SCHIZOPHRENIC PSYCHOSIS
A complex multigenetic disease

Multiple genetic risk factors
Susceptibility genes / at-risk haplotypes / protective alleles

Critical "genetic load" for spontaneous disease onset?

YES

"Genetic load" high

Potential cofactor: Perinatal neurotrauma

< Puberty onset ≥ Puberty onset

Spontaneous schizophrenia

NO

Healthy

Dysbalance by external factors

Neurotrauma

Infectious agents

Psycho-trauma

Substance abuse

Stressful life events

Aging

Late onset including atypical schizophrenic psychosis

Balance maintained Healthy carrier of a predisposition
Substance abuse psychosis

Eroding the Mind

Researchers have mapped brain decay caused by amphetamine use. The damage affects memory, emotion, and reward systems.

Average difference in brain tissue volume of amphetamine use.

Areas of greatest loss:
- Emotion, reward (limbic system)
- Motor function
Psychosis

(Scientific mystery & personal disaster)

- Psychosis is a severe mental illness characterized by distorted or non-existent sense of reality.
Antipsychotics/Major Tranquillizers/Neuroleptics
or
Anti-schizophrenic drugs

- **Psychosis**
  1. Schizophrenia
  2. Affective/mood disorders with psychotic features
     - Depression
     - Mania
     - Manic depressive illness (bipolar depression)
- Substance-induced
- Psychotic symptom associated with diseases e.g. dementia
• Etiology:
• Not known
• Strong but incomplete genetic predisposition
  • 1\textsuperscript{st} degree relatives – 10%)
  • 2\textsuperscript{nd} monozygotic twin – 50%)
• Neurodevelopmental disorder
• Environmental factor
• Symptoms:
• 1. Positive symptom: (result from Neurochemical Abnormality)
  • Increase dopaminergic transmission
  Respond well to $R_x$
1) Delusions (thought disorder)
  • often paranoid
can’t be rectified by reasoning
• Hallucinations: (perception disorder)
  • They may be
  • Visual
  • Auditory – more common
  • Tactile (CD Canine bugs)
• **c) Thought disorder**

  Wild train of thoughts
  irrational conclusion with the feeling that thoughts are inserted or withdrawn by an outside agency.

• Usually not like to be interfered, flight of ideas from one thought to other thought.

• Broadcast of ideas.
• d) Abnormal stereotypical behavior, usually aggressive.
• e) Defectiveness in selective attention, disorganized speech, and disorganized or agitated behavior
2. Negative Symptoms:

- seen in schizophrenia typically
- Result from brain atrophy
- 10% of patient commit suicide, don’t respond / less responsive to Rx

Emotional blunting.
Poor Socialization
_avolition
_alogia
_apathy
_amotivation
Cognitive dysfunction

- (strongest predictor of functional impairment among schizophrenia)
- particularly seen in
- working memory,
- processing speed,
- social cognition,
- problem solving below population norms
Neurochemical Basis:
1) Dopamine Theory
  positive symptoms --- Dopamine hyperactivity in mesolimbic and mesocortical pathway & amygdale

Inc dopaminergic activity—produce these symptoms e.g. levodopa, apomorphine

Blockade of Dopamine receptor Improve the symptoms
2) Glutamate Theory

- **Glutamate** excite GABA ergic striatal neurons
- DA inhibit GABA ergic striatal neurons which project to thalamus and constitute “sensory Gate”

Glutamate NMDA (N-methyl deaspartate) recep antagonists produce psychotic synd e.g. Phencyclidine, Katamine
3) 5 – HT Theories:

- 5 – HT dysfxn
- LSD & 5-HT$_2$ Receptors agonists produced schizophrenia like syndrome.

- Mostly of Anti-psychotics in addition to affect dopamine also back serotonin receptors.
**Functions**
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

**Functions**
- Mood
- Memory processing
- Sleep
- Cognition
4) **Current views:**

- Combination of DA hyperactivity with 5-HT & glutamate dysfxn.
1) Nigrostriatal Pathway:
- 75% of dopamine in brain

2) Mesolimbic mesocortical pathway:
- Projects from neurons near S.N to limbic system & Neocortex
- Behavioral effects
- Hyperactivity leads to schizophrenia.
• 3) Tubero-infundibular (Tubero-hypophyiscal) Pathway:

• Connects arcuate nuclei & paraventricular nuclei of the hypothalamus and post pituitary. Regulation of endocrine control – control MSH, GH, Prolactin.
• 4) Medullary Periventricular Pathway:
• From neurons of Motor Nucleus of Vagus to Periventricular nuclei

Eating behavior regulation
Satiety center to Bolimia Nervosa
Appetite Cetre to Anorexia Nervosa
5) Incertohypothalamic Pathway:
- From medial zone incerta to hypothalamus & Amygdala.
- Sexual drive, Microvasculatory function and temperature regulation.

6) Many local Dopaminergic Neurons in olfactory cortex & retina:
7) Dopaminergic transmission in periphery:
- Renal Vasculatory
 ANTIPSYCHOTIC DRUGS

• Produce improvement in the mood & behavior of a psychotic patient without excessive sedation & addiction

• (Greek----- take hold of nerves)
First Generation Antipsychotics Are D₂ Antagonists
Classification of Antipsychotic Drugs

• A) Classical Typical Neuroleptics:
  • 1. Phenothiazines:
    • a) Aliphatic Comp
      (less potent, sedation & weight gain)
      • Chloropromazine (Largactil)
      • Promazine
      • Triflupromazine
      • promethazine
b) Piperidine Derivative:

- Thioridazine (Melleril, less potent, Anti-Cholinergic)
- Mesoridazine (metabolite of thioridazine)
- Mepazine
- Piperacetazine
c) Piperazine Derivative:

- Fluphenazine (I/V preparation, slowly release)
- Perphenazine
- Trifluperazine
- Prochlorperazine (stemetil)
- Thioperazine
- Acetophenazine
- Carphenazine
2. Thioxanthines: (also available as DEPOT preparation)

- Thiothixene
- Clopentixol
- Flupenthixol
- Chlorprothixine
• 3. Butyrophenones 😐(highly potent)
  Haloperiodol
  Droperidol
  Benperidol
  trifluoperidol
B) Atypical Neuroleptics:

(MOA different from anti-psychotics)

1-Loxapine
2-Clozapine (agranulocytosis, bone marrow, depression)
3-Olanzapine (agranulocytosis)
4-Ziprasidone (patients resistant to other drugs. Also Rx of negative effects)
5-Molindone
• **5-Risperidone** (commonly used D$_2$, 5HT$_2$ selective activity for D$_4$ receptors)

• **6-Sulpiride** (D$_2$ selective)
  Remazopride
  Remoxipride

• **7-Pimozide** (D$_2$ selective, long acting indole)

• **8-Quetiapine**

• **9-Aripiprazole** (partial agonist at D2&5HT1a, alpha antagonist)
• FIRST GENERATION (typical, low potency)
  chlorpromazine
  prochlorperazine
  thioridazine
First GENERATION (typical, highly potent)
  fluphenazine
  haloperidol
  thiothixine
  pimozide
Drugs for psychoses & bipolar disorders

**Antipsychotics**
- Classic drugs (D₂ receptor affinity)
  - Chlorpromazine
  - Fluphenazine
  - Haloperidol
  - Thoridazine
  - Trifluoperazine
- Newer agents (5HT₂ receptor affinity)
  - Clozapine
  - Olanzapine
  - Quetiapine
  - Risperidone
  - Ziprasidone

**Bipolar drugs**
- Classic drug
  - Lithium
- Newer agents
  - Carbamazepine
  - Clonazepam
  - Olanzapine
  - Valproic acid
Phenothiazines

- Chemistry & Structure
- 3 ring structure
- 2 benzene rings linked together by S at 5
- &N at 1 position

- Pharmacokinetics
Phenothiazine derivatives

![Phenothiazine molecule]

Chlorpromazine: $\text{C}_2\text{H}_2\text{N} - \text{Cl}$

Aliphatic side chain: $\text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{N} - (\text{CH}_3)_2$
Phenothiazine derivatives

Chlorpromazine \((2) - \text{Cl} \quad (10) - \text{CH}_2 - \text{CH}_2 - \text{N} - (\text{CH}_3)_2\)

Thioridazine \((2) - \text{SCH}_3 \quad (10) - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_3\)

Trifluoperazine \((2) - \text{CF}_3 \quad (10) - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_3\)

Perphenazine \((2) - \text{Cl} \quad (10) - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{CH}_2 - \text{OH}\)

Fluphenazine \((2) - \text{CF}_3 \quad (10) - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{CH}_2 - \text{OH}\)

Aliphatic side chain

Thioridazine

Piperazine side chain

Thioxanthene derivative

Thiothixene \((2) - \text{SO}_2 \text{N}(\text{CH}_3)_2\)

Butyrophenone

Haloperidol

Substituting C for N in the nucleus
PARMACOKINETIC

- highly lipophilic,
- highly membrane- or protein-bound, accumulate in the brain, lung, and other tissues with a rich blood supply
- Cross placenta, secreted in milk
- extensive meta by CYPs and subsequent glucuronidation, sulfation, and other conjugations
**Negative Symptoms (flat affect, apathy)**
- Mesocortical pathway
  - Tegmentum
  - (Inhibited in schizophrenia)

**Positive Symptoms (delusions, hallucinations)**
- Mesolimbic pathway
  - Tegmentum
  - (Disinhibited in schizophrenia)

**Adverse Effects (eg, parkinsonism)**
- Nigrostriatal pathway
  - Substantia nigra

5-HT receptor blockers (eg, risperidone) increase release of DA to alleviate negative symptoms.

D2 receptor blockers (eg, haloperidol) inhibit DA release and alleviate positive symptoms.

Inhibited DA release results in loss of inhibition of excitatory ACh neuronal activity in corpus striatum.
Act on a variety of CNS & Peripheral receptors

- Post synaptic D2 receptor blockade in mesolimbic, mesocotical pathway
- 5 HT2 receptor blockade
- Alpha-1 adrenergic blockade
- Muscarinic receptor blockade
- Ganglion blockade
- Quinidine like effects
- Local anaesthetic like activity
Pharmacological Actions

- **CNS**
- NORMAL (NON-PSYCHOTICS)
  - unpleasant feelings due to
    Sleepiness, restlessness
- Autonomic effects: b/c of muscarinic blockade
IN PATIENTS:

**EFFECT ON BEHAVIOR & INTELLECT**

- No loss of intellectual functions and performance (clear sensorium)
- Alteration of deranged thought process
- Emotional quietening & Psychomotor slowing
- Decreased paranoid idea
- Decrease initiative
- Decrease aggressiveness in agitated person
- Indifference to environment & pain sensation
2. **Effect on motor activity**

a. Decreased spontaneous activity

b. Extra Pyramidal symptoms
   
   **Acute dystonias** *(acute)*
   
   tonic contractions of postural muscles
   
   e.g. torticollis

Akinesia

Akathisia
Tardive Dyskinesia

(Proliferation of $D_2$ receptors in C. striateum

- Disabling repetitive purposeless involuntar movements of Face, tongue, trunk, pelvis
- Perioral tremor (Rabbit syndrome)

Neuroleptic malignant syndrome
Effect on CTZ

*suppresses nausea, vomiting*

**Endocrical Effect**

↑ *prolactin*

↓ Gonadotrophins, ACTH & growth hormone

**Disturbed temp regulation**

Hypothermia/ Hyperthermia
EFFECT ON ANS

• a) ANTICHLINERGIC

• b) ADRENOCEPTORS BLOCKADE
  Orthostatic hypotension

• c) WEAK GANGLIONIC BLOCKADE:
  Both symp and P/symp ganglionic blockade.
RESP. CONTROL:

- *Depressant effect, sig in resp dis*

- No prominent effect in N individual

- No prominent effect in psychotic pt having N respiration
vi) ENDOCRINE EFFECT:
• hyperprolactinemia and inflextility DA, control prolactin (check its release), if block hyper prolactinemia manifested by Gynecomastia in infertility in male and female
ix) ANTIEMETIC ACTION:

Because of DA recept blockade in CRTZ. Useful in drug induced vomiting and other vomiting except motion sickness and vomiting in pregnancy.
2) CVS

i- Effects due to ANS
   dec stroke volume & TPR
   dec CO
   dec B.P
   (may cause reflex tachycardia due to postural hypotension)

ii- direct -ve inotropic effects

iii- quinidine like effect, increase QT interval
4. MISCELLANEOUS

LA effect

Renal effects

Effect on Liver

Antihistaminic action (H1 blocker)
Adverse effects

1-Neurological side effects-

- drowsiness, lethargy, sedation (in many cases desirable)
- Feels depressed (pseudo depression)
Parkinson’s like synd

- 1- switch to drug with less EPS (when possible)
- 2- anticholinergic
diphenhydramine , benztropine (IM)
- 3- non-anticholinergic ---- Amantadine

Perioral tremor (Rabbit syndrome)
EPS

1- Acute dystonias (within few hrs to 5 days)
   More who have never before taken antipsychotic drugs, adolescents, and young adults.
   Start with initial lower dosages

2- Akathisia (days & weeks)
   Doesn’t respond to antiparkinsonian drugs
   Improved by clonazepam and propranolol

3- Akinesia
• Tardive Dyskinesia
  (supersensitivity, D2 high recept)
  elderly 5 times more susceptible
  stereotyped, repetitive, painless, involuntary, quick choreiform (tic-like) movements of the face,
  more common in affective disorder

  withdrawal-emergent dyskinesias

  tolerate high doses of potent D antagonists with limited EPS
• **Neuroleptic malignant syndrome**
  homicidal less common suicidal less chances occure in extreme of disease.
• Rarely fatal except thio & mesoridazine
duer jto cacdio depressive neuro musculal, excitability. Convulsions.
• Pt. comatosed.
• Hypothermia, miosis, deep
• Tendon reflexes.
• Tachycacdia
DECREASE SEIZURE THRESHOLD:

• *High dose:*
  
  cause convulsion cause

  *epileptic patients*
  
  aggravate epilepsy

  inc dose req

  *latent epileptic*
  
  Potentiate cause of seizure
2. ANS effects

anticholinergic—dry mouth (Tolerance develops to anticholinergic effects)

ECG Changes

(No Physical Dependence, tolerance to antipsychotic effect)

Reverse Tolerance or super sensitivity.

Cholestatic Jaundice
5. Endocrinal effects
   galactorrhea (in females)
   gynaecomastia (in males)
   infertility,
6. failure of ejaculation

Hypothermia / Hyperthermia
METABOLIC EFFECTS weight gain---
d/tH1 blockade, inc appetite
hypertriglyceridemia --- weight-independent occurs within weeks & resolves within 6 weeks after medication discontinuation
result of derangements in glucose-insulin homeostasis

Hyperglycemia
result of derangements in glucose-insulin homeostasis, reversible after discontinuation
5. Dermatitis, photosensitivity

6. Opacities in lens and cornea
   accentuate the normal process of aging of lens

5. Increased risk of all-cause mortality
   elderly dementia patients, e.g., CVS events, pneumonia,
NEUROLEPTIC POISONING:

- Can be homicidal less common suicidal less chances occur in extreme of disease.

- Neuro muscular, excitability. Convulsions.
- Pt. comatose.
- Hypothermia, miosis, deep
- Tendon reflexes.
- Tachycardia
- Monitor vital functions.
- * Gastric lavage with activated charcoal
- *Saline catharsis (Na2SO4Mgo)
- * Fluid replacement
- * Pressor agents.
- Diaqzepam for seizures I/V.
A reminder advertisement – For prescribing information, please see PDR or available literature.
for prompt control of 

**senile agitation**

**THORAZINE**

Thorazine can control the agitated, belligerent senile and help the patient to live a composed and useful life.
Therapeutic Uses

A. Treatment of Psychiatric patient
   1. Schizophrenia
   2. Organic Psychosis
   3. Bipolar depression

B. Nausea & vomiting

C. Alcoholic hallucinination

D. Intractable Hiccough
• PIPERIDINE DERIVATIVE:
• THIORIDAZINE:
  – Block D2, x-1 & 5HT-2
  – B.A (20-30%)
  – Metabolite mesoridaine more active
  – More cacdiotoxic
  – Less extra pyramidal eff.
– More potent anti muscacinics

• Extrapyramidal (parkinsonian) symptoms due to blockade of D2 and balance is disturbed, in this case balance is not disturbed when cholinergic activity is
• **cvs** QUINIDINE LIKE effects, cardiac conduction defects, & sudden death
• **OCULAR adverse effects** Deposit in retina, browning of vision.
• Picture resemble that of retinitis pigmentosa pt.
• **Over dose**
  • pupils constricted
  hyotension, hypothermia
  neuromuscular excitability, convulsions
  , later dec tendon reflexes
  *fatal cardiac arrhythmias & death*
HALOPERDOL

highly potent
oral t\(_{1/2}\)----1 to 2 days
haloperidol decanoate has a t\(_{1/2}\) of 21 days less ANS effects
no weight gain
rarely jaundice
used for acute schizophrenia, huntington’s disease, Tourette syd
STE OF ACTION, PFC
D2 affinity of atypical agents

**Figure 3**: "Hit and Run" Binding of Atypical Antipsychotics

- **A**: Atypical antipsychotics bind loosely to postsynaptic dopamine receptors, illustrated by a smooth binding site that does not fit into the teeth of the receptor. (B) The hit: atypical antipsychotic binds to the receptor. Note that if the ligand enters its receptor without getting locked into the grooves of the receptor as do conventional antipsychotics. (C) The run: this loose fit allows atypical antipsychotics to rapidly dissociate, or slip off easily after binding only briefly.

Stahl SM. Stahl's Essential Psychopharmacology: 3rd ed. 2008. (Reproduced with permission, © Neuroscience Education Institute)
ATYPICAL ANTIPSYCHOTICS MOA

- Antagonism exerts the greatest effect on prefrontal and basal ganglia DA release and midbrain noradrenergic outflow, with recent data implicating 5-HT$_{2A}$ receptor polymorphisms.
- 60-75% D$_2$ receptor occupancy—antipsychotic efficacy.
- >78% of D$_2$ receptors in the basal ganglia ---- risk of EPS.
CLINICAL USES

• PSYCHOTIC DISORDER
  1- schizophrenia spectrum disorders,
  2- mania & hypomania----olanzapine
• Levo-Dopa induced psychosis----clozapine,quietapine
3-Manic phase of Bipolar disorder---
- Olanzapine/risperidone with lithium /valproic acid
continued many months after the resolution of psychotic and manic symptoms, typically in combination with a mood stabilizer such
• NON-PSYCHOTIC MENTAL ILLNESS

I- Anxiety disorder
   i- non manic excited states (with BZ)
   ii- OCD obsessive compulsive disorder
   iii- PTSD (post-traumatic stress disorder)
   iv- GAD --- quietapine, risperidone
• **II- Tourette's disorder** & tic disorder
  risperidone and aripiprazole, ziprasidone

**III- Huntington's disease** -- suppress the severity of choreoathetotic movements

**IV- Autism**-- risperidone

(Disruptive behavior, irritability, mental retardation)
• **V**-Agitated patients of Alzheimer’s & parkinsonism
• **VI**-Major depression----aripiprazole(as adjunctive in SSRI resistant major )
ADVERSE EFFECTS

Atypical antipsychotics

- Dopamine antagonism
  - Satiety

- Serotonin antagonism
  - Altered leptin processing

- Insulin secretion

- Insulin resistance
  - Altered glucose metabolism/transport

- Triglyceride levels

- Obesity
  - Type 2 diabetes
  - Metabolic syndrome

- Cardiovascular disease
CLOZAPINE

• Bind D2 with less affinity & for shorter duration, easily displaced
• 51-63% D₂ receptor blocked

• highest ratio of 5-HT₂ₐ/D₂ binding
  Binds with high affinity & blocks D₁, D₄, 5HT₂, M & alpha rec
CLOZAPINE

• D4 & 5HT2, alpha and H1 blocker D2 51-63% receptors selective
• CYPs 1A2, active metabolite N-desmethylclozapine
• Enzyme inducer of CYP1A2 e.g carbamazepine, smoking
dec dose by 50%. 
1- Twice more potent antag at 5HT2 than D2
2- also block D1, D3, D4, H1 & alpha 1
3- potent antimuscarinic
Brief occupation of D₂ by Quetiapine and Clozapine

- Haloperidol 7.5 mg/d (Nordstrom et al., 1992)
- D₂ threshold for antipsychotic effect
- Clozapine 350 mg/d
- Quetiapine 400 mg/d

% of D₂ receptors occupied

Hours after oral dose
– NOT USED IN MANIA
- ADVERSE EFF
- Sialorrhea (*inc* salivation, paradoxical)
- Seizures
- 0.8% *agranulocytosis*, immunemediated
  initial 6 months ---- highest risk
  TLC/DLC wkly for 6 mths then every 3 wks
• metabolic
  Weight gain,
  diabetes
  hypercholesterolemia

CVS
myocarditis

• ANS

• M1 blockade,
OLANZAPINE

- Twice more potent at HT2 than D$_2$
- Also has antidepressent eff

USES

- Epileptogenic
- Wt gain
- sedation
- **metabolic**
  - Weight gain,
  - diabetes
  - hypercholesterolemia
USES

PSYCHOSIS

manic phase of bipolar disorder
ARIPIPRAZOLE

- Partial agonist
- I/M, if emergency
- Meta—dehydroaripiprazole more active
- most weight and metabolically neutral atypical agents,
Partial agonist verse antagonist

![Graph showing the comparison between partial agonists and antagonists](image)

- 100 nM dopamine + aripiprazole
- 100 nM dopamine + haloperidol
- dopamine
- aripiprazole
- haloperidol

**Drug concentration (M)**

**DA response (as % of maximum)**
• Clinical use
• adjunctive use in antidepressant nonresponders
Figure 2. Mesolimbic and mesocortical dopamine pathway activities before and after aripiprazole administration.

a) Before aripiprazole administration, mesolimbic dopamine pathways are overactive and mesocortical dopamine pathways are underactive. b) After aripiprazole administration, mesolimbic dopamine pathway signalling is downregulated and mesocortical dopamine pathway signalling is upregulated. Aripiprazole acts to stabilize the dopamine signalling system.
1) efficacy for bipolar depression
2) Unipolar major depression—primary metabolite, norquetiapine, is a potent norepinephrine reuptake inhibitor.