg/mL oral solution<br>• 10- and 15-mg Abilify Discmelt orally disintegrating tablets<br>• IM 9.75 mg/1.3 mL<br>• Abilify Maintena extended-release 300- and 400-mg vial powder for suspension long acting injection |
| Asenapine (Saphris) | Initial: 5 twice daily<br>Target: 10–20 total daily dose | 10–20 | • 5- and 10-mg sublingual tablets |
| Clozapine (Clozaril, Fazaclo, Versacloz, also available generically) | Initial: 12.5–25/day<br>Target: 300–450 | 500–800 | • 25-, 50-, 100-, and 200-mg tablets<br>• FazaClo (orally disintegrating tablets) 12.5-, 25-, 100-, 150-, 200-mg<br>• Versacloz (oral suspension) 50 mg/mL |
| Iloperidone (Fanapt) | Initial: 1 twice daily<br>Target: 12–24 total daily dose | 24 | • 1-, 2-, 4-, 6-, 8-, 10-, 12-mg tablets |
| Lurasidone (Latuda) | Initial: 40<br>Target: 40–160 | 160 | • 20-, 40-, 60-, 80-, 120 mg tablets |
| Olanzapine (Zyprexa, also available generically) | Initial: 2.5-10<br>Target: up to –20 | 30–40[a] | • 2.5-, 5-, 7.5-, 10-, 15-, and 20-mg tablets<br>• Zyprexa Zydis (orally disintegrating tablets) 5, 10, 15, and 20 mg<br>• IM 10 mg vial (after reconstitution, ~5 mg/mL)<br>• Zyprexa Relprevv 210-, 300-, and 405-mg/vial powder for suspension long-acting injection |
| Paliperidone (Invega) | Initial: 6<br>Target: 6–12 | 6–12 | • 1.5-, 3-, 6-, and 9-mg tablets<br>• Invega Sustenna 39-, 78-, 117-, 156-, 234-mg prefilled syringes |
| Quetiapine (Seroquel, also available generically) | **Regular release**<br>Initial: 25 twice daily<br>Target: 300–750<br>**Extended release**<br>Initial: 300<br>Target 400–800 | 800 | • 25-, 50-, 100-, 200-, 300-, and 400-mg tablets<br>• Seroquel XR (extended-release tablets) 50-, 150-, 200-, 300-, and 400-mg tablets |
| Risperidone (Risperdal, also available generically) | Initial: 1–2<br>Target: 4–6 | 6–8 | • 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets<br>• 1 mg/mL (30 mL) solution<br>• Risperdal M-tab (orally disintegrating tablets) 0.5-, 1-, 2-, 3-, and 4-mg tablets<br>• Risperdal Consta long-acting injectable 12.5-, 25-, 37.5-, and 50-mg vial/kit |
| Ziprasidone (Geodon, also available generically) | Initial: 20 twice daily<br>Target: 120–160 total daily dose | 160–240[a] | • 20-, 40-, 60-, and 80-mg capsules<br>• IM 20 mg/mL |

## Comparative Side Effects Among the SGAs and Haloperidol

| Side Effect | Cloz | Risp[a] | Olan | Quet | Zip | Ari | Ilo | Asen | Lur | Hal |
|---|---|---|---|---|---|---|---|---|---|---|
| Anticholinergic side effects | +++ | ± | ++ (Higher doses) | + | ± | ± | ± | + | ± | ± |
| EPS at clinical doses | + | + | ± | ± | ± | ± | + | + | + | ++ |
| Dose-dependent EPS | 0 | ++ | + | 0 | + | ± | + | + | + | +++ |
| Orthostatic hypotension | +++ | ++ | + | ++ | + | + | ++ | + | + | ++ |
| Prolactin elevation | 0 | +++ | + | ± | + | 0 | + | ± | ± | + |
| QTc prolongation | + | ± | ± | + | + | ± | + | + | + | ± |
| Sedation | +++ | + | + | ++ | + | + | ++ | + | + | + |
| Seizures | ++ | ± | ± | ± | ± | ± | ± | ± | ± | ± |
| Weight gain | +++ | ++ | +++ | ++ | + | + | + | + | + | ± |
| Glucose dysregulation | ++ | + | ++ | + | ± | ± | ± | ± | ± | ± |
| Lipid abnormalities | +++ | + | +++ | ++ | ± | ± | ± | ± | ± | ± |

Cloz, clozapine; Risp, risperidone; Olan, olanzapine; Quet, quetiapine; Zip, ziprasidone; Ari, aripiprazole; Ilo, iloperidone; Asen, asenapine; Lur, lurasidone; Hal, haloperidol.

[a]Side effects similar for paliperidone.

0, absent; ±, minimal; +, mild or low risk; ++, moderate; +++, severe; EPS, extrapyramidal side effects; SGA, second-generation antipsychotic.

# First-Generation (Typical) Antipsychotics…



- The FGAs are high-affinity D2-receptor antagonists.
- During chronic treatment, they block 65% to 80% of D2 receptors in the striatum and other dopamine tracts in the brain.
- Clinical response is generally associated with 60% D2-receptor blockade, while 70% and 80% are associated with hyperprolactinemia and EPS, respectively.

# First-Generation (Typical) Antipsychotics



- Doses for FGAs are frequently given as chlorpromazine equivalents, which are defined as the FGA equipotent dose with 100 mg of chlorpromazine.
- The target dose recommendation for acute psychosis is 400 to 600 chlorpromazine equivalents.
- Generally, maintenance therapy is 300 to 600 chlorpromazine equivalents daily.
- All FGAs are equally efficacious when studied in equipotent doses

# First-Generation (Typical) Antipsychotics



**First-Generation (Typical) Antipsychotics[a]**

| Class | Agent (Brand Name) | Dosage Range (mg/day) | Chlorpromazine Equivalents (mg) | Available Formulations |
|---|---|---|---|---|
| Butyrophenone | Haloperidol (Haldol) | 5–30 | 2 | T, LC, I |
| Dibenzoxazepine | Loxapine (Loxitane, Adasuve) | 25–100 | 10 | C, IP |
| Diphenylbutylpiperidine | Pimozide (Orap) | 1–10 | 1–2 | T |
| Phenothiazines | Chlorpromazine (Thorazine) | 300–800 | 100 | T, LC, I, R |
| | Fluphenazine (Prolixin) | 2–40 | 2 | T, L, I |
| | Perphenazine (Trilafon) | 8–64 | 10 | T, LC |
| | Thioridazine (Mellaril) | 300–800 | 100 | T, LC |
| | Trifluoperazine (Stelazine) | 15–30 | 5 | T |
| Thioxanthenes | Thiothixene (Navane) | 5–40 | 4 | C |

[a]Low-potency antipsychotics include thioridazine, mesoridazine, and chlorpromazine. High-potency antipsychotics include haloperidol, fluphenazine, thiothixene, and pimozide.

C, capsule; C-SR, controlled or sustained release; I, injection; L, liquid solution, elixir, or suspension; LC, liquid concentrate; R, rectal suppository; T, tablet; IP, inhalation powder.

# Decanoates



- Long-acting, depot preparations are available for two FGAs (fluphenazine decanoate and haloperidol decanoate) in the United States.
- These compounds are esterified antipsychotics in sesame seed oil for deep intramuscular (IM) injection.
- Patients should be exposed to the oral form of the drug first to ensure tolerability.

# Decanoates



- With initial dosing of haloperidol decanoate, concomitant oral supplementation may be temporarily necessary while the drug accumulates, as steady state is achieved after four to five dosing intervals.
- Fluphenazine decanoate is dosed at 1- to 3-week intervals, but haloperidol decanoate is usually dosed once a month.

# Decanoates



- Generally, 12.5 mg (0.5 mL) of fluphenazine decanoate given every 2 weeks is approximately equivalent to 10 mg/day of fluphenazine orally.
- A maintenance haloperidol decanoate dose of 150 mg every 4 weeks is approximately equivalent to 10 mg/day of oral haloperidol.
- Initial decanoate injections should be preceded by a small test dose.

# Side Effects of the FGAs



- In general, the low-potency FGA agents are less likely to cause EPS than the high-potency agents.
- Of note, high potency and midpotency agents may cause less EPS than once believed and were similar to SGAs in the CATIE trial.

# Side Effects of the FGAs…



- The FGAs are commonly associated with EPS including:
  - Akathisia [motor or subjective restlessness],
  - Dystonia [muscle spasm], and
  - Pseudoparkinsonism [akinesia, tremor, and rigidity])
- caused by dopamine antagonism in the nigrostriatal pathways.

# Side Effects of the FGAs…



- **A. Akathisia**, the most common motor side effect of FGAs occurs in 20% to 40% of people.
- Roughly half of the cases of akathisia present within 1 month of antipsychotic initiation, though it may present within 5 to 10 days after the first dose or after an increase in dosage.
- Younger people and those taking high doses of high-potency antipsychotics are at greater risk for development of akathisia.

# Side Effects of the FGAs…



- **B. Acute dystonic** reactions are abrupt in onset and are usually seen within 24 to 96 hours after a first dose or increase in dosage.
- Characteristic signs and symptoms include abnormal positioning or spasm of the muscles of the head, neck, limbs, or trunk.
- Dystonia may occur in 10% to 20% of patients.
- There is higher risk for dystonia in young male patients and those taking high potency FGAs.

# Side Effects of the FGAs…



- **C. Pseudoparkinsonism** may be present in 30% to 60% of people treated with FGAs.
- The onset of symptoms is usually within 1 to 2 weeks after dose initiation or dose increase.
- Risk factors include older age, female gender, high doses, and possibly those with depressive symptoms.

# Side Effects of the FGAs…



- **D. Tardive Dyskinesis (TD):** is a movement disorder characterized by abnormal choreiform (rapid, objectively purposeless, irregular, and spontaneous) and athetoid (slow and irregular) movements beginning late in relation to initiation of antipsychotic therapy.
- It usually develops over several months or after at least 3 months of cumulative exposure to antipsychotics.
- Severity can range from mild and barely noticeable to severe, causing interference with ambulation.

# Side Effects of the FGAs…



- **D. Tardive Dyskinesis (TD)….**
- Visible TD symptoms may stigmatize persons taking antipsychotics.
- The estimated average prevalence of TD is 20% in patients given FGAs with a range of 13% to 36%.
- The incidence of new cases per treatment year with FGAs is approximately 5%.
- TD is reversible in one-third to half of cases with the cessation of the antipsychotic.

# Side Effects of the FGAs…



- **D. Tardive Dyskinesis (TD)…**
- When antipsychotics are tapered or discontinued, there is typically an transient worsening of abnormal movements.
- Risk factors for TD include older age; longer duration of antipsychotic treatment; and presence of EPS, substance abuse, and mood disorders.
- SGAs have a lower risk of TD than FGAs..

# Side Effects of the FGAs…



- **E. Neuroleptic malignant syndrome (NMS),**
- a life-threatening emergency characterized by severe muscular rigidity, autonomic instability, and altered consciousness, can occur uncommonly with all FGAs and may also occur with SGAs.
- Rapid dose escalation, use of high-potency FGAs at higher doses, and younger patients have a higher risk of NMS.

# Side Effects of the FGAs…



- **E. Neuroleptic malignant syndrome (NMS), …**
- When NMS is diagnosed or suspected, antipsychotics should be discontinued and supportive, symptomatic treatment begun (eg, antipyretics, cooling blanket, intravenous fluids, oxygen, monitoring of liver enzymes, and complete blood cell count).
- Dopamine agonists (eg, bromocriptine) should be considered in moderate to severe cases.

# Side Effects of the FGAs…



- **F. Dermatologic side effects and miscellaneous,**
- photosensitivity, and cataracts may occur with the phenothiazine FGAs.
- Sedation is mediated by H 1-receptor antagonism; anticholinergic side effects are caused from M 1-receptor antagonism; and α1-receptor blockade is associated with orthostatic hypotension and tachycardia.
- QTc prolongation may occur with the lower potency FGAs, and thioridazine has a black-box warning for QTc prolongation.

# Side Effects of the FGAs…



**Side Effects of First-Generation Antipsychotics**

| | EPS | Sedation | Anticholinergic Side Effects | Cardiovascular Side Effects | Seizure Effects/QTc Prolongation |
|---|---|---|---|---|---|
| Chlorpromazine | ++ | ++++ | +++ | ++++ | ++ |
| Thioridazine | ++ | ++++ | ++++ | ++++ | +++ |
| Loxapine | +++ | +++ | ++ | +++ | + |
| Trifluoperazine | +++ | ++ | ++ | ++ | + |
| Perphenazine | +++ | ++ | ++ | ++ | + |
| Thiothixene | +++ | ++ | ++ | ++ | + |
| Fluphenazine | ++++ | ++ | ++ | ++ | + |
| Haloperidol | ++++ | + | + | + | + |

+, very low; ++, low; +++, moderate; ++++, high; EPS, extrapyramidal side effects.

# Treatment Guidelines and Algorithms



- A widely accepted treatment algorithm in the United States is the Texas Implementation of Medication Algorithms (TIMA), developed by a national panel of experts and updated in 2008.
- Algorithms go beyond guidelines, providing a framework for clinical decision making.
- According to the TIMA schizophrenia algorithm, the SGAs (except clozapine) should be used as first-line treatment.

# Treatment Guidelines and Algorithms

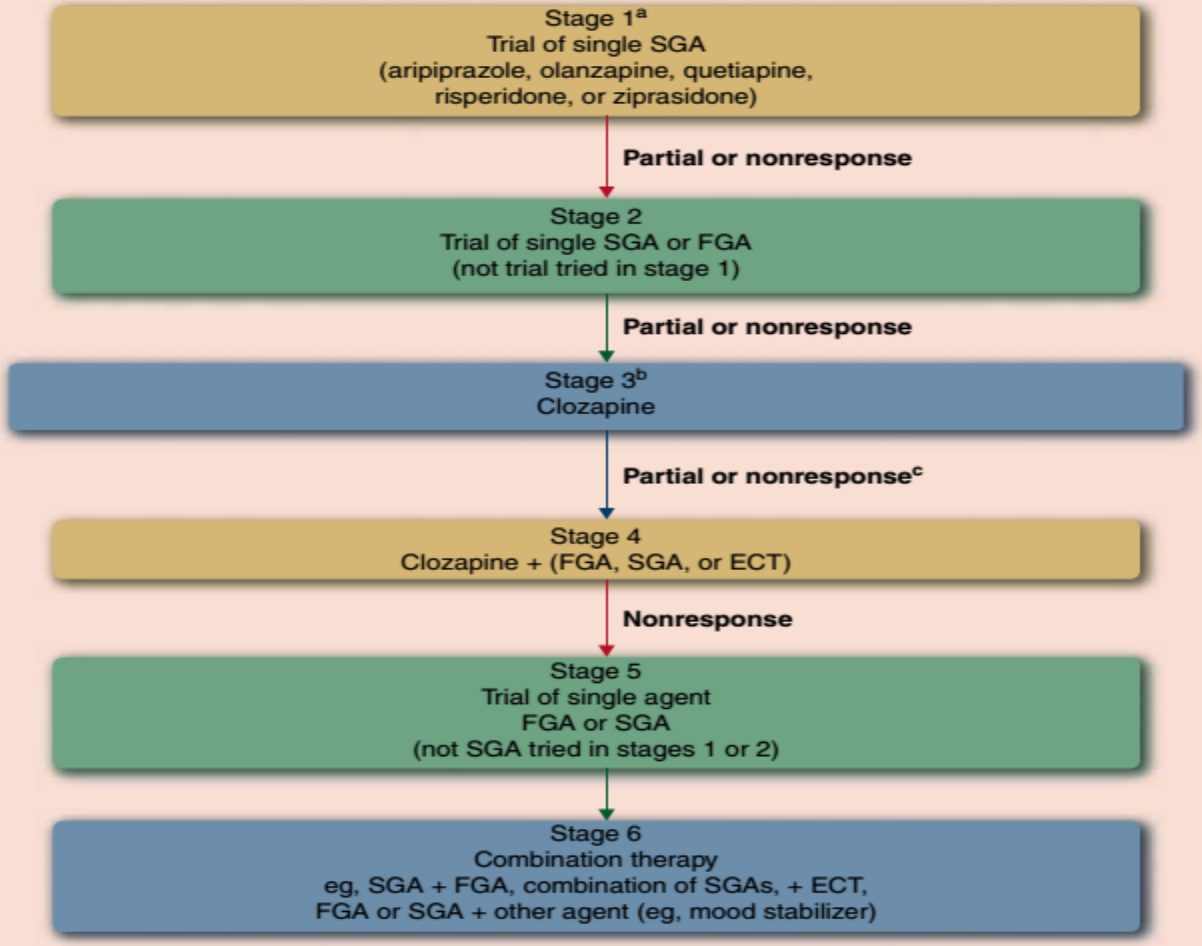


- Choice of SGA is guided by side-effect profiles and patient clinical characteristics.
- Treatment with a given drug should be continued for 4 to 6 weeks to assess response.
- If only partial response or nonresponse is noted, a trial of a second, SGA should be initiated.

**Choice of antipsychotic should be guided by considering the clinical characteristics of the patient and the efficacy and side-effect profiles of the medication.**

**Stages may be skipped depending on the clinical picture or history of antipsychotic failures.**

**First episode or never before treated with an SGA**




[a]If patient is nonadherent to medication, the clinician may use risperidone microspheres, haloperidol, or fluphenazine decanoate at any stage, but should carefully assess side effects.

[b]May consider earlier trial of clozapine if history of recurrent suicidality, violence, comorbid substance abuse, or persistent positive symptoms > 2 years. If persistent positive symptoms > 5 years, clozapine trial independent of number of preceding trials.

[c]Evaluate patient for other underlying or concomitant factors; consider adding cognitive behavioral therapy and other psychosocial interventions.

# Treatment Adherence



- Estimates of nonadherence to antipsychotics range from approximately 24% to 88% with a mean of approxi 50%.
- Subjects who are nonadherent have about a fourfold greater risk of a relapse than those who are adherent.
- For patients who have relapsed several times because of nonadherence, treatment with long-acting formulations should be encouraged.

# Treatment Adherence



- Risperidone, paliperidone, olanzapine, and aripiprazole are available as long-acting injectable formulations.
- Oral tolerability of these agent should be ensured prior to initiating them.

**Antipsychotic Dosing of Long-Acting Preparations**

| Drug | Starting Dose | Maintenance Dose | Comments |
|---|---|---|---|
| Aripiprazole long-acting injection (Abilify Maintena) | 400 mg monthly and 14 consecutive days of concurrent oral aripiprazole (10–20 mg) or current oral antipsychotic after first injection | 400 mg monthly | Establish tolerability with oral agent first<br>Dosage adjustments for CYP2D6 poor metabolizers, and in persons who take strong CYP2D6 or 3A4 inhibitors; recommend to avoid use if strong 3A4 inducer |
| Haloperidol decanoate | 20 × oral haloperidol daily dose; in the elderly use 10–15 × oral haloperidol daily dose;<br>Generally 100–450 mg/mo<br>Initial dose should not exceed 100 mg regardless of previous dose requirements (if > 100 mg, give 3–7 days apart) | 10–15 × oral haloperidol daily dose, generally 50–300 mg/mo | With initial dosing, oral supplementation may temporarily be necessary; deep IM injection generally with 21-gauge needle; maximum volume per injection site should not exceed 3 mL<br>Available in 50 and 100 mg/mL (5-mL vials and 1-mL ampules) |
| Fluphenazine decanoate | 1.2 × oral fluphenazine daily dose; generally 12.5–mg/2–3 weeks | Based on starting dose and clinical response<br>Generally 12.5–25 mg dosed at 2–4-week intervals (may be up to 6 weeks in some cases) | Can be administered IM or SC; 21-gauge needle, must be dry<br>Should not exceed 100 mg; when dosing above 50 mg, should increase in increments of 12.5 mg<br>Available in 25 mg/mL (5-mL vials) |
| Olanzapine (Zyprexa Relprevv) | **To target oral 10 mg/day dose:** Either 210 mg/2 week or 405 mg/4 week during first 8 weeks<br>**To target oral 15 mg/day dose:** 300 mg/2 week for first 8 weeks<br>**To target 20 mg/day oral dose:** 300 mg/2 week | **To target oral 10 mg/day dose:** after 8 weeks, give 150 mg/2 week or 300 mg/4 week<br>**To target oral 15 mg/day dose:** after 8 weeks, 210 mg/2 week or 405 mg/4 week<br>**To target 20 mg/day oral dose:** continue with 300 mg/2 week | Gluteal injection, 19-gauge needle<br>Do not confuse with rapid-acting IM injection<br>Must reconstitute with included diluent<br>Measure amount to inject from vial (there will be remaining suspension in vial)<br>Zyprexa Relprevv Patient Care Program: 3-hour observation period; patient must be accompanied to destination<br>No refrigeration needed, use within 24 hours, or immediately once suspension is in syringe |
| Paliperidone (Invega Sustenna) | Initiate with 234 mg on day 1 and 156 mg 1 week later, both in deltoid muscle | Recommended monthly maintenance dose is 117 mg (range, 39–234 mg) | First two doses must be given in the deltoid muscle; after that, monthly doses given in either the deltoid or gluteal muscle; available as 39-, 78-, 117-, 156-, and 234-mg prefilled syringes |
| Risperidone long-acting injection (Risperdal Consta) | 25 mg every 2 weeks | 25–50 mg every 2 weeks | Previous antipsychotics should be continued for 3 weeks after initial dose of risperidone long-acting injection<br>Recommended to establish tolerability with oral risperidone prior to initiation of long-acting injection<br>Available in 12.5-, 25-, 37.5-, and 50-mg vial/kit; must use needle supplied with kit, administer IM |

IM, intramuscular; SC, subcutaneous.

# Children and Adolescents



- The diagnosis of schizophrenia in children and adolescents is often challenging.
- The existence of prominent hallucinations or delusions helps make the diagnosis because they are not prominent in other disorders.
- 54% to 90% of patients developing schizophrenia before age 18 years have premorbid abnormalities such as withdrawal, odd traits, and isolation.

# Children and Adolescents…



- Treatment for psychotic children and adolescents ideally is intensive, comprehensive, and structured.
- Day treatment, hospitalization, or long-term residential treatment may be necessary.
- Pharmacologic treatment is indicated if psychotic symptoms cause significant impairments or interfere with other interventions.
- Children and adolescents are more vulnerable to EPS, particularly dystonias, than are adults.

# Children and Adolescents…



- Because of concerns about EPS and TD in children and adolescents, it is recommended that antipsychotic therapy be initiated with SGAs.
- Aripiprazole, risperidone, quetiapine, olanzapine, and paliperidone are approved by FDA for the treatment of schizophrenia in pediatric and adolescent populations.
- Initiation and target dosing is lower for adolescents than adults.

# Children and Adolescents…



- Agents with significant sedative and anticholinergic side effects are not preferred because they can interfere with thinking.
- Compared with adults, children and adolescents tend to gain more weight when taking these agents.
- Young patients should be started on lower doses than adults and should be titrated at a slower rate.
- Side effects should be monitored closely initially and throughout therapy.

# Elderly



- Psychotic symptoms in late life (after 65 years of age) generally result from an ongoing chronic illness; however, a small percentage of patients develop psychotic symptoms de novo, defined as late-life schizophrenia.
- However, other illnesses with psychotic symptoms are common in this population; approximately one-third of patients with Alzheimer disease, Parkinson disease, and vascular dementia experience psychotic symptoms.

# Elderly



- Antipsychotics can be safe and effective for the treatment of schizophrenia in the elderly, if used at lower doses than those commonly used in younger adults.
- Older adults are particularly vulnerable to the side effects of the FGAs.
- Pseudoparkinsonism reportedly occurs in more than 50% of elderly patients receiving these agents, and the cumulative annual incidence of TD in middle-aged and elderly patients is greater than 25%.

# Elderly



- Orthostasis, estimated to occur in 5% to 30% of geriatric patients, is a major contributing factor to falls that often lead to injuries and loss of independence.
- Low-potency antipsychotics and clozapine are more likely to cause significant orthostasis.
- Antipsychotics may cause or worsen anticholinergic effects, including constipation, dry mouth, urinary retention, and cognitive impairment.

# Elderly



- Greater antipsychotic-associated impairment in cognitive functioning may occur in the elderly compared to younger adults. In the elderly, this can lead to decreased independence, a very problematic issue.
- As a result of data showing a statistically significant increase in mortality in elderly dementia patients taking SGAs, a black-box warning was added to the manufacturer's information for all antipsychotics.
- Patients and families should be informed of this risk before using these agents in patients with dementia

# Dually Diagnosed Patients



- Estimates of the proportion of schizophrenia patients abusing alcohol and/or illicit drugs range from 40% to 60%.
- Generally, the most common drugs of abuse are cannabis, cocaine, and alcohol.
- Substance use often worsens the clinical course and complicates treatment.

# Dually Diagnosed Patients



- Dually diagnosed patients are more likely to be nonadherent with treatment.
- They have a poorer response rate to the FGAs, more severe psychosis, and higher rates of relapse and rehospitalization than patients who are not abusing substances.

# Dually Diagnosed Patients



- EPS may occur more frequently in substance-abusing patients, and alcohol use is a risk factor for developing TD.
- SGAs are effective in this population, and they may cause a reduction in the use of drugs and alcohol.

# Treatment-Resistant Patients



- For 20%-30% of people with schizophrenia, drug treatment is ineffective.
- A standard definition of Rx resistance is persistent positive symptoms despite treatment with at least 2 different antipsychotics given at adequate doses for an adequate duration (4–6 weeks). In addition, patients must have a moderately severe illness and have a persistence of illness for at least 5 years.
- Highly symptomatic and require extensive periods of hospitalization.

# Clozapine



- Clozapine remains the only drug with proven superior efficacy in treatment-resistant patients, and
- It is the only drug approved for treatment-resistant schizophrenia, with response rates of 30% to 50%.
- It is efficacious after nonresponse to other SGAs, in partially responsive patients and patients who have had a poor response to other medication for years.

# Clozapine



- Clozapine should be considered after two failed antipsychotic trials but may be considered sooner if the individual patient situation warrants.
- Additionally, it has a beneficial effect for aggression and suicidality and is FDA approved for treatment of suicidal behavior in people with psychosis.

# Clozapine



- Clozapine's use is limited by the regulatory requirements resulting from the risk for agranulocytosis (0.86%–1% of patients), which is a rare but potentially life-threatening side effect.
- Other rare side effects include seizures and myocarditis.
- Other common unpleasant side effects include sedation, dizziness, constipation, enuresis, weight gain, and hypersalivation

# Acutely Psychotic Patients



- Although verbal interventions are recommended as initial management, most psychiatric emergencies require both pharmacologic and psychological interventions.
- Safe and effective IM formulations are available for a number of FGAs and three SGAs (aripiprazole, ziprasidone, and olanzapine).
- These IM SGAs are now recommended as first-line therapy in agitated schizophrenia patients.

# Acutely Psychotic Patients



- IM benzodiazepines, most often lorazepam with or without concomitant oral antipsychotics are also used.
- Concomitant IM olanzapine and benzodiazepines may cause cardiorespiratory depression and should be avoided if possible.
- High doses of FGAs, termed *rapid neuroleptization*, are no longer recommended.

# Pregnancy and Lactation



- Women with schizophrenia, even those who are unmedicated, have a significantly greater risk of obstetrical compilations (eg, stillbirth, infant death, preterm delivery, low infant birth weight, and infants who are small for gestational age).
- Women taking antipsychotics who become pregnant should not discontinue them without consulting their health care professionals.

# Pregnancy and Lactation



- High-potency FGAs have a low risk for congenital abnormalities; however, limb defects and dyskinesias are reported.
- Low-potency phenothiazine antipsychotics may increase the risk of congenital abnormalities when used in the first trimester.
- There appears to be little risk associated with first-line SGA.

# Pregnancy and Lactation



- A labeling change for antipsychotic has been implemented by the FDA to address the potential risk for EPS and symptoms of withdrawal in newborns whose mothers were treated with antipsychotics in the third trimester.
- Withdrawal symptoms may include agitation, abnormal muscle tone, tremor, …which may last for hours to days after delivery.
- In some newborns, specific treatment is not needed, whereas in others, longer hospital stays may be required.

# Pregnancy and Lactation



- Although SGAs are excreted in breast milk, most case reports document a low frequency of deleterious effects on the infant.
- Women taking prolactin sparing SGAs (SGAs other than risperidone and paliperidone) may have enhanced fertility compared with women taking other antipsychotics because they are less likely to be anovulotory.
- Therefore, women of childbearing potential taking antipsychotics must be educated about birth control.

- Second Generation Antipsychotic Dosing recommendation In special population. Reading assignment.

# Adjunct Treatments



- Anticholinergic medications (eg, benztropine, 1 to 2 mg two times daily; trihexyphenidyl, 1 to 3 mg three times daily; and diphenhydramine, 25 to 50 mg two times daily) are used to treat EPS.
- They may be prescribed prophylactically with high-D2-binding agents or in patients at risk for EPS or for treatment of EPS.

# Adjunct Treatments



- β-Blockers (eg, propranolol 30–120 mg/day) are sometimes effective for patients who develop akathisia.
- In some situations, such as on an inpatient unit, the concomitant use of benzodiazepines (eg, lorazepam 1–3 mg/day) with the SGAs may be necessary for agitation or insomnia.

# Adjunct Treatments



- Antidepressants may be useful for patients with schizophrenia who have depressive symptoms.
- Because suicide and depression are linked, aggressive treatment is necessary when depression is present.
- SSRIs are the preferred agents, but they may inhibit the CYP450 enzymes.
- Mood stabilizers, have long been used adjunctively with the antipsychotics to treat the schizoaffective disorder.

# Adjunct Treatments



- Approx. 30% of Rx resistant patients given clozapine do not respond, and another 30% have only a partial response.
- Limited treatment options are available for these patients.
- A number of augmentation strategies have been tried, including FGAs, SGAs, mood stabilizers, minocycline, antidepressants, transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT).

# Psychosocial Treatment



- Psychosocial support helps improve functional outcomes.
- Residual symptoms often persist
- Psychosocial interventions, as adjuncts to pharmacotherapy, are designed to improve psychosocial functioning, self-esteem, and life satisfaction.
- These treatments are mainly used as targeted treatments for social and cognitive impairments.
  - A few of the best-supported and most promising approaches are social skills training (SST), cognitive behavioral therapy (CBT), acceptance commitment therapy, and cognitive remediation (CR).

# Patient Education



- Key considerations include:
- Involve families in the education and treatment plans because family psychoeducation may decrease relapse, improve symptomatology.
- Be clear that there is no cure for schizophrenia.
- Explain common and rare but dangerous side effects.
- Stress the importance of medication and treatment adherence for improving long-term outcomes.
- Decision making on the best course of treatment should be a shared process.

# OUTCOME EVALUATION



## Symptom Monitoring

Many assessments are available to objectively rate positive and negative symptoms, level of function, and life satisfaction.

The most commonly used scales include:

- Positive and Negative Symptom Scale (PANSS)
- Brief Psychiatric Rating Scale (BPRS)
- Clinical Global Impression (CGI) Scale

# Side-Effect Monitoring…



**Monitoring of White Blood Cell Count and Absolute Neutrophil Count During Clozapine Treatment**

| | Hematologic Values | Frequency of WBC and ANC Monitoring |
|---|---|---|
| Before clozapine initiation | Recommended levels: WBC ≥ 3.5 × $10^3$/$mm^3$ (3.5 × $10^9$/L) and ANC ≥ 2 × $10^3$/$mm^3$ (2 × $10^9$/L)<br>No history of a myeloproliferative disorder or clozapine-induced agranulocytosis | |
| Initiation to 6 months | WBC ≥ 3.5 × $10^3$/$mm^3$ (3.5 × $10^9$/L) and ANC ≥ 2 × $10^3$/$mm^3$ (2 × $10^9$/L) | Weekly for 6 months |
| 6–12 months | WBC ≥ 3.5 × $10^3$/$mm^3$ (3.5 × $10^9$/L) and ANC ≥ 2 × $10^3$/$mm^3$ (2 × $10^9$/L) | Every 2 weeks for 6 months |
| After 12 months of therapy | WBC ≥ 3.5 × $10^3$/$mm^3$ (3.5 × $10^9$/L) and ANC ≥ 2 × $10^3$/$mm^3$ (2 × $10^9$/L) | Every 4 weeks |
| Whenever clozapine is discontinued | | Weekly for at least 4 weeks from day of discontinuation |
| Mild leukopenia or granulocytopenia | WBC value lies between 3 × $10^3$/$mm^3$ (3 × $10^9$/L) and 3.5 × $10^3$/$mm^3$ (3.5 × $10^9$/L) or ANC lies between 1.5 × $10^3$/$mm^3$ (1.5 × $10^9$/L) and 2 × $10^3$/$mm^3$ (2 × $10^9$/L) | Twice weekly until returned to recommended levels |
| Moderate leukopenia or granulocytopenia | WBC value lies between 2 × $10^3$/$mm^3$ (2 × $10^9$/L) and 3 × $10^3$/$mm^3$ (3 × $10^9$/L) or ANC value lies between 1 × $10^3$/$mm^3$ (1 × $10^9$/L) and 1.5 × $10^3$/$mm^3$ (1.5 × $10^9$/L) | Interrupt therapy; monitor daily until WBC > 3 × $10^3$/$mm^3$ (3 × $10^9$/L) and ANC > 1.5 × $10^3$/$mm^3$ (1.5 × $10^9$/L); then twice weekly until back to recommended levels |
| Severe leukopenia or granulocytopenia or agranulocytosis | WBC < 2 × $10^3$/$mm^3$ (2 × $10^9$/L) or ANC < 1 × $10^3$/$mm^3$ (1 × $10^9$/L)<br>ANC ≤ 0.5 × $10^3$/$mm^3$ (0.5 × $10^9$/L) (agranulocytosis) | Discontinue treatment and do not rechallenge; monitor daily until WBC > 3 × $10^3$/$mm^3$ (3 × $10^9$/L) and ANC > 1.5 × $10^3$/$mm^3$ (1.5 × $10^9$/L); then twice weekly until back to recommended levels |

ANC, absolute neutrophil count; WBC, white blood cell count.

# Side-Effect Monitoring…



**Monitoring Protocol for Patients on Second-Generation Antipsychotics**

| | Baseline | 4 Weeks | 8 Weeks | 12 Weeks | Quarterly | Annually | Every 5 Years |
|---|---|---|---|---|---|---|---|
| Personal or family history[a] | X | | | | | X | |
| Weight | X | X | X | X | X | | |
| Waist circumference | X | | | | | X | |
| Blood pressure | X | | | X | | X | |
| Fasting plasma glucose | X | | | X | | X | |
| Fasting plasma lipids | X | | | X | | | X |