Psychopharmacology Institute

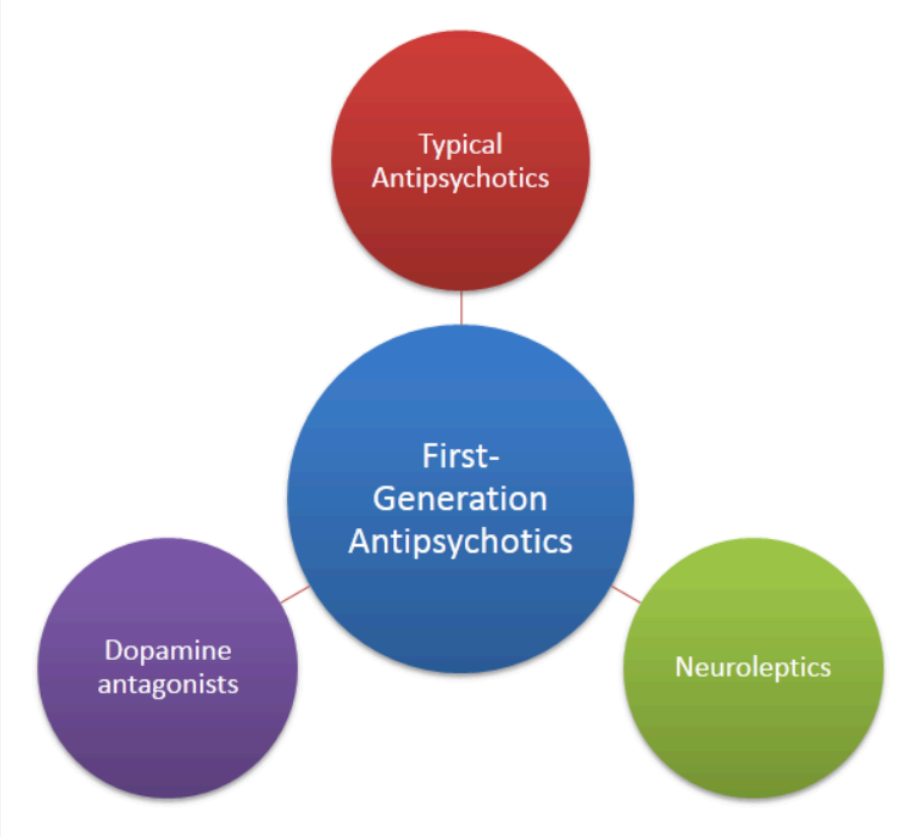
First-Generation Antipsychotics: An Introduction

Flavio Guzman, M.D.
Editor,
Psychopharmacology Institute

First-generation antipsychotics (FGAs) are drugs used primarily for the treatment of schizophrenia and related psychotic disorders. The use of FGAs has declined in the last few years, mainly because of an increase in prescriptions of second-generation agents. Since FGAs are considerably less expensive than newer antipsychotics, they remain a valuable option in the treatment of psychotic disorders. This article is an introduction to terminology, mechanism of action, classifications and potency of conventional antipsychotics.

History and Definitions

First-generation antipsychotics are also known as: typical antipsychotics, dopamine antagonists, neuroleptics and classic antipsychotics. Each term has important historical and conceptual implications.



Neuroleptics

The term "neuroleptic" refers to the ability of a drug to cause a syndrome known as “neurolepsis”. This syndrome has three main features [1]:

- Psychomotor slowing
- Emotional quieting
- Affective indifference

Initially, clinicians deduced that this symptomatology was a reliable sign of antipsychotic efficacy. Later it was discovered that these effects are not required for therapeutic actions.

Dopamine antagonists

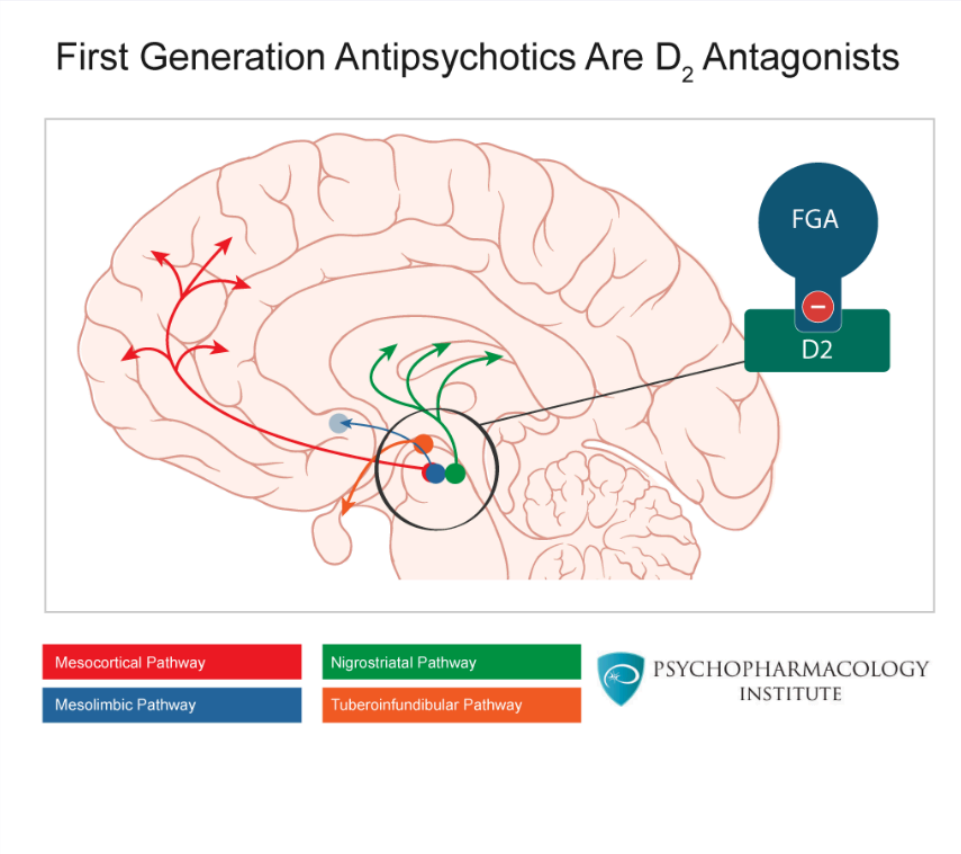
The designation dopamine antagonists proposes differentiating FGAs and SGAs based on general pharmacodynamic differences. According to this terminology, SGAs are known as dopamine-serotonin antagonists, mainly because of their high affinity for 5HT2A receptors [2].

Typical Antipsychotics

This is the most commonly used term in clinical practice. It is based on the view that second-generation antipsychotics (SGAs) have atypical properties, such as a low risk of extrapyramidal symptoms (EPS). Drugs that do not have atypical properties are considered typical or conventional antipsychotics. The problem was that the original concept of atypicality (low EPS risk) changed to a broader definition that included efficacy for negative and cognitive symptoms in schizophrenia [3]. This definition was revised after the CATIE trial failed to confirm that SGAs are more effective than FGAs (with the exception of clozapine for treatment-resistant schizophrenia). In order to avoid confusion regarding effectiveness in schizophrenia, the World Psychiatric Association suggested the term first-generation antipsychotics.

Mechanism of Action

The exact mechanism of action of antipsychotic drugs is unknown. According to the dopamine theory of schizophrenia, positive symptoms are the result of overactivity in the mesolimbic dopamine pathway. This is in part based on the observation that drugs that increase dopaminergic availability (L-DOPA, cocaine, amphetamines) can trigger psychotomimetic effects in individuals not affected by schizophrenia [2]. As the image below shows, first-generation antipsychotics are D2 antagonists. As a result, they reduce dopaminergic neurotransmission in the four dopamine pathways.



Effects of first-generation antipsychotics on the four dopamine pathways

The implications are the following:

Mesocortical pathway.

Research on schizophrenia pathophysiology suggests that a dysfunction of this pathway is associated with cognitive impairments and disturbances of emotions and affect (negative symptoms). Blockade of the mesocortical pathway by high doses of first-generation antipsychotics can induce secondary negative symptoms and cognitive effects.

Mesolimbic pathway: Antipsychotic effects

As explained earlier, overactivity of this pathway is thought to be involved in the pathophysiology of positive symptoms of schizophrenia. Blockade of D2 receptors in the mesolimbic pathway has been proposed as a possible mechanism of antipsychotic action of first-generation agents.

Nigrostriatal pathway: Extrapyramidal Symptoms

Antagonism of D2 receptors in the nigrostriatal pathway is associated with increased risk of extrapyramidal symptoms.

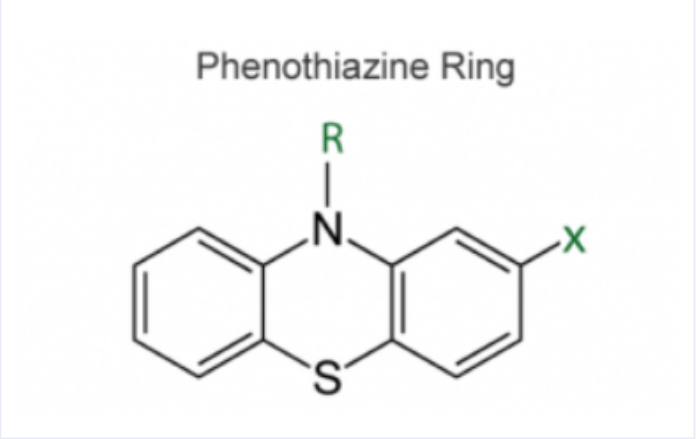
Tuberoinfundibular pathway: Hyperprolactinemia

Dopamine acts as a prolactin-inhibiting factor, D2 blockade increases prolactin levels by promoting its release in the pituitary gland.

Chemical Classification

Phenothiazines

The phenothiazines are the largest chemical group, comprising more than 40 compounds (only the most relevant are listed below) grouped under three subtypes.



Drugs in this group share the same three-ring structure with different side chains joined at the nitrogen atom of the middle ring. The activity of the group can be affected by substitutions at position 2 or 10. The phenothiazines are categorized into three subclasses based on substitutions at position 10: aliphatic, piperidine, and piperazine phenothiazines. Table 1 is a selection of the most commonly prescribed phenothiazines, the list also specifies potency according to side chain subtype.

Table 1- Phenothiazines chemical classification

Chemical Class	Side Chain	Drug
Phenothiazines	Aliphatic (low/medium-potency agents)	Chlorpromazine
		Levomepromazine
		Promazine
		Trifluprom azine
	Piperidine (low/medium potency agents)	Mesoridazine
		Pericyazine
		Pipotiazine
		Thioridazine
	Piperazine (medium/high-potency agents)	Perphenazine
		Fluphenazine
		Trifluoperazine

Butyrophenones, thioxanthenes, dihydroindolones, dibenzepines and diphenylbutylpiperidines

Table 2 lists non-phenothiazine first-generation antipsychotics. This list does not include all non-phenothiazine antipsychotics available worldwide, but offers an overview of the most commonly used agents.

Table 2: Non-phenothiazine antipsychotics

Chemical Class	Drug
Butyrophenones (high-potency agents)	Benperidol
	Droperidol
	Haloperidol
Thioxanthenes (low/medium-potency agents)	Clopenthixol
	Flupenthixol
	Thiothixene
	Zuclopenthixol
Dihydroindolones (low/medium-potency agents)	Molindone
Dibenzepines (low/medium-potency agents)	Clotiapine
	Loxapine
Diphenylbutylpiperidines (high-potency agents)	Fluspirilene
	Pimozide

Receptor Affinity Profile

	Dosage forms	D2 Activity	5HT2 Activity	Muscarinic Activity	Alpha-1 adrenergic Activity	Antihistamine Activity
Chlorpromazine (Thorazine)	T, I	++++	++++	++++	++++	++++
Fluphenazine (Prolixin)	T, L, I, I (LA)	++++	++	+	+	++
Perphenazine (Trilafon)	T	++++	++++	+	++	+++
Trifluoperazine (Stelazine)	T	++++	+++	+	++	++
Thioridazine (Mellaril)	T	++++	++++	++++	++++	++++
Mesoridazine (Serentil) +withdrawn from US market in 2004	T	++++	++++	+++	++++	++++
Haloperidol (Haldol)	T, L, I, I (LA)	++++	++	+	+	+
Molindone (Moban) *discontinued by manufacturer in 2010	T	+++	+	++	+	+
Thiothixene (Navane)	C	++++	+	+	++	+++
Loxapine (Loxitane)	C	+++	++++	++	+++	++++

Level/degree of effect: (+) – low (++) – moderate (+++) – high (++++) – very high Adapted from Hahn, Albers and Reist. Psychiatry, 2008 Edition

Adverse Effects Profile

Drug	Sedating effects	Anticholinergic effects	Extrapyramidal side effects	Hypotensive effects
Chlorpromazine	High	High	Low	IM-High PO-Moderate
Fluphenazine	Low	Low	Very high	Low
Haloperidol	Very low	Very low	Very high	Very low
Loxapine	Moderate	Low	Moderate	Moderate
Molindone	Very low	Low	Moderate	Low
Perphenazine	Low	Low	High	Low
Pimozide	Low	Low	High	Very low
Thioridazine	High	High	Low	High
Thiothixene	Low	Low	High	Low
Trifluoperazine	Low	Low	High	Low

Antipsychotic Potency: Chlorpromazine Equivalent Doses

First-generation antipsychotics can be classified according to their potency. All FGAs are compared to chlorpromazine for equivalence purposes. Potency should not be confused with effectiveness. For example, if we know that haloperidol is more potent that chlorpromazine, it means that a lower dose of haloperidol is required to achieve the same therapeutic effect, but not that haloperidol is more effective than chlorpromazine. The table below shows doses equivalent to 100 mg of chlorpromazine, this table is a combination of two sources: The Maudsley Prescribing Guidelines [5], and the Manual of Clinical Psychopharmacology [6].

Drug	Maudsley Prescribing Guidelines	Manual of Clinical Psychopharmacology
Chlorpromazine	100 mg/day	100 mg/day
Fluphenazine	2 mg/day	2 mg/day
Trifluoperazine	5 mg/day	5 mg/day
Flupentixol	3 mg/day	
Zuclopentixol	25 mg/day	
Haloperidol	3 mg/day	2 mg/day
Sulpiride	200 mg/day	
Pimozide	2 mg/day	
Loxapine	10 mg/day	10 mg/day
Molindone		10 mg/day
Perphenazine		10 mg/day
Prochlorperazine		15 mg/day
Thioridazine		100 mg/day
Thiothixene		4 mg/day

Key points

- First-generation antipsychotics are also known as typical antipsychotics, conventional or classic antipsychotics and dopamine antagonists.
- FGAs reduce dopaminergic neurotransmission in the four dopamine pathways by blocking D2 receptors.
- FGAs differ in potency, not effectiveness.
  - High-potency: haloperidol, fluphenazine
  - Mid-potency: perphenazine, loxapine
  - Low-potency: chlorpromazine

References

1. Stahl, S M. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 3rd ed. New York: Cambrigde University Press; 2008
2. Sadock, B J., V A. Sadock, and P Ruiz. Kaplan and Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins, 2009.
3. Grunder, G., H. Hippius, and A. Carlsson. "The 'Atypicality' of Antipsychotics: A Concept Re-Examined and Re-Defined." Nat Rev Drug Discov 8.3 (2009): 197-202
4. Schatzberg, AF, Nemeroff, C . The American Psychiatric Publishing Textbook of Psychopharmacology. 4th ed. American Psychiatric Publishing, 2010.
5. Taylor, D; Paton,C ; Kapur, S (Editors)The Maudsley Prescribing Guidelines in Psychiatry, Wiley-Blackwell; 11th Edition,2011
6. Schatzberg, AF., Cole, JO, and DeBattista, C. Manual of Clinical Psychopharmacology. 7th ed. American Psychiatric Publishing, 2010.