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## First Generation Antipsychotics: Pharmacokinetics, Pharmacodynamics, Therapeutic Effects and Side Effects: A Review

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### Review Article

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#### ABSTRACT

The pharmacokinetics, pharmacodynamics, therapeutic effects and side effects of common first generation antipsychotics is reviewed, and the possible relevance treatment for the side effects is discussed. The first-generation antipsychotics (FGAs) also known as, typical antipsychotics, dopamine antagonists, neuroleptics, traditional, old generation and classic antipsychotics represent the first group of effective agents for schizophrenia and other psychotic illnesses. They include all of the antipsychotics in the following groups: phenothiazines, butyrophenones, thioxanthenes, dibenzoxazepines, dihydroindoles, and diphenylbutylpiperidines. Primary mechanism of action of first-generation antipsychotics is postsynaptic blockade of the dopamine receptor (D-2 receptor). As a result, they reduce dopaminergic neurotransmission in dopamine pathways. All antipsychotics are considered equally effective. Rationale for determining which medication to use is based on side effect profile. First-generation antipsychotics are well absorbed when they are administered orally or parentally. As with most drugs, oral administration leads to less predictable absorption than parenteral administration. Plasma concentrations of the drugs usually reach peak levels 1 to 4 hours after ingestion and 30 to 60 minutes after intramuscular (IM) administration. They are metabolized in the liver by CYP450 enzymes. Three of the CYP450 enzymes such as CYP1A2, CYP2D6 and CYP3A4 are involved in metabolism of first generation antipsychotics. The most serious side effects of dopamine receptor antagonists are neurological and are largely confined to the extrapyramidal motor system. Acute dystopia, Akathesia, Drug-Induced Parkinsonism, neuroleptic malignant syndromes and tardive dyskinesia are common extrapyramidal side effects associated with use first generation antipsychotics. Postural hypotension, tachycardia, sedations, blurred vision, dry mouth, constipation, urinary retention, and memory dysfunction are common non neurologic side effects of FGAs.

### INTRODUCTION

The first-generation antipsychotics (FGAs) represent the first group of effective agents for schizophrenia and other psychotic illnesses. They include all of the antipsychotics in the following groups: phenothiazines, butyrophenones, thioxanthenes, dibenzoxazepines, dihydroindoles, and diphenylbutylpiperidines <sup>[1,2]</sup>. All of these agents are antipsychotics that are associated with EPS at their clinically effective dosages. Although the FGAs have gradually been replaced by the second-generation (SGAs) in the United States, the FGAs remain the most commonly prescribed in many parts of the world. 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 <sup>[3,4]</sup>.

These agents are highly effective for nearly all disorders that result in psychotic thought processes. However, these drugs have important limitations: they can cause acute and chronic neurological symptoms that significantly limit their effectiveness; they are ineffective or only partially effective for a substantial proportion of psychotic patients; the minimally effective dosage has frequently not been determined and therefore patients may be over- or undermedicated; and they have limited efficacy for some of the most important signs and symptoms of the most common psychotic illness, schizophrenia. In higher dosages, the motor symptoms may induce negative symptoms, such as akinesia, emotional blunting, apathy, and cognitive impairment. Despite their limitations, dopamine receptor antagonists have played an important role in the management of psychosis <sup>[4]</sup>.

## HISTORY AND DEFINITIONS OF FIRST-GENERATION ANTIPSYCHOTICS

The modern era of psychopharmacology began with the discovery of chlorpromazine, the first effective antipsychotic, in the early 1950s <sup>[4]</sup>. The dopamine receptor antagonists are antipsychotics rather than antischizophrenic. That is, they are effective for treating psychosis, regardless of its cause. Antipsychotics are standard treatments for many patients with organic psychoses, bipolar illness, major depressions with psychotic features, and schizoaffective disorder <sup>[5,6]</sup>.

The first-generation antipsychotics (FGAs) represent the first group of effective agents for schizophrenia and other psychotic illnesses. Typical antipsychotics (sometimes referred to as Dopamine antagonists, first generation antipsychotics, conventional antipsychotics, classical neuroleptics, traditional antipsychotics, or major tranquilizers) are a class of antipsychotic drugs first developed in the 1950s and used to treat psychosis (in particular, schizophrenia <sup>[4]</sup>). Typical antipsychotics may also be used for the treatment of acute mania, agitation, and other conditions. They include all of the antipsychotics in the following groups: phenothiazines, butyrophenones, thioxanthenes, dibenzoxazepines, dihydroindoles, and diphenyl butylpiperidines (**Figure 1**).



**Figure 1.** Chemical structure common to all phenothiazine antipsychotics.

### Neuroleptics

Indicate tendency of these agents to have neurological side effects and thus to appear to “take the neuron”. This term is based on the observation that neurological side effects are inevitably associated with the associated antipsychotic activity of these agents. The main symptoms include psychomotor slowing, emotional quieting and 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

According to this terminology, SGAs are known as dopamine-serotonin antagonists, mainly because of their high affinity for 5HT<sub>2A</sub> receptors. The designation dopamine antagonists propose differentiating FGAs and SGAs based on general pharmacodynamic differences <sup>[4,7]</sup>.

### Typical Antipsychotics

This term is based on the view that second generation antipsychotics (SGAs) have atypical properties, such as low risk of extrapyramidal symptoms (EPS). It is the most commonly used term in clinical practice. 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. 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 <sup>[4,7]</sup>.

## MECHANISM OF ACTION (FGAs)

**The Dopamine Hypothesis:** The dopamine hypothesis states that antipsychotics reduce psychotic symptoms by decreasing dopamine activity. It was originally proposed by Arvid Carlsson from Sweden and other basic scientists based on the observation that haloperidol and chlorpromazine raised the levels of dopamine metabolites in dopamine-rich areas of mouse brain. These drugs had inconsistent effects on other neurotransmitters. They interpreted these findings as indicating that these two agents were

acting as dopamine antagonists and that self-regulating systems were compensating by increasing dopamine production. Other investigators noted that FGAs inhibit the activation and stereotypical behaviours of rodents that are induced by amphetamine. This effect has been found to be a reasonably reliable predictor of antipsychotics activity in patients. Moreover, the dose-response relationships in animals provide information about the likely clinical dosage range for patients. These behaviours are thought to be mediated by dopamine and have been used as screening devices to identify compounds that are likely to have clinical efficacy as antipsychotics. Other evidence supporting a role of dopamine in psychosis comes from the observation that all drugs-at least to this date-capable of reducing psychosis are also dopamine antagonists, including partial dopamine agonists. Moreover, agents that are associated with increased dopamine activity such as amphetamine, methylphenidate, or cocaine tend to increase dopamine neurotransmission and also tend to worsen patients with schizophrenia who are in clinically unstable conditions <sup>[4,7,8]</sup>.

According to the dopamine theory of schizophrenia, positive symptoms are the result of an over activity 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 first-generation antipsychotics are D2 antagonists. As a result, they reduce dopaminergic neurotransmission in the four dopamine pathways <sup>[9]</sup>.

## EFFECTS OF FIRST-GENERATION ANTIPSYCHOTICS ON THE FOUR DOPAMINE PATHWAYS

### **Nigrostriatal Pathway: Extrapyramidal Symptoms**

In which fibres originate from the A9 region of the pars compacta and project rostrally to become widely distributed in the caudate nucleus and the putamen. One of the major functions of dopamine in nigrostriatal pathway is movements. Antagonism of D2 receptors in the nigrostriatal pathway is associated with increased risk of extrapyramidal symptoms <sup>[4,8]</sup>.

### **Tuberoinfundibular Pathway: Hyperprolactinemia**

This originates in the arcuate nucleus of the hypothalamus and projects to the median eminence. Dopamine acts as prolactin-inhibiting factor or its synonyms with prolactin inhibiting factor in tuberoinfundibular pathways. D2 blockade in this pathway increases prolactin levels by promoting its release in the pituitary gland causing hyperprolactinemia <sup>[4,7]</sup>.

### **Mesocortical Pathway**

In which the dopaminergic fibers also arise from the A10 region (the ventral tegmental area) and project to the frontal cortex and septohippocampal regions. Schizophrenia pathophysiology suggests that a dysfunction of mesocortical 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 <sup>[4,9]</sup>.

### **Mesolimbic Pathway: Antipsychotic Effects**

Where the dopaminergic projections originate in the ventral tegmental area, the A10 region, and then spread to the amygdala, pyriform cortex, lateral septal nuclei and the nucleus accumbens. Over activity of mesolimbic dopamine 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 <sup>[4,10]</sup>.

## CHEMICAL CLASSIFICATION OF ANTIPSYCHOTICS

The dopamine receptor antagonists may be sub classified according to either their chemical structure or their clinical effects. According to this system, agents are classified as low-, mid-, and high-potency effects. This later method is probably more useful to clinicians since this classification provides <sup>[8]</sup>.

Antipsychotics can also be divided according to their chemical structure (graphical formulas of selected antipsychotics are shown below). The early antipsychotics, especially the phenothiazines (e.g., chlorpromazine and trifluoperazine) and the thioxanthenes (egflupentixol and zuclopenthixol), are structurally related to antihistamines such as promethazine <sup>[8]</sup>. The substituted benzamides include sulpiride (generally considered 'first-generation') and amisulpride (considered 'second-generation') <sup>[2]</sup>.

The usefulness of chemical classification to the clinician is probably limited, but similarities in adverse effects among members of groups such as phenothiazines and thioxanthenes are worth understanding. The antipsychotic drugs come from a number of chemical classes, each with somewhat different pharmacokinetic properties. The differences can have important effects on the clinical use of the drugs. The phenothiazines and the thioxanthenes share structural similarities and have a number of shared metabolic pathways. The same is true for the butyrophenones and the diphenylbutylpiperidines <sup>[4,7,8]</sup>.

### **Phenothiazines**

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

phenothiazines are categorized into three subclasses based on substitutions at position 10: aliphatic, piperidine, and piperazine phenothiazines [3,4,7-10].

**Phenothiazine Compounds:** Three subclasses:

- Aliphatic derivatives (e.g., chlorpromazine (Thorazine))
- Piperidine derivatives (e.g., thioridazine (Mellaril) am): relatively less potent
- Piperazine derivatives (e.g., fluphenazine (Prolixin)): relatively more potent.

**Thioxanthene Compounds:** Example: thiothixene (Navan e).

**Butyrophenones:** Haloperidol (Haldol)-most widely used butyrophenone.

**Miscellaneous Chemical Structures:**

- Pimozide (Orap)
- Olanzapine (Zyprexa)
- Molindone (Moban)
- Quetiapine
- Clozapine (Clozaril)
- Risperidone (Risperdal)
- Loxapine (Loxitane)

**Table 1** shows a selection of the most commonly prescribed phenothiazines, the list also specifies potency according to side chain subtype.

**Table 1.** Phenothiazines chemical classification [4,7,8].

Chemical class	Side Chain	Drug
Phenothiazines	Aliphatic	Chlorpromazine (Thorazine, largactil)
		Levomepromazine
		Promazine
	Piperidine	Triflupromazine
		Mesoridazine
		Pericyazine
		Pipotiazine
	Piperazine	Thioridazine (melleril)
		Perphenazine
		Fluphenazine
		Trifluoperazine (stelazine)

### Thioxanthenes

This group shares a similar three-ring structure with the phenothiazines, but has a carbon atom substituted for nitrogen at position 10. Chlorprothixene (Taractan) is an effective low-potency aliphatic thioxanthene agent with an antipsychotic potency and a side-effect profile similar to its phenothiazine counterpart, chlorpromazine. Thiothixene (Navane), clopenthixol (Sordinol), and flupenthixol (Depixol) are thioxanthenes with a piperazine substitution. Again, their clinical characteristics resemble those of their phenothiazine counterparts [4,7,8].

### Butyrophenones

This class of antipsychotic drugs is characterized by a substituted phenyl ring, which is attached to a carbonyl group attached by a 3-carbon chain to a tertiary amino group. Most of the clinically useful butyrophenones have a piperidine ring attached to the tertiary amino group. Haloperidol is the representative drug for this class. It and other butyrophenones tend to be potent D2 antagonists and have minimal anticholinergic and autonomic effects. Haloperidol, a substituted piperidine, is the most commonly used (and oldest) drug from this class. Other important butyrophenones include droperidol (Dropletan), a short-acting, sedating compound that is commonly used to control agitation; and spiperone (Spiroperidol), an agent with very high affinity for D2, 5-HT2a, and 5-HT2b receptors that is commonly utilized for labelling receptors in animal studies and in positron emission tomography (PET) scanning [4,7,8].

### Dibenzoxazepines

This class of antipsychotics drugs has a three-ring structure with a seven-member center ring. Loxapine (Loxapac), a

dibenzoxazepine, is the only drug from this group that is available in the United States. Clozapine, a dibenzodiazepine, differs from loxapine in having a nitrogen instead of an oxygen atom in the middle ring, as well as differences in side chains <sup>[4,10]</sup>.

### Dihydroindoles

These derivatives are structurally related to serotonin, melatonin, and indole hallucinogens, such as dimethyltryptamine. The only dihydroindole available in the United States is molindone (Moban). This agent has a low incidence of weight gain (compared to clozapine) <sup>[4]</sup>.

### Diphenylbutylpiperidines

This group of agents are similar in structure to the butyrophenones. Pimozide (Orap), the only diphenylbutylpiperidine available in the United States (indication Tourette's syndrome) is derived from the butyrophenonebenperidol. It has a long half-life: 20 to 26 hours. Doses of 20 mg or higher are associated with seizure risk and QTc prolongation. This agent has been removed from the market for those reasons. Penfluridol (Semap) and fluspirilene (experimental) are antipsychotics from this group that are not available in the United States.

**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 <sup>[4]</sup>.

**Table 2.** Non-phenothiazine antipsychotics.

Chemical class	Drug
Butyrophenones	Haloperidol
	Droperidol
	Benperidol
Thioxanthenes	Thiothixene
	Flupenthixol
	Clopenthixol
	Zuclopenthixol
Dihydroindolones	Molindone
Dibenzepines	Clotiapine
	Loxapine
Diphenylbutylpiperidines	Fluspirilene
	Pimozide

## PHARMACODYNAMICS OF ANTIPSYCHOTICS

### Action of Antipsychotics on Different Types of Neurotransmitter Receptor

Relevance to side effects first generation antipsychotics, as exemplified by chlorpromazine, have been structurally modified to produce drugs with greater affinity for dopamine receptors while retaining some of their activity on other receptor systems (e.g., on alpha1 adrenoceptors, 5-HT2 receptors and histamine1 receptors). In the non-phenothiazine series, a high degree of specificity for the D2 receptors has been achieved with sulpiride and pimozide, with haloperidol showing antagonistic effects on the 5-HT2 and alpha1 adrenoceptors in addition to its selectivity for D2 receptors. The cis-(Z) isomers of the thioxanthenes are potent neuroleptics that, in addition to their selectivity for D2 receptors, also show antagonistic effects on D1, 5-HT2 and alpha1 adrenergic receptors; cis(Z)- flupenthixol has a greater effect on D1 receptors than cis-(Z)-clopenthixol. It should be emphasized that the effect of such drugs on 5-HT2 receptors is weak <sup>[3,4]</sup> (**Table 3**).

**Table 3.** Receptor Affinity Profile of FGAs.

Drugs	D2 Activity	5HT2 Activity	Muscarinic Activity	Alpha-1 adrenergic Activity	Antihistamine Activity
Thioridazine	Very high	Very high	Very high	Very high	Very high
Haloperidol	Very high	Moderate	Low	Low	Low
Perphenazine	Very high	Very high	Low	Moderate	High
Trifluoperazine	Very high	High	Low	Moderate	Moderate
Chlorpromazine	Very high	Very high	Very high	Very high	Very high
Fluphenazine	Very high	Moderate	Low	Low	Moderate
Thiothixene	Very high	Low	Low	Moderate	High
Loxapine	Very high	Very high	Very high	Very high	Very high

In the phenothiazine series of neuroleptics, thioridazine has less anti-muscarinic potency than chlorpromazine, but appears to be equally active as an antagonist of 5-HT2 and D2 receptors; like chlorpromazine, however, it is a potent alpha1 adrenoceptor antagonist. In contrast, the potent phenothiazine neuroleptic perphenazine is only slightly less selective in blocking D2 receptors than haloperidol but, unlike the latter, has a greater antagonistic effect on histamine receptors. With the typical neuroleptics in wide clinical use (e.g., chlorpromazine, thioridazine, haloperidol, pimozide, flupenthixol and clopenthixol), there would appear to

be a correlation between their D2 antagonistic potency and their clinical potency; presumably the ability of these drugs to block 5-HT<sub>2</sub> receptors to varying extents is also evidence that the serotonergic system is involved in their clinical activity in some way [7,8,11].

The actions of neuroleptics on histamine, muscarinic and alpha<sub>1</sub> adrenergic receptors explain the side effects of these drugs, i.e., sedation, anticholinergic effects and hypotensive effects, respectively, which are generally considered to be undesirable and can lead to poor patient compliance [7,8].

### Antipsychotic Potency: Chlorpromazine Equivalent Doses

The neuroleptics that are widely available may be divided into two general categories, those with low potency (such as chlorpromazine and thioridazine) and those with high potency (exemplified by haloperidol, trifluoperazine and pimozide). The former groups have a lower propensity to cause extrapyramidal side effects but are more sedative and likely to cause postural hypotension and have anticholinergic side effects. *In-vitro* studies have shown that chlorpromazine has an affinity for all five types of dopamine receptor and has some preference for D<sub>2</sub> and D<sub>3</sub> receptors. By contrast, haloperidol is more potent than chlorpromazine for the D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> receptors with a low affinity for the D<sub>1</sub> and D<sub>5</sub> receptors.

Potency is an important variable in terms of pharmacodynamic properties of these medicines. Potency determines the predictable side effects of the antipsychotics. Low potency medications cause more sedation, Anti-ACh, Orthostatic hypotension. High potency medications cause more EPS 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 than 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 [4,8].

The **Tables 4** shows doses equivalent to 100 mg of chlorpromazine, this table is a combination of two sources.

**Table 4.** Antipsychotic equivalent doses with chlorpromazine [7].

Drug	Chlorpromazine 100 mg/day
Fluphenazine	2 mg/day
Trifluoperazine	5 mg/day
Flupentixol	3 mg/day
Zuclopentixol	25 mg/day
Haloperidol	3 mg/day
Sulpiride	200 mg/day
Pimozide	2 mg/day
Loxapine	10 mg/day
Thioridazine	100 mg
Flupenazinediconate (depot, modicate)	25 mg/day

### Antipsychotics Efficacy

All antipsychotics are considered equally effective. Rationale for determining which medication to use is based on side effect profile. Primary mechanism of action is Postsynaptic blockade of the D-2 receptor "D-2, me too". Newer agents e.g., Clozaril Have significant activity at the D-1 receptor; Risperdal and Zyprexa have significant 5-HT<sub>2</sub> activity [1,3,4].

## PHARMACOKINETICS OF ANTIPSYCHOTICS

### Absorption

In general, the FGAs are well absorbed when they are administered orally or parentally. As with most drugs, oral administration leads to less predictable absorption than parenteral administration. Liquid concentrates are absorbed slightly more rapidly than pills. Plasma concentrations of the drugs usually reach peak levels 1 to 4 hours after ingestion and 30 to 60 minutes after intramuscular (IM) administration. In general, IM preparations reach their peak concentrations sooner than oral drugs and as a result have an earlier onset of action. For example, IM administration of most antipsychotics results in peak plasma levels in about 30 minutes with clinical effects emerging within 15 to 30 minutes [3,4].

### Half-lives and Steady state

Antipsychotics usually reach steady state in about three to five half-lives. Thus, steady state levels for chlorpromazine, haloperidol, and most other FGAs are reached in about 3 to 5 days since their half-lives are about 24 hours [4].

### Bioavailability

The bioavailability (that is, the amount of drug reaching the systemic circulation) is substantially greater—as much as tenfold—when FGAs are administered parenterally. Most FGAs are highly protein bound. For example, more than 90 percent of drugs such as fluphenazine and haloperidol is bound to plasma protein. The remaining unbound portion is the drug that is available

for passing through the blood-brain barrier. In theory, conditions that alter the amount of plasma protein such as malnutrition will also alter the amount of bioavailable antipsychotic drug. This is potentially important for drugs that are protein bound for 98 percent or more [4].

### Metabolism and Elimination

As we see in previous sections, most FGAs are metabolized by the cytochrome P450 2D6 and P450 3A subfamilies in the liver. Since these same isoenzymes also metabolize a number of drugs that are commonly combined with antipsychotics, a number of important drug-drug interactions are possible. The systemic clearance of FGAs is high as the result of a high hepatic extraction ratio. As a result, only negligible amounts of the unchanged drug are excreted by the kidneys. Phenothiazines, thioxanthenes, and their metabolites are excreted in the urine and the faeces.

**Table 5** shows pharmacokinetic of selected first generation antipsychotics [3,4,5].

**Table 5.** Pharmacokinetics of Selected antipsychotics.

Drug	Bioavailability (%)	Protein- Binding (%)	t <sub>1/2</sub> (h)	Cp 12 hrs Post dose (ng/mL)
Chlorpromazine	10–33	90–95	8–35	100–300
Thioridazine	25–33	99	9–30	200–800
Perphenazine	~25	90–95	8–21	0.5–5.0
Fluphenazine	20–50	90–95	14–24	0.2–3.0
Haloperidol	40–70	92	12–36	2.0–18.0
Thiothixene	~50	90–95	34	1.0–5.0

Cp-Concentration in plasma after 12 hours

## SIDE EFFECTS OF ANTIPSYCHOTIC DRUGS

### Neurological Side Effects

The most serious side effects of dopamine receptor antagonists are neurological and are largely confined to the extrapyramidal motor system. EPS are particularly frequent with typical antipsychotics but can also be observed in second generation antipsychotics (e.g., risperidone). EPS are more common in young people, especially if intellectually disabled, if there is central nervous system damage, and in drug-naïve individuals. These Extrapyramidal symptoms (EPS) are, in turn, separated into acute effects that occur in the first days or weeks of treatment and chronic effects that occur after patients have received medications for months or years [12,13] (**Table 6**).

**Table 6.** Summary of main side effects of typical neuroleptics [3,4,7,8].

Side effect	Possible cause
Acute EPS (Parkinsonism, dystonias, akathisia)	Dopamine blockade of basal ganglia- All potent typical neuroleptics
Sedation	Due to histamine1 blockade- All less potent neuroleptics
Skin pigmentation	Dopamine-melanin conversion- All less potent neuroleptics
Jaundice	Bile duct obstruction- Chlorpromazine
Hypotension	Due to $\alpha_1$ receptor blockade- All less potent neuroleptics
Tachycardia and other anticholinergic effects	Due to muscarinic receptor blockade- All less potent neuroleptics
Cardiac conduction defects	Muscarinic blockade, Na <sup>+</sup> channel blockade-Thioridazine, chlorpromazine, sertindole
Agranulocytosis, skin rashes	Allergic reactions- Many neuroleptics, clozapine

### Acute Extrapyramidal Syndromes (EPS)

All of the dopamine receptor antagonists are associated with EPS. Since EPS, particularly parkinsonism, is believed to be caused by decreased dopamine activity in the basal ganglia, it suggests that this toxic effect is inescapable given that blockade of D2 receptors is associated with the antipsychotics effect of these agents. Also, this relationship explains why the potency of FGAs for causing EPS is related to their affinity for D2 receptors in the basal ganglia. Acute EPS, which include dystonia, akathisia, and drug-induced parkinsonism, have their onset relatively soon after the initiation of antipsychotics drug treatment. They remit soon after the drugs are discontinued. In contrast, tardive EPS syndromes occur after months of treatment and commonly persist after medications are discontinued [12,13].

### Acute Dystonia

Develops within a few hours to 5 days after first dose. It is Muscle spasm of tongue, face, neck and back. Symptoms include Oculogyric crisis (involuntary upward deviation of eyeballs), Opisthotonos (tetanic spasm of back muscles, causing trunk to arch forward, while head and lower limbs are thrust backwards), Laryngeal dystonia can impair respiration.

Ten percent of drug-induced dystonias occur during the first hours of drug treatment, and 90 percent occur within the first 3 days. Common types of dystonia include opisthotonos, a rigid contraction of the back muscles with arching; retrocollis and torticollis of the neck; oculogyric crisis, a spasm in which an eye or both eyes are turned upward; macroglossia and tongue

protrusion, which can lead to choking; and laryngeal dystonias. Rarely, dystonias of laryngeal or pharyngeal muscles can lead to sudden death.

Younger patients, particularly young males, are more likely to develop dystonias. They are more common when patients are treated with large dosages of high-potency FGAs. Dystonias almost always respond rapidly to anti-parkinsonian medications and can usually be prevented by either pre-treatment with anti-parkinsonian medications or by limiting the antipsychotics dosage prescribed. Dystonic reactions occur in about 40 percent of patients who are treated with high-potency drugs without prophylactic antiparkinsonian medications.

Management includes Anticholinergics (Benztropine, diphenhydramine IM/IV) or diazepam 10 mg state for severe cases, lower or split dosing, Switch agent, add scheduled benhexol (artane) with antipsychotic (artane 2-14 mg not for more than 2 weeks/day initial starting dose 2-5 mg day) and is advisable to avoid artane at bed time due to insomnia <sup>[14]</sup>.

### **Drug-Induced Parkinsonism**

Patients on dopamine receptor antagonists may experience all of the common motor symptoms of idiopathic parkinsonism including rigidity, bradykinesia, shuffling gait, and tremor. These side effects commonly occur during the first 5 to 30 days of treatment and may persist until the dosage is lowered or FGAs are discontinued. Examination will usually reveal a positive glabella tap. This motor disturbance affects about 30 percent of patients who are chronically treated with dopamine receptor antagonists. The first evidence of drug-induced parkinsonism may be a diminished arm swing or decreased facial expressiveness. Risk factors for drug-induced parkinsonism include increasing age, dosage, a history of parkinsonism, and underlying basal ganglia damage (e.g., vascular insult).

Management includes Centrally acting anticholinergics (scheduled behexol or artane) / diphenhydramine / benhexol with antipsychotics) and amantadine. Avoid levodopa as it may counteract antipsychotic effects. Switch to atypical antipsychotics for severe symptoms <sup>[7,8,13]</sup>.

### **Akathisia**

Develop within first days to months of therapy. It is feeling of inner feeling of restlessness. symptoms include Compulsive, restless movement, inability to sit and stand still. Symptoms of anxiety, agitation, pacing, feeling of urge to move are also observed. The most common clinical manifestations consist of shifting the weight from foot to foot, walking on the spot, inability to keep the legs still, feelings of inner restlessness, and the shifting of body positions in a chair. Patients with akathisia may describe a compelling urge to walk or to initiate movement. In mild cases, patients may experience a subjective feeling of restlessness, but not show increased motor activity. Akathisia may appear in the second or third day of antipsychotic treatment, but more frequently has its onset after 5 days.

Management includes: Beta blockers (propranolol)- (20 mg-120 mg/ day), Benzodiazepines (e.g., lorazepam), Anticholinergics (e.g., benztropine, benhexol) or Reduce antipsychotic dosage or switch to low potency agent <sup>[4,7,8,13]</sup>.

### **Neuroleptic Malignant Syndrome (NMS)**

Neuroleptic malignant syndrome (NMS) is an uncommon but potentially fatal complication of FGAs. Its main clinical features include hyperthermia, severe muscular rigidity, autonomic instability including hyperthermia, tachycardia, increased blood pressure, tachypnea, and diaphoresis, and changing levels of consciousness. It usually presents as muscular rigidity and progresses to elevated temperature, fluctuating consciousness, and unstable vital signs. These symptoms are often associated with elevations in creatine phosphokinase (CPK) and aldolase. Less common are elevations in liver transaminases, leukocytosis, myoglobinemia, and myoglobinuria. Acute renal failure may also occur. Mortality in well-developed cases has been reported as ranging from 20 to 30 percent and may be higher when depot forms are used. Recent improvement in the early recognition of NMS has led to a substantially decreased mortality rate.

The NMS is more common when high-potency FGAs are prescribed in high doses and when dosage is escalated rapidly. The syndrome is twice as common in men as in women and is more likely to be present in younger patients. Clinicians should be concerned about any patient who demonstrates severe muscular rigidity and a rising body temperature, since early diagnosis and treatment can be life-saving <sup>[4,7]</sup>.

### **NMS-Differential Diagnosis**

Head trauma, meningitis, Parkinson's disease, status epilepticus, sepsis, pheochromocytoma, malignant hyperthermia, heat stroke, serotonin syndrome, sudden discontinuation of dopamine agonists. Consider NMS in any patient on antipsychotics with a fever of unknown origin and a change in mental status.

### **NMS-Pathophysiology**

Mechanism(s) poorly understood -associated with-

#### **I. Central dopamine blockade-**

- i. Hypothalamus -hyperpyrexia, tachycardia, blood pressure lability
  - ii. Basal ganglia-rigidity, muscle damage
- II. Direct effect of dopamine on muscle- Increased muscle cell metabolism-hyperpyrexia, rigidity.

### Management of NMS

When NMS is diagnosed or suspected, neuroleptics should be discontinued and supportive and symptomatic treatment should begin. This may include treating EPS with antiparkinsonian medications, correcting fluid and electrolyte imbalances, treating fevers, and managing cardiovascular symptoms such as hyper- or hypotension. Recent studies indicate that dantrolene (Dantrium) may be effective for treating severe NMS. Treatment begins with IV administration of 0.8 to 2.5 mg/kg every 6 hours, with a maximum of 10 mg/kg daily. When the symptoms subside and the patient can swallow, dantrolene is administered orally in dosages of 100 to 200 mg daily. Bromocriptine can then be added at doses of 20 to 30 mg daily in four divided doses. Amantadine may be helpful if the other agents are not sufficient. The course of treatment is commonly 5 to 10 days unless a long-acting injectable agent has been used.

### Chronic Extrapyrimalidal Syndromes

**Tardive Dyskinesia:** It comprises involuntary movements of the tongue, lips and face (such as protrusion or twisting of the tongue, lip-smacking, puffing of the cheeks, sucking of the lips and chewing) often combined with abnormal involuntary movements of the trunk and limbs, termed choreiform or choreoathetoid movements. Despite the association of tardive dyskinesia with the introduction of neuroleptics, it is evident that 5–15% of elderly people who have never received neuroleptics also show an orofacial dyskinesia, the prevalence rate of the condition in schizophrenic patients on neuroleptics being variously reported to be between 0.5 and 56% (mean of 20%). Patients with TD may have any or all of a number of abnormal movements. These frequently consist of mouth and tongue movements, such as lip smacking, sucking, and puckering as well as facial grimacing. Other movements may include irregular movements of the limbs, particularly choreoathetoid-like movements of the fingers and toes and slow, writhing movements of the trunk. Younger patients tend to develop slower athetoid movements of the trunk, extremities, and neck. Although seriously disabling dyskinesia is uncommon, a small proportion may affect walking, breathing, eating, and talking.

The differential diagnosis of TD includes a number of disorders of the basal ganglia (including Huntington's disease, Wilson's disease, and Sydenham's chorea), striatal hypercalcifications, hyperthyroidism, hypoparathyroidism, tardive Tourette's disorder, and dyskinesias related to other drugs, such as L-dopa and amphetamines. Abnormal movements were also described in patients with schizophrenia before the introduction of antipsychotics medications [15,16].

#### Management of TD

- Some manufacturers suggest drug withdrawal at earliest signs of TD (fine vermicular movements of tongue) may halt its full development.
- Gradual drug withdrawal (to avoid dyskinesia)
- Use lowest effective dose
- Atypical antipsychotic for mild TD
- Clozapine for severe, distressing TD
- Inconsistent results with: Diazepam, clonazepam, valproate Propranolol, clonidine, Vitamin E.

### Histamine H1 Blockage: Possible Clinical Consequences

Common symptoms of histamine blockage include: Sedation, drowsiness, Weight gain, Hypotension [4].

### Alpha-1 Receptor Blockade: Possible Clinical Consequences

Common symptoms of histamine blockage include: Postural hypotension, Reflex tachycardia, Dizziness [4,7,8].

### Muscarinic Receptor Blockade

Common symptoms of histamine blockage include: Blurred vision, Dry mouth, Sinus tachycardia, Constipation, Urinary retention, Memory dysfunction [4,7,8].

## INDICATIONS FOR DOPAMINE RECEPTOR ANTAGONISTS [3,4,7,8]

- Acute psychotic episodes in schizophrenia and schizoaffective disorder
- Maintenance treatment in schizophrenia and schizoaffective disorders
- Mania

- Depression with psychotic symptoms
- Delusional disorder
- Borderline personality disorder
- Substance-induced psychotic disorder o Delirium and dementia
- Mental disorders due to a medical condition o Childhood schizophrenia
- Pervasive developmental disorder o Tourette's syndrome
- Huntington's disease.

#### **Other Indications**

- Antipsychotics are also effective for treating ballismus, an illness characterized by abnormal activity of the axial and proximal musculature
- Severe emesis associated with chemotherapy.
- Patients with intractable hiccups are sometimes aided by FGAs.
- Metoclopramide (Reglan), a dopamine receptor antagonist, is commonly prescribed for patients with gastroesophageal reflux and delayed gastric emptying.

### **CONCLUSION**

The first-generation antipsychotics (FGAs) are first group of effective agents for schizophrenia and other psychotic illnesses. Primary mechanism of action of first-generation antipsychotics is postsynaptic blockade of the dopamine receptor (D-2 receptor). As a result, they reduce dopaminergic neurotransmission in dopamine pathways. All antipsychotics are considered equally effective. Rationale for determining which medication to use is based on side effect profile.

Plasma concentrations of First-generation antipsychotics usually reach peak levels 1 to 4 hours after ingestion and 30 to 60 minutes after intramuscular (IM) administration. They are metabolized in the liver by CYP450 enzymes. Three of the CYP450 enzymes such as CYP1A2, CYP2D6 and CYP3A4 are involved in metabolism of first generation antipsychotics.

Use of First-generation antipsychotics is associated with most serious side effects of dopamine receptor antagonists are neurological and are largely confined to the extrapyramidal motor system. Acute dystopia, Akathesia, Drug-Induced Parkinsonism, neuroleptic malignant syndromes and tardive dyskinesia are common extrapyramidal side effects associated with use first generation antipsychotics. Postural hypotension, tachycardia, sedations, blurred vision, dry mouth, Constipation, Urinary retention, and Memory dysfunction are common non neurologic side effects of FGAs.

Concomitant use of medication metabolized by the same enzyme with First-generation antipsychotics and inhibitors of these enzymes should be carried out with caution and adequate supervision. In addition, concomitant use of other drugs metabolized by same enzyme may predispose individual for side effects or reduce the effectiveness of the drugs. Prescribing advice should highlight the possibility of drug interactions when multiple drugs are prescribed concomitantly.

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