

# Psychosis

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## Symptoms:

Positive symptoms:

Hallucinations (especially auditory hallucinations, hearing voices)

Delusions (especially paranoia)

Disordered thought

Negative symptoms:

Blunted emotions (flat affect)

Social withdrawal

Apathy, lack of motivation

Anhedonia (inability to experience pleasure)

Poor attention and memory

## Causes of Psychosis:

↑DA (dopamine)

↑5-HT (serotonin)

↑NE (norepinephrine)

↓NMDA receptor signal (a type of glutamate receptor)

↓ACh (acetylcholine)

## Antipsychotic Drugs:

Typical (classical, first-generation) antipsychotics:

Mechanisms:

Dopamine D2 antagonism (desired, on-target)

Muscarinic ACh antagonism (unwanted, off-target)

Histamine antagonism (off-target)

Examples:

Thorazine (chlorpromazine) – This was the first antipsychotic to be discovered, it was introduced in 1952. It was one of the first blockbuster pharmaceuticals, and it revolutionized psychiatric treatment. It allowed huge numbers of patients to move out of mental asylums. Normal dosage is 100 to 2,000 mg/day.

Haldol (haloperidol) – Popular, available in IV, IM, and oral dose forms. Normal dosage is 1 to 20 mg/day, showing that it is much more potent than chlorpromazine.

Side effects:

Extrapyramidal symptoms: Tardive dyskinesia (can be permanent), akathisia (a special kind of restlessness), oculogyric crisis, pseudoparkinsonism, dystonia (painful rigid muscles). Extrapyramidal symptoms are **on-target side effects**, because they are caused by the D2 receptor, which was the desired target.

Anticholinergic effects: These are **off-target side effects** caused by the blockage of muscarinic ACh receptors. Constipation, dry mouth, increased heart rate.

Sedation (this is partially on-target and partially off-target)

Atypical (second-generation) antipsychotics:

Mechanisms:

D2 antagonism (on-target)

5-HT<sub>2A</sub> antagonism (on-target)

Examples:

Clozaril (clozapine) – The first atypical antipsychotic, introduced in 1971 (in Europe).

Zyprexa (olanzapine) – Notorious for causing massive weight gain and diabetes.

Risperdal (risperidone)

Seroquel (quetiapine) – Also popular as a sleep aid (hypnotic).

Abilify (aripiprazole) – This is actually a D2 partial agonist, not a pure antagonist. This gives it unusual effects. Abilify is especially popular as an add-on for antidepressants.

Side effects:

Atypical antipsychotics were originally advertised as causing fewer extrapyramidal symptoms (EPS) than classical antipsychotics, but this is not universally true. Haldol causes lots of tardive dyskinesia, whereas clozapine causes very little and can actually treat tardive dyskinesia. However, some drugs deviate from this rule of thumb: chlorpromazine causes comparatively little EPS, while risperidone causes a fair amount.

Weight gain

## Psychotomimetic Drugs:

Classical stimulants:

Mechanism: ↑DA

Specific mechanism: Inhibit DA reuptake, and sometimes cause DA release

Examples: Amphetamine (Adderall), methamphetamine, cocaine, methylphenidate (Ritalin), MDMA (ecstasy)

Psychedelics:

Mechanism: ↑5-HT

Specific mechanism: 5-HT<sub>2A</sub> partial agonism

Examples: LSD, psilocybin (in mushrooms), mescaline (in peyote cactus), DMT (in ayahuasca), 2C-B, DOB

Dissociative anesthetics:

Mechanism: ↓NMDA receptor signal

Specific mechanism: NMDA receptor antagonism

Examples: PCP, ketamine

Deliriants:

Mechanism: ↓ACh

Specific mechanism: Muscarinic ACh receptor antagonism

Examples: Scopolamine, *Datura* spp., Benadryl (diphenhydramine)

κ opioid agonists:

Mechanism: κ opioid receptor agonism

Examples: Salvinorin A (in *Salvia divinorum*), pentazocine (a painkiller)

Notes: Salvinorin A may also be a D2 partial agonist, and this may also be important for its psychotomimetic effects.

Cannabinoids:

Mechanism: CB1 cannabinoid receptor agonism

Examples: THC (in marijuana), Spice, K2, JWH-018

Notes: Cannabinoids do not reliably induce psychosis, unlike all the drugs mentioned above. It is a more idiosyncratic and unpredictable reaction.

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