

Schizophrenia

An extensive review

By

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- Introduction
- Bible Verses
 - Philippians 2:4 (NKJV)– Let each of you look out not only for his own interests, but also for the interests of others.
 - James 5:17 (KJV) – Elias was a man subject to like passions as we are, and he prayed earnestly that it might not rain: and it rained not on the earth by the space of three years and six months.
 - Hebrews 4:15 (KJV) – For we have not an high priest which cannot be touched with the feeling of our infirmities; but was in all points tempted like as we are, yet without sin.
- Schizophrenia is a mental disorder characterized by such symptoms as delusions, hallucinations, disorganized speech, disorganized behavior, and marked social and occupational dysfunction. The primary symptoms of schizophrenia include the hallucinations and delusions; the secondary symptoms include alogia, being autistic, anhedonia, flat affect, being asocial, and having amotivation. The nucleus accumbens of the limbic system is involved in the positive symptoms of schizophrenia. The causes of schizophrenia are both multigenic and various environmental factors; there is a disturbance in the neural circuits and the neurotransmitters. The dorsolateral prefrontal cortex is involved in the cognitive deficits; the ventromedial prefrontal cortex is involved in any affective components. The COMT gene influences the dopamine available. Dopamine is excessive in the limbic brain of those with schizophrenia; the dopamine is low in the dorsolateral prefrontal cortex of those with schizophrenia. The prevalence of schizophrenia is 1 percent of the population.
- schizophrenia, antipsychotics, receptors, and side effects
 - D2 antagonism
 - EPS
 - endocrine effects
 - H1 antagonism
 - ↑ weight
 - ↑ sedation
 - 5HT2C antagonism
 - ↑ weight
 - AchM1 antagonism
 - GI symptoms (↓ motility, ↑ constipation, ↓ secretions)
 - ↑ sedation
 - ↓ memory

- NE (alpha) antagonism
 - ↑ orthostatic hypotension
 - ↓ sexual functioning
 - ↑ weight
 - ↑ sedation
- schizophrenia, atypical neuroleptics, and CV disease

Schizophrenics are high in cardiac deaths (46% increased rate of cardiac deaths). Several factors may play a role:

 - Obesity: Obesity occurs in 42% of schizophrenics versus 32% in the general population. The atypical neuroleptics may play a role with their H1 antagonism and their increase of leptin that increases appetite; clozapine and olanzapin pose the greatest risk here. The sedentary lifestyle and lack of exercise of many schizophrenics no doubt play a role.
 - Smoking: Schizophrenics increase their CV risks by smoking (70% smoke versus 20% in the general population). Schizophrenics who smoke have less cognitive impairment possibly because nicotine increases dopamine; thus, smoking may serve an adaptive function.
 - Diabetes Mellitus: Schizophrenics have higher rates of diabetes mellitus (DM); DM increases CV deaths. Atypical neuroleptics (except ziprasidone/Geodon perhaps) increase the risk of diabetes mellitus. The atypical neuroleptics affect insulin sensitivity; clozapine and olanzapine impair Ach stimulated secretion by blocking Ach-M3 receptors; the atypical neuroleptics may also block glucose transport.
 - Metabolic Syndrome: The atypical neuroleptics (except perhaps ziprasidone (Geodone perhaps) can induce metabolic syndrome of abdominal obesity, increased triglycerides, lower HDL cholesterol, increased blood pressure, and impaired fasting glucose; all are risk factors for CV death.
- schizophrenia, atypical neuroleptics, and increased weight

Schizophrenics on atypical neuroleptics tend to have increased appetites. The atypicals that increase appetite may do this through antagonism at two receptors:

 - H1
 - 5HT2C
- schizophrenia and brain circuits

Various brain circuits malfunction in schizophrenia including:

 - mesolimbic: positive symptoms
 - mesocortical (prefrontal cortex): negative symptoms
 - nucleus accumbens: negative symptoms
 - dorsolateral prefrontal cortex (DLPFC): cognitive symptoms
 - ventromedial prefrontal cortex (VMPFC): affective symptoms
 - orbital frontal cortex: aggressive symptoms
 - dopamine projections from the substantia nigra and ventral tegmental area in the midbrain to:
 - DLPFC

- VMPFC
 - thalamus
 - striatum
- glutamatergic connections in:
 - DLPFC
 - thalamus
 - hippocampus
 - nucleus accumbens
 - striatum
 - cerebellum
- dopamine supersensitivity and elevated D2 (dopamine receptors)
- schizophrenia and cognitive defects

Cognitive defects in schizophrenia have a greater effect on functioning than either positive or negative symptoms. The cognitive deficits include:

 - ↓ memory
 - ↓ verbal fluency
 - ↓ executive functioning
 - ↓ attention
 - ↓ social and vocational functioning secondary to ↓ cognition

Since low dopamine is in the frontal lobes it is believed to contribute to the cognitive impairment in schizophrenia, and since atypical neuroleptics increase dopamine in the frontal lobes by blocking 5HT2A, they may help in decreasing cognitive impairment in schizophrenia.

Cholinesterase inhibitors such as galantamine (Reminyl) and donepezil (Aricept) have been used off-label in an attempt to enhance cognitive functioning in some patients with schizophrenia. Schizophrenia may have:

- a deficit in the Ach nicotinic receptor
- decreased hippocampal Ach muscarinic receptor binding
- decreased density of Ach interneurons in the ventral striatum

Thus, AchIs that ↑ Ach and/or AchN might help some schizophrenics with possible beneficial influences in attention and memory.

- schizophrenia and CV (cardiovascular) risk

CV risk are higher in schizophrenia.

	<u>Catie Study</u>	<u>Controls</u>
diabetes	13%	3%
smoking	70%	20%
↑ BP	30%	20%

- schizophrenia and early intervention

Early intervention seems to have a positive effect in schizophrenia. The neuroleptics may afford protection against brain cell death, dysregulation of chemical neurotransmission in the synapse, general neurotoxicity, and loss of gray matter in the frontal, temporal, and parietal lobes. Prodromal symptoms include:

 - positive symptoms

- ↑ paranoid feelings
 - ↑ derealization
 - ↑ perceptual abnormalities
 - negative symptoms
 - ↑ flat affect
 - ↑ amotivational
 - ↓ speech or ↑ disorganized speech
 - affective
 - ↑ depression
 - ↑ anxiety
 - ↑ anger
 - ↑ suicidal ideations
 - behavioral
 - ↓ school performance
 - ↑ social withdrawal
 - ↓ hygiene
 - ↑ aggression
- schizophrenia: etiology

Schizophrenia is multifactorial in etiology: neurogenerative, neurodevelopmental, and environmental. Genes and neuronal factors involved include:

 - dysbindin
 - neuroglulin
 - BDNF
 - DISC-1
- schizophrenia and exercise

Exercise can decrease mortality rate in several ways including:

 - seven hours per week of exercise—↓ mortality rate by 50%
 - ↓ weight
 - ↓ BP
 - in diabetes mellitus II—↓ mortality rate by approximately 60% over 12 years
- schizophrenia: extrapyramidal side effects (EPS)

EPS in schizophrenia increases with:

 - increasing age
 - age of onset
 - male gender
 - a longer duration of treatment
 - past history of obstetric complications
 - first-generation antipsychotics
- schizophrenia and monitoring atypical antipsychotics

Monitoring risk factors is common with atypical neuroleptic use. Below are considerations:

	baseline	1 week	2 weeks	3 weeks	12 weeks	5 years
weight (BMI)	✓	✓	✓	✓	✓	
waist	✓				✓	

blood sugar	✓			✓	✓	
BP	✓			✓	✓	
lipids	✓			✓		✓
family history	✓					

Check weight often.

Check BP, blood sugar, and lipids fairly often.

- schizophrenia and neuroleptic discontinuation in Catie
Reason for antipsychotic discontinuation in the Catie study included, in order:
 - intolerability (sedation, etc.)
 - patient decision
 - lack of efficacy
- schizophrenia: neurological abnormalities
Neurological abnormalities in schizophrenia include:
 - lesions in the inferior frontal and inferior parietal cortices
 - less tissue in the motor cortex, basal ganglia, and cerebellum
 - a small total brain volume
 - oversized sulci
- schizophrenia: NMDA receptor theory
Six brain circuits are often described including:
 - cortical brainstem → ↓Glu → ↓D → DLPC, VMPC → cognitive, negative, and affective symptoms
 - corticostriatal Glu pathway → ↓Glu → ↑D in NA → ↓GABA thalamic filter → ↑ cognitive symptoms
 - thalamocortical Glu pathway → ↓Glu → ↑D in NA → ↓GABA thalamic filter → ↑post. symptoms of schizophrenia
 - corticothalamic Glu pathway → ↓Glu → ↑D → sensory overload
 - corticocortical Glu pathway
 - mesolimbic D → ↓Glu → ↑D in NA → ↓GABA thalamic filter → ↑ post. symptoms of schizophrenia
- schizophrenia and relapse rates
A relapse rate of 30-50% occurs after one year of treatment in schizophrenia with typical neuroleptics.; 75% experience relapse after treatment discontinuation.
- schizophrenia: resistant cases and novel polypharmacy
Novel agents to consider adding to neuroleptics in resistant schizophrenia include:
 - glutamate modulators
 - memantine (Namenda)
 - GABA agonists
 - valproate
 - benzodiazepines
 - glutamate agonist
 - glycine
 - D-cycloserine

- D-serine
 - D-alanine
 - glutamate indirect agonist
 - sarcosine (N-methyl glycine)
 - NSAID
 - COX-2 inhibitor
 - other NSAIDs
 - cognitive enhancing agents
 - alpha 7 nicotinic receptor agonists
 - D1 receptor agonists
 - AMPA glutamatergic receptor agonists
 - neuroprotective agents
 - BDNF (brain-derived neurotrophic factor)
 - NGF
 - lithium
 - SSRIs
 - myelin repair agent
 - citalopram (Celexa)
 - glutamate agonists
 - D cycloserine
 - D serine
 - D alanine
 - glycine
 - NADPH (nicotinamide adenine dinucleotide phosphate) oxidase for ketamine-induced psychosis
- schizophrenia: risk factors for heart disease

	<u>schizophrenic</u>	<u>general population</u>
↑ BP	19% (30% in Catie)	15-20%
BMI >27	42%	27%
smoking	70-80%	24%
- schizophrenia: two theories of neurotransmitter etiology

The dopamine hypothesis of schizophrenia states that an overactive mesolimbic dopamine pathway causes positive symptoms (hallucinations, delusions) and that an underactive mesocortical dopamine pathway causes negative (alogia, asocial, amotivation), affective, and cognitive symptoms. The NMDA receptor hypofunction hypothesis of schizophrenia states that hypofunction of NMDA receptors result in less glutamate and less GABA in the ventral tegementa area of the midbrain. A GABA interneuron results in high dopamine in the limbic brain but low dopamine in the frontal cortex. Thus, more dopamine in the mesolimbic pathway causes positive symptoms. However, less glutamate in the mesocortical pathways causes less dopamine in the dorsolateral prefrontal cortex causing cognitive symptoms and less dopamine in the ventromedial prefrontal cortex causing affective and negative symptoms. Also, dopamine is increased in the thalamus which decreases GABA which results in increased sensory input that is seen in schizophrenia. A summary of the main issues includes:

D (mesocortical) ↓
 Glu (mesocortical) ↓
 D (mesolimbic) ↑
 Glu (mesolimbic) ↓
 GABA (thalamus) ↓ → ↑ sensory input

PCP (a drug of abuse) and ketamine (an IV drug for general anesthesia) are NMDA antagonists and thus, cause low glutamate; they are known for producing psychotic symptoms.

Drugs of the future may enhance actions at the glycine co-transmitter site of NMDA. Glycine, D-serine (from L-serine), and D-cycloserine have been tried for the negative and cognitive symptoms of schizophrenia. Gly-T₁ inhibitors such as N-methyl-glycine (that increase glycine) are also in testing. Another name for N-methyl-glycine is sarcosine. Direct NMDA antagonists would decrease GABA inhibitory actions with resulting increased glutamate and increased Ach that would risk excitotoxicity; thus, indirect agonist through glycine co-transmitter site of NMDA is likely.

- schizophrenia: two treatments for help
 The mainstay of treatment for schizophrenia is medication (neuroleptics often first) plus psychosocial intervention. The same is true for bipolar disorder: medication (mood stabilizers often first) plus psychosocial intervention.
- antipsychotic drugs: generic, chemical, brand names

Drug	Sedative Effect	Anticholinergic Effect	Extrapyramidal Effect
benzisoaxazole			
risperidone (Risperdal) (Risperdal tablets) (Risperdal M tab) (Risperdal Consta)	low	low	low
paliperidone (Invega)			
butyrophenones			
droperidol (Inapsine— <i>injection only</i>)	low	low	high
haloperidol (Haldol)			
dibenzodiazepines	low	low	high
clozapine (Clozaril)			
loxapine (Loxitane, Daxolin)	high	high	very low
dibenzothiazepine	medium	medium	high
quetiapine (Seoquel)			
diphenylbutylpiperidine	high	low	very low
pimozide (Orap)			
ziprasidone (Geodon)	low	low	high
indolone	medium	low	low
molindone (Moban)			
phenothiazines	medium	medium	high
aliphatic			
chlorpromazine (Thorazine)			
piperidines	high	medium	low
mesoridazine (Serentil)			
thioridazine (Mellaril)	medium	medium	medium

piperazines	high	high	low
fluphenazine (Prolixin, Permitil)			
perphenazine (Trilafon)			
trifluoperazine (Stelazine)	medium	low	high
quinolinone	low	low	high
aripiprazole (Abilify)	medium	low	high
thienbenzodiazepine			
olanzapine (Zyprexa, Zydys)	low	low	low
thioxanthene			
thiothixene (Navane)	high	medium	low
	low	low	high

- antipsychotic drugs: injectable forms
Injectable forms of antipsychotic drugs include haloperidol deconoate, fluphenazine decanoate, fluphenazine enanthate, ziprasidone, risperidone, aripiprazole, chlorpromazine, and droperidol (Inapsine).
- antipsychotic drugs: nuances of interest
 - Second-generation drugs [risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon), aripiprazole (Abilify), paliperidone (Invega)]
 - have fewer EPS [clozapine (Clozaril) and quetiapine (Seroquel) have the least risk]
 - increased benefits on negative symptoms
 - less prolactin elevation [except for risperidone (Risperdal) and paliperidone (Invega)]
 - may induce metabolic syndrome with increased weight, increased blood lipids, increased diabetes mellitus [except ziprosidone (Geodon) may be an exception]
 - Clozapine (Clozaril) can induce seizures and agranulocytosis (1%)
 - 75% of patients with psychosis relapse after treatment discontinuation
 - 10-15% of patients with first episode schizophrenia are resistant to drug treatment
 - 25-50% of long-term schizophrenic patients have persistent symptoms
 - Clozapine (Clozaril) is the best in treatment refractory cases, but side effects often preclude its use; olanzapine is the second best
 - 30% of schizophrenics with significant positive symptoms have poor response to conventional antipsychotics; 50% have a partial response
 - 70% of schizophrenics have negative symptoms (alogia, apathy, affect blunting, anhedonia, and autistic thinking)
 - 60% of schizophrenics have cognitive impairment
 - Clozapine (Clozaril) is approved for use in schizophrenics with suicidal ideations
 - All second-generation antipsychotics [except clozapine (Clozaril) and paliperidone (Invega)] are approved for manic phase of bipolar disorder

- All second-generation antipsychotics [except clozapine (Clozaril), quetiapine (Seroquel), and paliperidone (Invega)] are approved for mixed episodes of bipolar disorder
- Olanzapine (Zyprexa) and aripiprazole (Abilify) are approved for maintenance treatment of bipolar disorder
- 25% of patients with MDD (major depressive disorder) have psychotic symptoms (delusions, hallucinations)
- Concerning conventional antipsychotics, high-potency drugs are preferable to low-potency drugs (with more anticholinergic actions and cardiovascular side effects) in delirious patients with psychotic symptoms
- Concerning conventional antipsychotics, they are highly protein bound; have high antihistamine and anticholinergic effects; can cause orthostatic hypotension and extrapyramidal symptoms; and are D2 antagonists in the limbic area and hypothalamus. Because they depress the hypothalamus endocrine effects can result. Because of the release of MSH (melanocyte stimulating hormone), skin pigmentation can occur. Weight gain can occur because of the antihistamine and anticholinergic effects.
- Although often used, antipsychotic drugs are not officially approved for the treatment of dementia in older people; these drugs render an increased risk of death (1.6-1.7 compared with placebo)
- Pimozide (Orap), haloperidol (Haldol), and risperidone (Risperdal) have been used the most in Tourette's disorder
- Treatments of EPS and other side effects include:
 - akathisia (20-25%)—treatment is with benzodiazepine and betaadrenergic blockers;
 - dystonia—treatment is with anticholinergic drugs;
 - parkinsonian side effects—treatment is with anticholinergics or amantadine;
 - tardive dyskinesia (20%) with chronic treatment, 50% in elderly, 1.5-4% overall—change to a second-generation drug (risk of TD with olanzapine is .52% and 7.45% with haloperidol);
 - neuroleptic malignant syndrome (hyperthermia, rigidity, autonomic instability, increased CPK, leukocytosis, confusion)—1-2% risk; treatment has most often been done with dantrolene and bromocriptine.
- Cardiovascular side effects are possible. Hypotension is most common with chlorpromazine (Thorazine), thioridazine (Mellaril), clozapine (Clozaril), and quetiapine (Seroquel)
- Chlorpromazine (Thorazine) and ziprasidone (Geodon) may cause prolongation of the QT interval
- Antacids decrease absorption of antipsychotics

- Weight neutral typical antipsychotics include Molar and Loxitane; a weight neutral atypical antipsychotic is Geodon. Asenapine (sublingual preparation) is also weight neutral
- IM preparations of neuroleptics include: ziprasidone (Geodon), aripiprazole (Abilify 9.75 mg/1.3 ml), chlorpromazine (Thorazine), haloperidol (Haldol), fluphenazine, risperidone (Risperdal Consta)
- Quick-release forms of neuroleptics include: Zydys, Abilify Dismelt, Risperdal M tab
- Liquid preparations of neuroleptics include: Abilify, Risperdal, and Mellaril
- The atypical antipsychotics with their 5HT_{2A} antagonism and resulting increase of dopamine in the frontal lobes may help the negative symptoms of schizophrenia. The glutamate agonists (glycine, D-cycloserine) that increase glutamate and thus dopamine in the frontal lobes may also help the negative symptoms in schizophrenia. D-serine appears more promising than either D-cycloserine or glycine (crosses blood-brain barrier easier).
- Risperdal and Abilify have been approved for the treatment of schizophrenia in adolescents ages 13 to 17 years and for the short term treatment of manic or mixed episodes of bipolar I disorder in children and adolescents ages 10 to 17 years. Risperdal is also approved for the treatment of autism in children. Abilify has similar approvals.
- Quetiapine as Seroquel SR has been approved at a starting dose of 300 mg at hs.
- Abilify has been approved as an adjunct in treatment in resistant depression
- Atypical antipsychotics work by
 - 5HT_{2A} and 5HT_{2C} antagonism. The 5HT_{2A} antagonism causes dopamine release; this decrease extrapyramidal symptoms, decreases negative symptoms, decreases positive symptoms since 5HT_{2A} antagonisms decrease glutamate release (glutamate may increase hallucinations), and decreases hyperprolactinemia.
 - D₂ antagonism or
 - D₂ receptor partial agonist (Abilify)
 - 5HT_{1A} receptor partial agonist (Geodon, Abilify, Risperdal, Seroquel, Clozaril). The 5HT_{1A} receptors increase dopamine release. The 5HT_{1A} agonists effects are similar to the 5HT_{2A} antagonism effects.
- NMDA “gentle” agonists might improve the negative symptoms of schizophrenia. These include:
 - D-serine (a glycine site agonist) – the best possibly
 - D-alanine (a glycine site agonist)
 - D-cycloserine (a glycine site agonist)

- Glycine transporter inhibitors might help in schizophrenia. These include sarcosine. It is actually an NMDA antagonist but because of its mechanism of action, it increases glutamate.
- Antagonists of presynaptic metabotropic glutamate receptors might help in schizophrenia
- Agonists at the postsynaptic metabotropic glutamate receptors (type 2, 3) might help in schizophrenia, no weight gain
- In the Catie study Risperdal had the least drop-out due to intolerability
- Bifeprunox is a new D2 partial agonist in testing as an antipsychotic
- When antipsychotics fail augmentation strategies include adding:
 - divaloprex
 - lamotrigine
 - antidepressant
- Weight gain may be the greatest in an antipsychotic that has both 5HT2C antagonism plus H1 antagonism
- Erythropoietin is being considered for neuroprotection in schizophrenia with hopes of improving cognitive function; it is neuroprotective in stroke patients
- Asenapine is in testing as the first true sublingual antipsychotic
- Famous studies on the effectiveness of antipsychotics include:

Catie double blind	Cutlass rather blind	Soho observational
USA	UK	Europe
SGAs perphenazine FGAs	SGAs FGAs	SGAs FGAs
no first episode no treatment resistant	> 1 mo since first episode no substance use	included first episode included treatment resistant patients
FGA comparable to SGA, Zyprexa best but worst on side effects SGA and FGA similar on negative symptoms	no SGA advantages no EPS in SGAs and FGAs clozapine better	FGAs and risperidone higher on EPS and prolactinemia, less sexual side effects on quetiapine, more weight on olanzapine

- Genetic differences in races exist that affect the dosing of neuroleptics; Asians require a lower dose of clozapine.
- Those with ↓ RGS4 gene that regulates G-protein signaling of D, 5HT1, and AchM have a poor response to antipsychotics based on a study in Africa and Europe
- Mexican-Americans have ↑ metabolism in P450 2D6 and P450 2C19, and thus may need higher doses of antipsychotics
- Asenapine is a neuroleptic with less weight gain
- New drugs and/or possible drugs include:

- asenapine, a sublingual preparation (schizophrenia and bipolar disorder)
 - RG 2417 (bipolar disorder)
 - TS-032 (schizophrenia), a metabolic glutamate agonist
 - bifeprunox, a partial agonist at D₂ and 5HT_{1A}, serizotan is similar to bifeprunox
 - amisulpride, partial agonist of D₂ at low dose
 - sulpiride, partial agonist of D₂ at low dose
 - NMDA antagonists of the future possibly
 - glycine agonist such as d-serine possibly
 - glucine T1 antagonist such as sacosine possibly
 - metabotropic glutamate R presynaptic receptor (decreases glutamate release), a possibility
 - AMPA—kines (a glutamate receptor subtype), allosteric modulation a possibility
 - sigma 1 agonist/antagonist (actions on NMDA receptors), a possibility
 - iloperidone (and SDA with alpha 1 antagonism), a possibility
 - 5HT_{2A} selective antagonist, a possibility
 - gepirone (a 5HT₁ partial agonist), a possibility
 - 5HT_{2C} antagonist or agonist, a possibility
 - 5HT₆ (increases BDNF), a possibility
 - 5HT₇ antagonists—current drugs that have 5HT₇ effects are clozapine, risperidone, quetiapine, paliperidone, loxapine, ziprasidone, zotepine, cyamemazine, and zotepine
 - D₃ antagonist, a possibility
 - CDMT inhibitor, a possibility
 - NRI, a possibility
 - alpha 7 nicotine cholinergic agonist, a possibility
 - alpha 4 beta 2 AchN partial agonist, a possibility
 - AchM agonist, a possibility
 - rimonabant (a cannabinoid antagonist)
 - neurotensin antagonist, a possibility
- antipsychotics: recent thoughts
The famous CATIE study showed that the old typical antipsychotics may be as effective as the new atypical antipsychotics. The typical antipsychotics have more EPS and TD, but the atypical antipsychotics have more metabolic syndrome. Clients seem to feel better on the atypical antipsychotics.
 - antipsychotics and weight gain
Many antipsychotics induce weight gain through antihistaminic side effects. The antipsychotics that are usually weight neutral are ziprasidone (Geodon), molindone (Moban—appetite suppressant effect), and perhaps loxapine (Loxitane); aripiprazole (Abilify) is also one of the better ones at not causing weight gain in some people.
 - Conclusion
 - Bible Verses

- Philippians 2:4 (NKJV) – Let each of you look out not only for his own interests, but also for the interests of others.
- James 5:17 (KJV) – Elias was a man subject to like passions as we are, and he prayed earnestly that it might not rain: and it rained not on the earth by the space of three years and six months.
- Hebrews 4:15 (KJV) – For we have not an high priest which cannot be touched with the feeling of our infirmities; but was in all points tempted like as we are, yet without sin.