Schizophrenia

- Schizophrenia is a chronic heterogeneous syndrome of disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect, cognitive deficits, and impaired psychosocial functioning.

- Increased ventricular size, decreased brain size, and brain asymmetry have been reported.

- Lower hippocampal volume may correspond to impairment in neuropsychological testing and poorer response to first-generation antipsychotics (FGAs).

- *Dopaminergic hypothesis. Psychosis may result from hyper- or hypoactivity* of dopaminergic processes in specific brain regions. This may include the presence of a dopamine (DA) receptor defect.

- Positive symptoms may be more closely associated with DA receptor hyperactivity in the mesocaudate, while negative symptoms and cognitive symptoms may be most closely related to DA receptor hypofunction in the prefrontal cortex.

- *Glutamatergic dysfunction. A deficiency of glutamatergic activity produces* symptoms similar to those of dopaminergic hyperactivity and possibly symptoms seen in schizophrenia.

- *Serotonin (5-HT) abnormalities. Schizophrenic patients with abnormal* brain scans have higher whole blood 5-HT concentrations, and these concentrations correlate with increased ventricular size.

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processes (loose associations); ambivalence (contradictory thoughts); flat, inappropriate, or labile affect; autism (withdrawn and inwardly directed thinking); uncooperativeness, hostility, and verbal or physical aggression; impaired self-care skills; and disturbed sleep and appetite.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.

DIAGNOSIS

The *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text* revision, specifies the following criteria for the diagnosis of schizophrenia:

✓ 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.

DESIRED OUTCOME

- 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.

- 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.

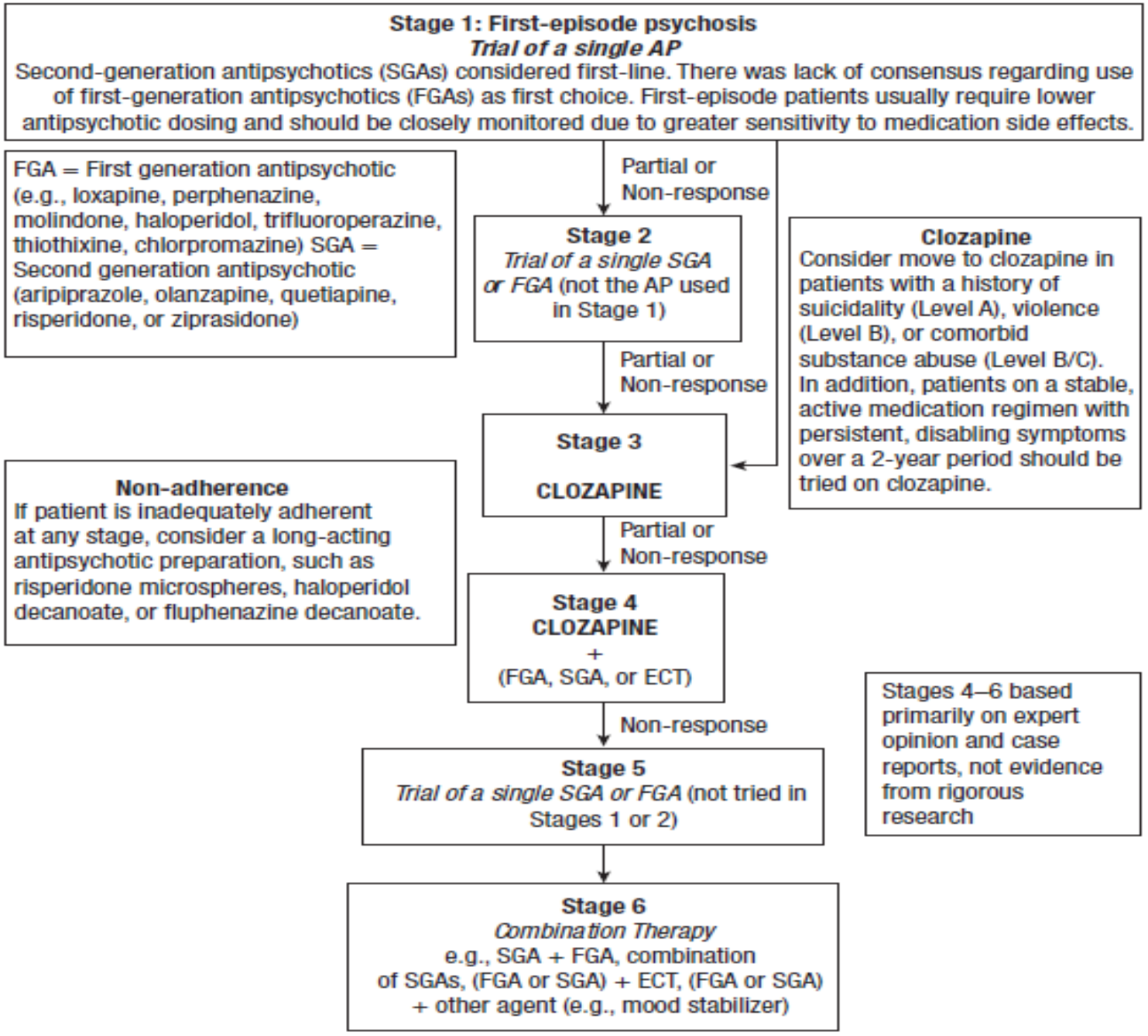
- Selection of an antipsychotic should be based on (1) the need to avoid certain side effects, (2) concurrent medical or psychiatric disorders, and (3) patient or family history of response.

- All FGAs are equal in efficacy in groups of patients when used in equipotent doses.

- Dosage equivalents (expressed as chlorpromazine [CPZ]-equivalent dosages— the equipotent dosage of an FGA compared with 100 mg of CPZ) may be useful when switching from one FGA to another FGA drug.

- 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.

- 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).


Stage 1: First-episode psychosis
Trial of a single AP
Second-generation antipsychotics (SGAs) considered first-line. There was lack of consensus regarding use of first-generation antipsychotics (FGAs) as first choice. First-episode patients usually require lower antipsychotic dosing and should be closely monitored due to greater sensitivity to medication side effects.
FGA = First generation antipsychotic (e.g., loxapine, perphenazine, molindone, haloperidol, trifluoroperazine, thiothixine, chlorpromazine) SGA = Second generation antipsychotic (aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone)
Partial or Non-response
Stage 2
Trial of a single SGA or FGA (not the AP used in Stage 1)
Partial or Non-response
Stage 3
CLOZAPINE
Partial or Non-response
Stage 4
CLOZAPINE
+
(FGA, SGA, or ECT)
Non-response
Stage 5
Trial of a single SGA or FGA (not tried in Stages 1 or 2)
Stage 6
Combination Therapy
e.g., SGA + FGA, combination of SGAs, (FGA or SGA) + ECT, (FGA or SGA) + other agent (e.g., mood stabilizer)
Clozapine
Consider move to clozapine in patients with a history of suicidality (Level A), violence (Level B), or comorbid substance abuse (Level B/C). In addition, patients on a stable, active medication regimen with persistent, disabling symptoms over a 2-year period should be tried on clozapine.
Non-adherence
If patient is inadequately adherent at any stage, consider a long-acting antipsychotic preparation, such as risperidone microspheres, haloperidol decanoate, or fluphenazine decanoate.
Stages 4–6 based primarily on expert opinion and case reports, not evidence from rigorous research

Generic Name	Trade Name	Traditional Equivalent Dose (mg)	Usual Dosage Range (mg/day)	Manufacturer's Maximum Dose (mg/day)[a]	Dosage Forms[b]
Traditional antipsychotics (first-generation antipsychotics)					
chlorpromazine	Thorazine	100	100–800	2,000	T,L,LC,I,C-ER,S
fluphenazine	Prolixin	2	2–20	40	T,L,LC,I,LAI
haloperidol	Haldol	2	2–20	100	T,LC,I,LAI
loxapine	Loxitane	10	10–80	250	C,LC
molindone	Moban	10	10–100	225	T,LC
perphenazine	Trilafon	10	10–64	64	T,LC,I
thioridazine	Mellaril	100	100–800	800	T,LC
thiothixene	Navane	4	4–40	60	C,LC
trifluoperazine	Stelazine	5	5–40	80	T,LC,I
Atypical antipsychotics (second-generation antipsychotics)					
aripiprazole	Abilify	NA	15–30	30	T,O,L
clozapine	Clozaril	NA	50–500	900	T,O
olanzapine	Zyprexa	NA	10–20	20	T,I,O
paliperidone	Invega	NA	3–9	12	ER
quetiapine	Seroquel	NA	250–500	800	T
risperidone	Risperdal	NA	2–8	16	T,O,L
risperidone	Risperdal Consta	NA	25–50 mg every 2 weeks	50	LAI
ziprasidone	Geodon	NA	40–160	200	C,I

- 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

- During weeks 2 and 3, the goals should be to improve socialization, selfcare habits, and mood. Improvement in formal thought disorder may require an additional 6 to 8 weeks.

- Most patients require a dose of 300 to 1,000 mg of CPZ equivalents (of FGAs) daily or SGAs in usual labeled doses. Dose titration may continue every 1 to 2 weeks as long as the patient has no side effects.

- If symptom improvement is not satisfactory after 8 to 12 weeks, a different strategy should be tried.

- 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.

The principle for conversion from oral antipsychotics to depot formulations is as follows:

✓ Stabilize on an oral dosage form of the same agent (or at least a short trial of 3 to 7 days) to be sure the medication is tolerated adequately.

- ✓ 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.

- 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.

Relative Side-Effect Incidence of Commonly Used Antipsychotics

	Sedation	EPS	Anticholinergic	Orthostasis	Weight Gain	Prolactin
Aripiprazole	+	+	+	+	+	+
Chlorpromazine	++++	+++	+++	++++	++	+++
Clozapine	++++	+	++++	++++	++++	+
Fluphenazine	+	++++	+	+	+	++++
Haloperidol	+	++++	+	+	+	++++
Olanzapine	++	++	++	++	++++	+
Perphenazine	++	++++	++	+	+	++++
Quetiapine	++	+	+	++	++	+
Risperidone	+	++	+	++	++	++++
Thioridazine	++++	+++	++++	++++	+	+++
Thiothixene	+	++++	+	+	+	++++
Ziprasidone	++	++	+	+	+	+

Agents to Treat Extrapyramidal Side Effects

Generic Name	Equivalent Dose (mg)	Daily Dosage Range (mg)
Antimuscarinics		
Benztropine[a]	1	1–8[b]
Biperiden[a]	2	2–8
Trihexyphenidyl	2	2–15
Antihistaminic		
Diphenhydramine[a]	50	50–400
Dopamine agonist		
Amantadine	NA	100–400
Benzodiazepines		
Lorazepam[a]	NA	1–8
Diazepam	NA	2–20
Clonazepam	NA	2–8
β-Blockers		
Propranolol	NA	20–160