ANTIPSYCHOTIC DRUGS

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2019

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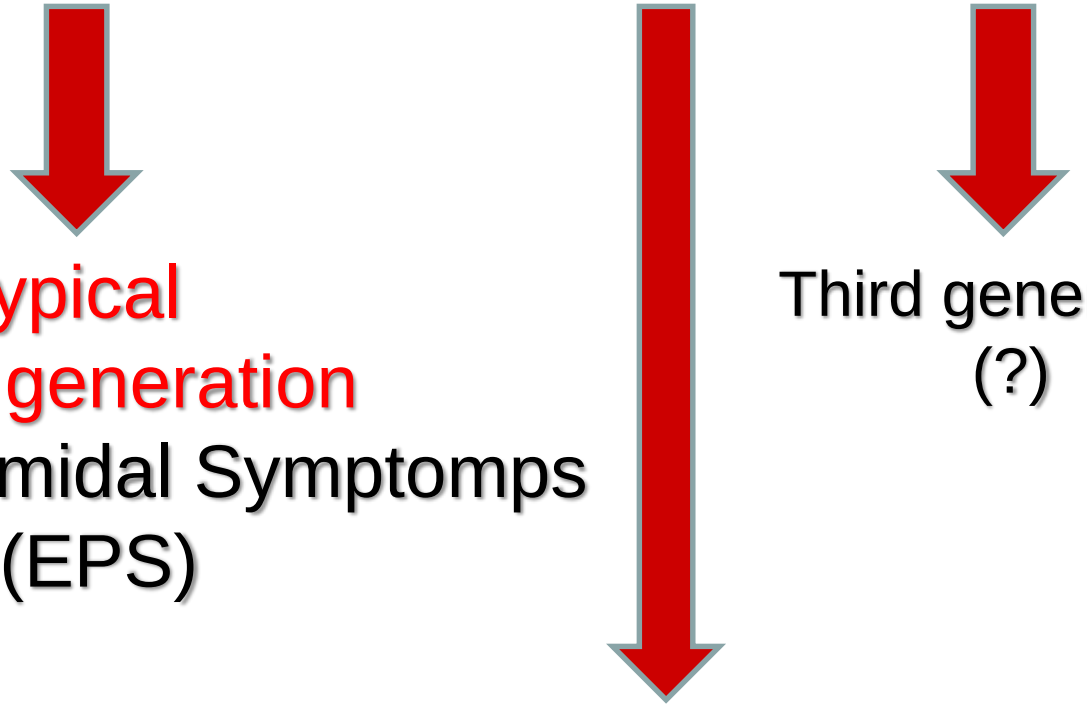
ANTIPSYCHOTIC DRUGS

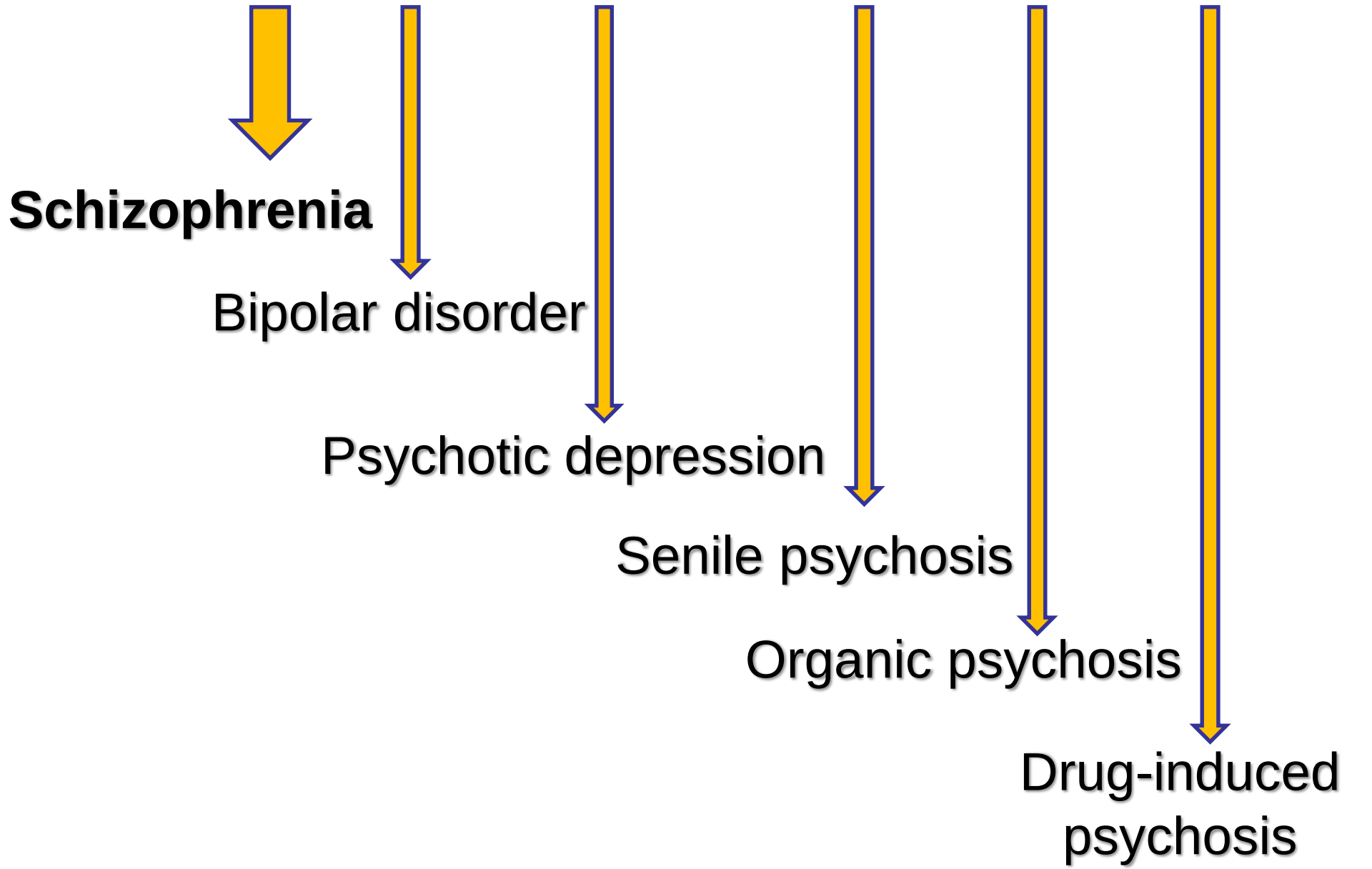


Typical
First generation
↑ Extrapyramidal Symptomps (EPS)

Third generation
(?)

atypical
Second generation
↓ EPS

ANTIPSYCHOTIC DRUGS



THE SYMPTOMS OF SCHIZOPHRENIA

Positive symptoms:

- ❑ Hallucinations (vesion, hearing, smelling, taste, touch)
- ❑ Delusion (of reference; of grandeur; of paranoid)
- ❑ Loss of contact with reality
- ❑ Reality distortion
- ❑ Thought disorder (loose associations)
- ❑ Disorganized thinking
- ❑ Paranoia – (systematized delusions)
- ❑ Bizarre behaviour
- ❑ Verbal, physical aggression

THE SYMPTOMS OF SCHIZOPHRENIA

Negative symptoms:

- Bradyphrenia (reduced, poor thinking)
- Asociality (antisocial behaviour)
- Anhedonia (absence of pleasure)
- Alogia (speechlessness, poverty of speech)
- Reduced drive and motivation
- Carelessness (poor social problem solving)

THE SYMPTOMS OF SCHIZOPHRENIA

Cognitive deficit (disorganizational)

- ❑ Short-term memory impairment.
- ❑ Long-term memory impairment.
- ❑ Verbal memory impairment.
- ❑ Attention impairment.
- ❑ Reduced ability to abstract.
- ❑ Reduced vigilance.

Schizophrenia

Epidemiology: 1%.

Etiology: unknown, but has multifactorial causes.

Pathophysiology: ↑vent. size (3rd and L. ventricles in subtypes of schizophrenics), small ↓ in brain size, obvious ↓ in cortical size of the left temporal lobe).

CAUSES OF SCHIZOPHRENIA

1. GENETICS.

The risk 40 %, in case both parents have schizophrenia.

CAUSES OF SCHIZOPHRENIA

2. NEUROCHEMISTRY

A- DOPAMINE HYPOTHESIS: Amphetamine, L-DOPA, Positron emission tomography (PET) support the following:

- ↑ in D_2-R densities in the head of the caudate nucleus and ↓ in the prefrontal cortex.
- ↓ in D_1-R densities in the caudate nucleus and the prefrontal cortex.

Mesolimbic
(+) symptoms
↓
DR
hyperactivity

↓
lack of volition (wish)
cognitive dysfunction
core features of
schizophrenia

↓
DR
hypofunction
↑
(-) symptoms

Dopamine Pathways

- **Mesolimbic** (VTA-limbic system)

  (+) Symptoms

- **Mesocortical** (VTA-frontal lobe)

  (-) Symptoms

- **Nigro-Striatal**

  Coordination of voluntary movement. D_2-blockade results in extrapiramidal symptoms (EPS)

- **Tubero-Infundibular**

  Prolactin, Thermoregulation

ANTIPSYCHOTICS & DA RECEPTORS

- **D_1-like family (D_1, D_5, G_s-coupled):**

  activation results in ↑ adenylyl cyclase activity, ↑ cAMP.

  Note: The potency of antipsychotic drugs is not correlated with their affinity for D_1.

- **D_2-like family (D_2, D_3 and D_4) G_i-coupled:**

  stimulation results in ↓ adenylyl cyclase activity, ↓ cAMP.

  Note: The affinity for D_2 is correlated with the therapeutical potency of the drugs.

2. NEUROCHEMISTRY

B- SEROTONIN HYPOTHESIS.

LSD and mescaline produce schizophrenia-like symptoms.

5-HT_{2A}, 5-HT_{2C} , 5-$HT_{6/7}$ receptors.

5-HT_2 G_q/G_{11}-coupled

5-HT_{2A} : target of LSD

Atypical AP agents are D-R antagonists or partial agonists and have 5- HT_2 -R antagonist action, which reverse the worsening effect induced by 5-HT agonists in schizophrenics.

2. NEUROCHEMISTRY

C- GLUTAMATE HYPOTHESIS

Phencyclidine and dizolcipine (NMDA antagonists) are modeling both the (+) and (-) symptoms of schizophrenia.

These symptoms are effectively blocked by 5-HT_2A and atypical agents than by D_2 antagonists.

↓ D_1 (at the presynaptic site) of prefrontal cortex → ↓ glutamatergic activity (import. in memory).

GYLCINE TRANSPORTER

ANTIPSYCHOTICS & OTHER RECEPTOR

- α_1, H_1, M: responsible for side effects

- effect on other receptors:

e.g. 5-HT_{2A} and M may ↓ EPS.

But peripheral unwanted effects ↑

ANTIPSYCHOTICS & SCHIZOPHRENIA
Terminology

Chlorpromazine
1952
EPS in human
catalepsy in animals

↓

Neuroleptics
major tranquilizers

↓

typical

RESERPINE
1954 for short time

↓

Less beneficial
More side effects (EP)

Clozapine, 1959
No or fewer EPS in human

↓

atypical

CLASSIFICATION OF ANTIPSYCHOTICS

- Based on clinical features:
  (typical and atypical).
- Based on the potency:
  (high and low / medium clinical efficacy).
- Based on chemical structures:

Phenothiazines
Thioxanthene
Butyrophenones
Others

↓

typical

BENZAMIDES
DIBENZAPINES
OTHER HETEROCYCLES

↓

atypical

CLASSIFICATION OF ANTIPSYCHOTICS

Typical

- **Phenothiazines**

  Dimethylamine analogues: Chlorpromazine.

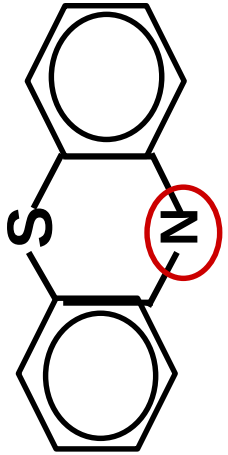
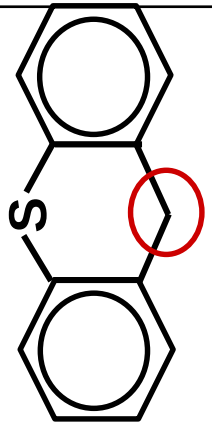
  Piperazine analogues: Trifluoroperazine, Fluphenazine, Perphenazine.

  Piperidine analogues: Thioridazine

- **Thioxanthenes**
- **Butyrophenones (phenyl-butyl-piperidines):**

  Haloperidol.

- **Diphenyl-butyl-piperidines:** Pimozide, Fluspirilene.

	Dimethylamine analogues	Piperazine analogues
 **Phenothiazines**	- ChlorpromazineWeak potency M, H and α antagonist	- Fluphenazine High efficacy **Depot inj. (IM).**
 Thioxanthenes	chlorprothixene-(high clinical potency)	- Flupenthixol **Dept inj** - Thiothixene: High potency, EPS (medium) - zuclopenthixol

High efficacy: Tardive dyskinesia

PHENOTHIAZINES

Dimethylamine-analogues

High affinity for D_1, D_2, D_3, D_4-receptors.

(chlorpromazine, levomepromazine). Week antipsychotic

Chlorpromazin: action-low clinical potency, but have pronounced sedative and antihistamine effects.

Affinity: 5HT2A= α1> D2 > D1.

Side Effects: Dry mouth, sedation, EPS (medium)

Neuroleptic malignant syndrome, Orthostatic hypotension

Fotoszenzibilizáció, Mydriasis, ↑Prolactin.

First-Generation (Typical) Antipsychotics
PHENOTHIAZINES

Piperidine-analogues: have low efficacy, but strong antichlonergic effects (thioridazine and its active metabolite, mesoridazine, pipothiazine).

Thioridazine Enantiomers Structural: EPS (medium), peripheral atropine-like side effect, cardiotoxicity (↑ QT)

Piperazine-analogues:

(fluphenazine, perfenazine, trifluoperazine).
Fluphenazine: high efficacy agents-(high clinical potency), with less anticholinergic, sedative and, hypotensive effects depot inj. (25mg/ml, IM).
Side effects: EPS, Hypotens,Tardiv dysk.

Prochlorperazine and thiethylperazine: Antiemetics

THIOXANTHENES

High affinity for D_1, D_2, D_3, D_4-receptors like phenothiazine analogues.

Dimethylamine-analogues: chlorprothixene-(high clinical potency)

D_1= D_2 high, potent agent, high affinity H_1 and M.

Side effects: EPS, Tardive dyskinesia, akathisia

Piperazin-analogues:

Flupenthixol:

Tabl. or Depot inj.(2-3weeks) for patients of poor compliance.

Side effects: EPS, atropine like effects, hyperprolactinemia.

Thiothixene: High potency, EPS (medium)

clopenthixol (racemic mixture) and its active ciz isomer zuclopenthixol.

First-Generation (Typical) Antipsychotics

Butyrophenone analogues (phenylbutylpiperidines):

High selectivity for D_2-R, have week binding to (D_1, 5-HT, H_1, α_1 and M) receptors.

Haloperidol: the most widely used typical antipsychotic with EPS with high clinical potency). Acute_ps

Other indications: severe vomiting, hiccup.

Droperidol (has sedative effect). Is used in neuroleptanalgesia.

First-Generation (Typical) Antipsychotics

- Good action on (+) symptoms.
- No effect on (-) symptoms.

SIDE EFFECTS:

- **EPS** (dystonia, akathisia, parkinsonism, tardive dyskinesia)
- Neuroleptic malignant syndrome
- Hyperprolactinaemia
- Others: dry mouth, weight-gain

First-Generation (Typical) Antipsychotics

Side effects	**time**	**treatment**
Dystonia	Hours	anticholinergics
Akathisia	Days	Anticholinergics Benzodiazepines Propranolol
Akinesia	weeks	
Tardive dyskinesia	neuroleptic-induced DR hypersensitivity (?)	Valbenazine VMAT2 inhibitor
Neuroleptic malignant syndrome		stop medication Cooling, BZDs, Bromocriptine Dantrolene

ATYPICAL ANTIPSYCHOTICS (SECOND GENERATION)

- Diminished tendency to cause EPS.
- Have efficacy on (+) and (-) symptoms (?).

clozapine, olanzapine, quetiapine, risperidone, paliperidone, sertindole, ziprasidone, Lurasidone, Cariprazine, asenapine, and aripiprazole

ATYPICAL ANTIPSYCHOTICS

1. MIXED (5-HT/DA) ANTAGONIST EFFECTS.

DA + 5-$HT_{2A/C}$-(may 5-$HT_{6,7}$)
(clozapine, olanzapine, quetiapine, sertindol (cardiotoxic), ziprasidon).

2. SELECTIVE ANTAGONIST EFFECT ON D_2/D_3-Rs.

No binding to D_1 or other receptors
(sulpiride, amisulpiride).

Lower affinity for H_1-,α_1,- and M receptors.

3. PARTIAL AGONISTS

D_2 and 5-HT_{1A} (aripiprazol).

ATYPICAL ANTIPSYCHOTICS

4. ANTAGONISTS WITH LOWER AFFINITY FOR D_2-R

\+ fast dissociation (clozapine, quetiapine).

5. PRONOUNCED ACTION ON MESOLIMBIC SYSTEM

olanzapine, quetiapine, sertindol.

Have small EPS and endocrine dysfunctions.

ATYPICAL ANTIPSYCHOTICS
Classification based on Chem. str

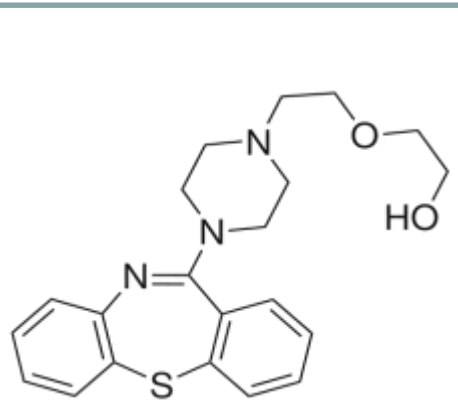
BENZAMIDES: (sulpiride, amisulpiride).

- amisulpiride differs from the classical and atypical antipsychotics: no affinity for 5HT, α-adrenergic, $H_1$and cholinergic receptors.

DIBENZAPINES AND OTHER TRICYCLIC DRUGS: (clozapine, olanzapine, quetiapine).

BENZISOXAZOLE ANALOGS: risperidone

DIBENZEPINES (TRICYCLIC STRUCTURES)



Quetiapine

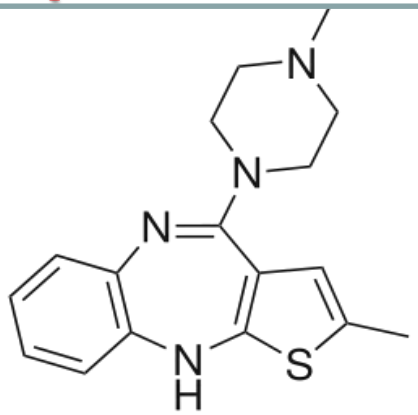
Low clinical potency

QT interval

High affinity for D-,

5-HT_{2A}-R

Lower EPS, TD

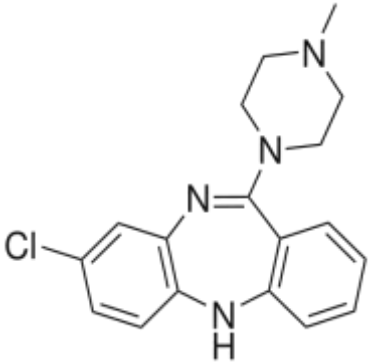


Olanzapine

High clinical potency

5-HT_{2A} receptors, D_2 and other receptors

Fewer EPS



Clozapine

Low D_4, 5-HT_2

Medium clinical potency

refractory schizophrenia

modest affinity for DRs

Has affinity for H1, α, M receptors

No EPS

MH: agranulocytosis

Seizures

Hypersalivation (M2?)

Greater weight gain and metabolic problems (unwanted).

All have effect in bipolar disorder

ATYPICAL ANTIPSYCHOTICS

BENZAMIDES

Amisulpride

- High affinity D_2 , D_3
- No affinity D_1-, D_4-, D_5
- No affinity α, H, M
- No affinity for 5HT

Use: acute and chronic schizophrenia

Sulpiride

- Inhibits the presynaptic auto-,

+ postsynaptic D_2

- Principle place: mesolimbic
- EPS (treated with antiparkins).
- ↑QT-intervallum

Dihydrocarbostyril

Aripiprazole: high clinical potency,

- high affinity, partial D_2 agonist (low intrinsic activity)

- acts as antagonist in mesolimbic region.

Use: also in bipolar disorder, major depressive disorder

Side effects: weight gain, akathisia, insomnia

Benzothiazole analogues:

Ziprasidone

Medium clinical potency

antagonist at D_2, 5-HT_{2A}, and 5-HT_{1D} and agonist at 5-HT_{1A} receptor
Side effects: long QT (unwanted), EPS (tremor, dystonia, akathisia),PD

ziprasidon and aripiprazol 5-HT_{1A} (anxiolytic effect).

5-HT_{1A} -Rs are somatodendritic autoreceptors that inhibit 5-HT release.

Imidazindole analogues: sertindole

ATYPICAL ANTIPSYCHOTICS

BENZISOXAZOLE ANALOGUES

(risperidone and its metabolite paliperidon)

High affinity D_2, 5-HT_2

High potency

No affinity for M, week affinity α_2, H_1

Binds to α_1

Use: Acute and chronic schizophrenia

Side effect: EPS (dose-related), hyperprolactinemia, modest weight gain and metabolic disorders

ATYPICAL ANTIPSYCHOTICS

Lurasidone: novel, D_2, 5-HT_2 and $_7$ antagonist

Cariprazine: new Hungarian, schizophrenia, bipolar disorder

Affinity: D3 > D2 (partial agonist) >>>>

5 $HT_{2A \text{ and } C}$ (inverse agonist); and antagonist ($5HT_7$),

$5HT_{1A}$ (partial).

Asenapine

Bitopertine and sarcoserine: glycine transporter inhibitor (type I)

ANTIPSYCHOTICS (UNWANTED EFFECTS)

I. RELATED TO DA INHIBITION:

EPS.

Neuroleptic Malignant Syndrome.

Hyperprolactinaemia.

II. OTHER CENTRAL SIDE EFFECTS: (Sedation, decrease seizure threshold (I.gener. chlorpromazine, Clozapine, olanzapine, sulpiride, amisulpride, ziprasidone), confusion, weight gain (Clozapine, olanzapine, zotepine > risperidone=quetiapine > amisulpride, aripiprazole, lurasidone, asenapine and ziprasidone), other hypothalamic-pituitary effects.

III. CARDIOVASCULAR SIDE EFFECTS: Orthostatic hypotension, QT prolongation (e.g. ziprasidone).

IV. OTHERS: blood disorders, agranulocytosis (clozapine), jaundice, ↑ serum levels of enzymes, photosensitivity, rash, retinopathy, cataract.

Extrapyramidal Symptoms (EPS)

- ❑ Dystonias (acute)
- ❑ Parkinsonism
- ❑ Akathisia
- ❑ Neuroleptic Malignat Syndrome (NMS)
  - Muscle rigidity, fever, sweating, delirium
- ❑ Tardive Dyskinesia (TD), Late developing
  - fly catching, lip smacking
  - HM: DA receptor supersensitivity

Atypical antipsychotics

↑ risk of metabolic changes (diabetes, lipid profile):
Clozapine, olanzapine

Weight gain: clozapine ≥ olanzapine > risperidone ≥ quetiapine

EPS: clozapine no; then resperidone > olanzapine ≥ ziprasidone≥ aripiprazole ≥ quetiapine
↑ Prolactine secretion: resperidone, Paliperidone
olanzapine small others no

↑**QT interval:** Ziprasidone > quetiapine ≥ risperidone > olanzapine ≥ Clozapine

Sedation: Clozapine > olanzapine ≥ quetiapine

Atypical antipsychotics

For bipolar depression:

quetiapine, olanzapine, lurasidone (+ fluoxetine)

Unipolar depression (adjunktive treatment):

aripiprazole, quetiapine, olanzapine.

For agitation + bipolar depression + schizophrenia:

Ziprasidone, aripeprazol (haloperidol but ↑ EPS).