DRUGS THAT ACT IN THE CNS

Antipsychotics

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SCHIZOPHRENIA

Schizophrenia is a type of chronic psychosis characterized by **delusions, hallucinations** (often in the form of voices), and thinking or speech disturbances.

The onset of illness is often during **late adolescence** or early adulthood.

It occurs in about 1% of the population and is a chronic and disabling disorder.

Schizophrenia has a strong **genetic component** and probably reflects some fundamental biochemical abnormality, possibly a dysfunction of the mesolimbic or mesocortical **dopaminergic** neuronal pathways.

Antipsychotic drugs/ Neuroleptics/ Major tranquilizers

Antipsychotic drugs are **not curative**, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment

The antipsychotic drugs are divided into **first- and second-generation agents**. The first-generation drugs are further classified as "**low potency**" or "**high potency**."

This classification does not indicate clinical effectiveness of the drugs, but rather specifies **affinity for the dopamine D2** receptor, which, in turn, may influence the adverse effect profile of the drug.

FIRST-GENERATION ANTIPSYCHOTIC (low potency)
Chlorpromazine THORAZINE
Thioridazine
FIRST-GENERATION ANTIPSYCHOTIC (high potency)
Fluphenazine PROLIXIN
Haloperidol HALDOL
Loxapine LOXITANE
Perphenazine
Pimozide ORAP
Prochlorperazine COMPAZINE
Thiothixene NAVANE
Trifluoperazine STELAZINE
SECOND-GENERATION ANTIPSYCHOTIC
Aripiprazole ABILIFY
Asenapine SAPHRIS
Clozapine CLOZARIL
Iloperidone FANAPT
Lurasidone LATUDA
Olanzapine ZYPREXA
Paliperidone INVEGA
Quetiapine SEROQUEL
Risperidone RISPERDAL
Ziprasidone GEODON

Antipsychotic drugs/ First-generation

The first-generation antipsychotic drugs (also called **conventional**, **typical**, or **traditional** antipsychotics) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of **dopamine D2 receptors**.

First-generation antipsychotics are more likely to be associated with movement disorders known as **extrapyramidal symptoms (EPS),** particularly drugs that bind tightly to dopaminergic neuroreceptors, such as haloperidol .

Movement disorders are less likely with medications that bind weakly, such as *chlorpromazine* .

No one drug is clinically more effective than another.

Antipsychotic drugs/ Second-generation

The second-generation antipsychotic drugs (also called "**atypical**" antipsychotics) have a lower incidence of EPS than the first-generation agents but are associated with a higher **risk of metabolic side effects**, such as **diabetes, hypercholesterolemia, and weight gain**.

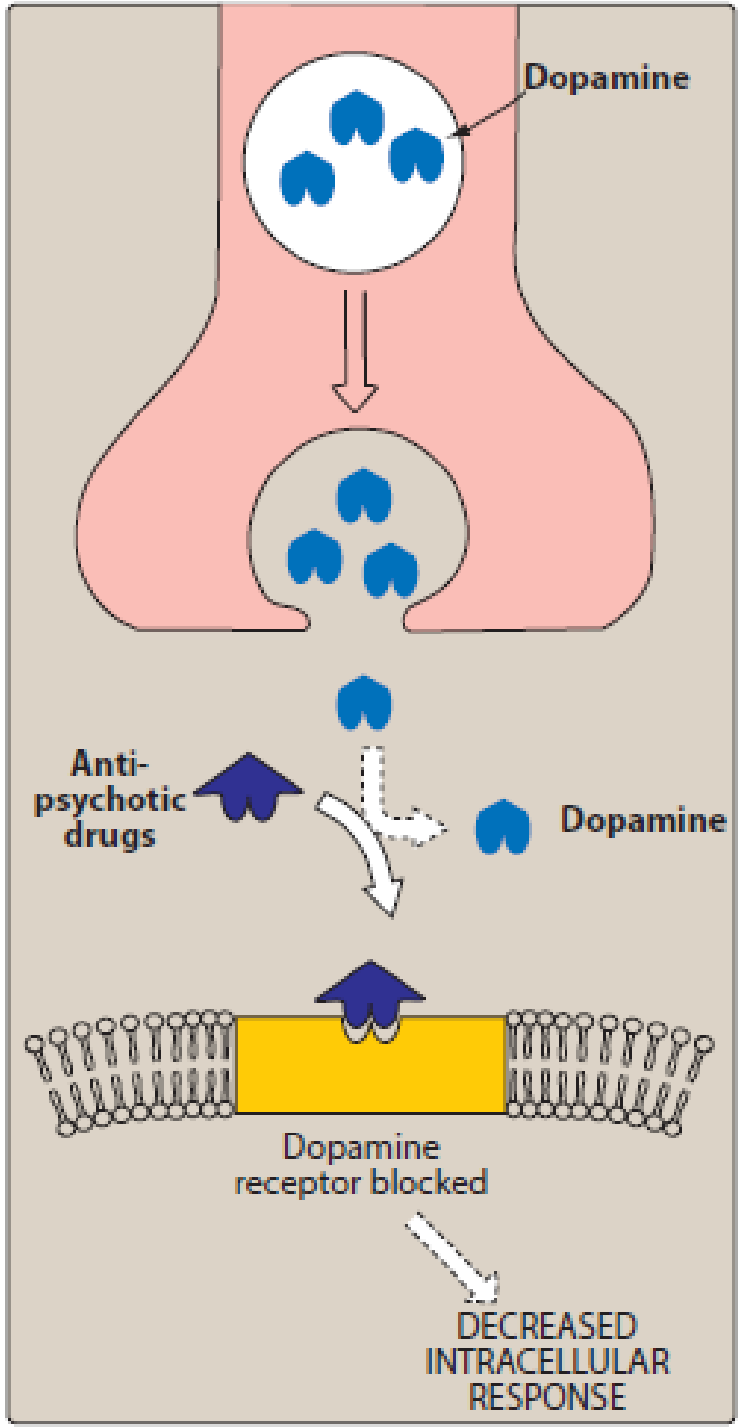
The second-generation drugs appear to owe their unique activity to blockade of both **serotonin and dopamine**.

Second-generation agents are generally used as **first-line therapy** for schizophrenia to **minimize the risk of EPS** associated with the first-generation drugs that act primarily at the dopamine D2 receptor.

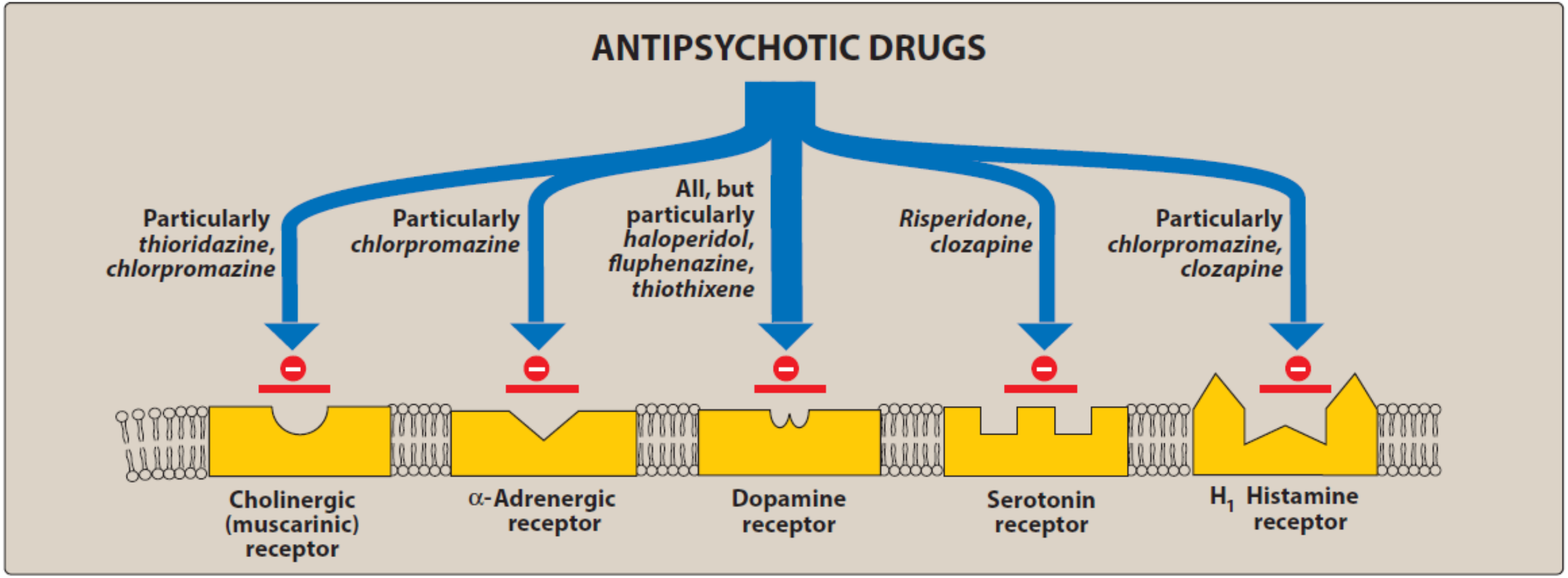
Antipsychotic drugs/ Mechanism of action

Dopamine antagonism: All of the **first-generation** and most of the second-generation antipsychotic drugs block **D2 dopamine** receptors in the brain and the periphery.

Serotonin receptor–blocking activity: Most of the **second** generation agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly **5-HT2A receptors**.



Antipsychotic drugs/ Action



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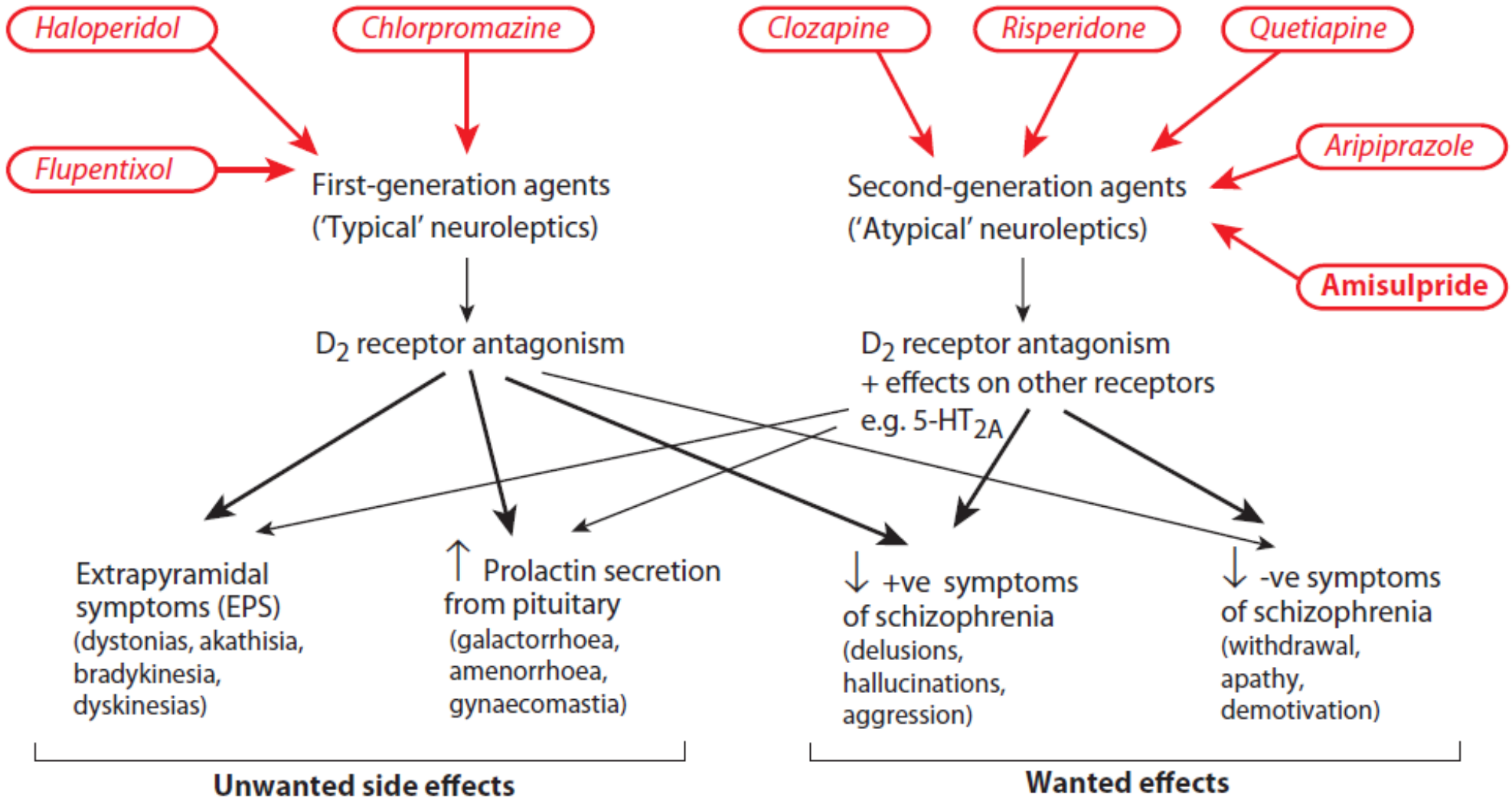


Antipsychotic drugs/ Action

The clinical effects of antipsychotic drugs appear to reflect a blockade at **dopamine and/or serotonin** receptors.

However, many of these agents also block **cholinergic, adrenergic, and histaminergic** receptors.

The undesirable side effects of antipsychotic drugs often result from pharmacological actions at these other receptors.

Antipsychotic drugs/ Action

1. Antipsychotic effects:

All antipsychotic drugs can reduce hallucinations and delusions associated with **schizophrenia** (known as **"positive" symptoms**) by blocking **D2 receptors** in the mesolimbic system of the brain.

The **"negative" symptoms**, such as blunted affect, apathy, and impaired attention, as well as **cognitive impairment**, are not as responsive to therapy, particularly with the first-generation antipsychotics.

Many second-generation agents, such as clozapine, can ameliorate the negative symptoms to some extent.

Antipsychotic drugs/ Action

2. Extrapyramidal effects:

Dystonias (sustained contraction of muscles leading to twisting, distorted postures), **Parkinson-like symptoms, akathisia** (motor restlessness), and **tardive dyskinesia** (involuntary movements, usually of the tongue, lips, neck, trunk, and limbs) can occur with both acute and chronic treatment.

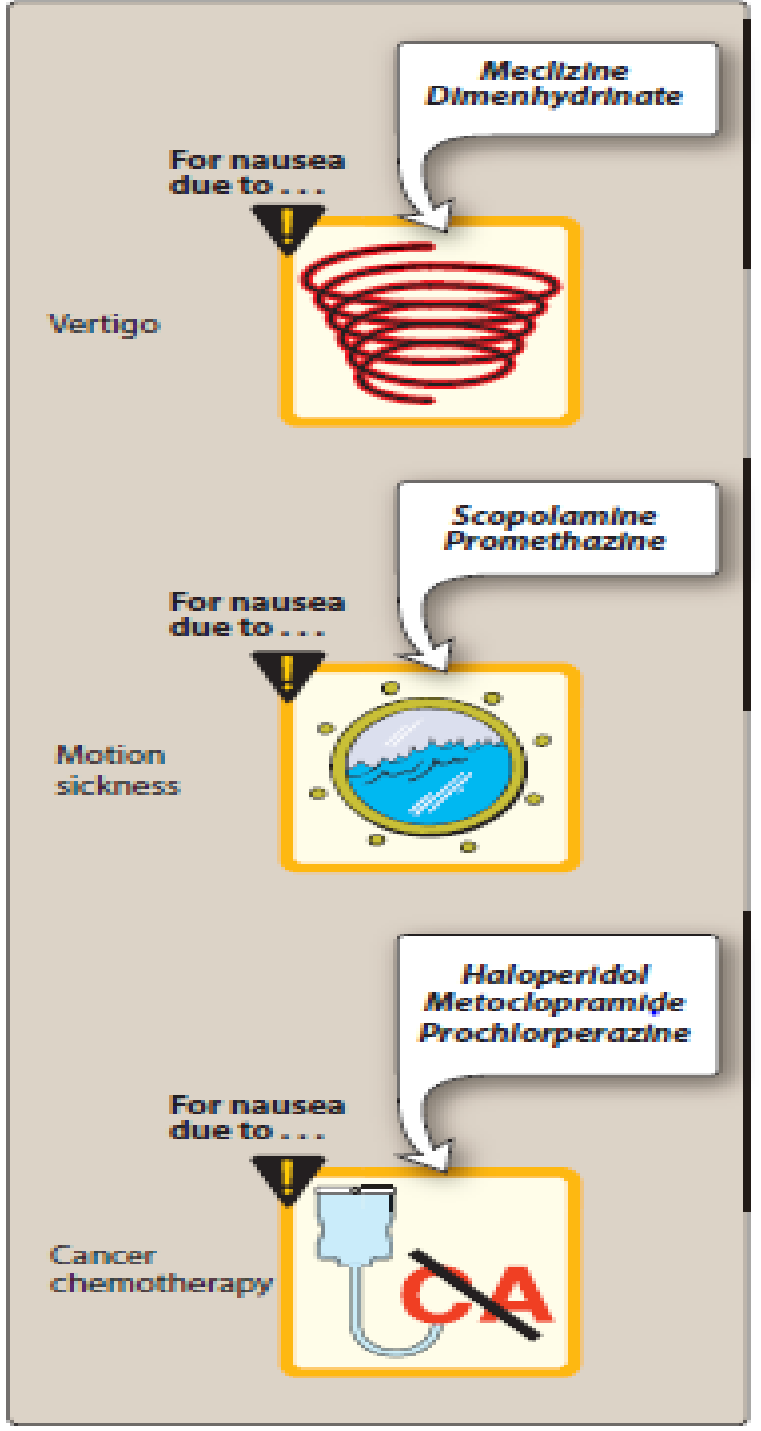
Blockade of dopamine receptors in the **nigrostriatal pathway** probably causes these unwanted movement symptoms.

The second generation antipsychotics exhibit a lower incidence of EPS.

Antipsychotic drugs/ Action

3. Antiemetic effects:

With the exception of aripiprazole, most of the antipsychotic drugs have antiemetic effects that are mediated by blocking **D2 receptors of the chemoreceptor trigger zone** of the medulla.



Antipsychotic drugs/ Action

4. Anticholinergic effects:

Some of the antipsychotics, particularly **thioridazine, chlorpromazine, clozapine, and olanzapine,** produce anticholinergic effects.

These effects include blurred vision, dry mouth (**the exception is clozapine, which increases salivation),** confusion, and inhibition of gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention.

The anticholinergic effects may actually assist in **reducing the risk of EPS** with these agents.

Antipsychotic drugs/ Action

5. Other effects:

Blockade of **α-adrenergic receptors** causes orthostatic hypotension and light-headedness.

The antipsychotics also alter **temperature-regulating mechanisms** and can produce poikilothermia (condition in which body temperature varies with the environment).

In the pituitary, antipsychotics block **D2 receptors**, leading to an increase in **prolactin** release.

Sedation occurs with those drugs that are potent antagonists of the H1-histamine receptor, including chlorpromazine, olanzapine, quetiapine, and clozapine.

Sexual dysfunction may also occur with the antipsychotics due to various receptor-binding characteristics.