A Rational Ordering of the Actions of Antipsychotic Drugs

Glenn Schwarcz, MD
Washington, DC

Most major actions of the antipsychotic drugs stem from one of the four antagonistic functions common to all these drugs. Antidopaminergic activity in the mesolimbic system results in the primary desired effect, control of psychosis. Antidopaminergic activity also occurs in other brain areas. Dopamine blockade in the nigrostriatal pathway results in extrapyramidal symptoms and tardive dyskinesia. Blockade in the tuberoinfundibular tract of the hypothalamus causes elevated circulating prolactin. Central H_1 histaminic receptors are also blockaded by these drugs, causing sedation. The anti-alpha adrenergic activity of the antipsychotics results in orthostatic hypotension, and antimuscarinic activity results in the atropinic picture commonly seen with these drugs. The mnemonic "the anti-fours" is used to order the four major pharmacological effects: anti-dopaminergic, anti-H_1 histaminic, anti-alpha adrenergic, and anti-muscarinic.

Among the most complex and theoretically demanding medications in all of medicine are the phenothiazine-type antipsychotics. Their diverse and seemingly unrelated actions can overwhelm the novice as well as the experienced physician.

This article presents an organized approach to rationally understanding the pharmacology of these medications. Although it is clear that the structures and minor or idiosyncratic side effects of some of the antipsychotics may vary, all of the major classes—phenothiazines, butyrophenones, thioxanthenes, dihydroindolones (eg, molindone), and dibenzoxazepines (eg, loxapine)—are similar enough in their main actions to be considered as one class. They will therefore be referred to as the antipsychotics, as that is their best appreciated action.

The "Anti-Fours"

While there are numerous less frequent and idiosyncratic side effects of the antipsychotics, their main actions can be broken up into four major antagonistic functions, which can be nicknamed the "anti-fours." These are (1) antidopaminergic, (2) anti-H_1 histaminic, (3) anti-alpha adrenergic, and (4) anti-muscarinic. These four antagonistic actions constitute the crux of the action of all antipsychotics (Table 1).

From the Department of Psychiatry, Howard University School of Medicine, and St Elizabeth's Hospital, Washington, DC. Requests for reprints should be addressed to Dr. Glenn Schwarcz, O'Malley Division, St Elizabeth's Hospital, Washington, DC 20032.

0094-3509/82/020263-05$01.25

Table 1. The "Anti-Fours"

Pharmacological Action	Clinical Picture
Anti-dopaminergic:	
In the mesolimbic system	Antipsychotic activity
In the nigrostriatum	Extrapyramidal side effects and tardive dyskinesia
In the hypothalamic tuberoinfundibular tracts	High prolactin syndrome with amenorrhea, galactorrhea, and gynecomastia
Anti-H_1 histaminic	Sedation
Anti-alpha adrenergic	Orthostatic hypotension
Anti-muscarinic	Atropinic side effects

Antidopaminergic

It is well known that all drugs used to treat psychoses block dopamine. It does not follow that dopamine overactivity is the cause of schizophrenia, although that very hypothesis, the dopamine theory of schizophrenia, has been espoused.[1] It may be that dopamine blockade is only indirectly related to amelioration of psychosis. Nevertheless, as the dopamine theory of schizophrenia is the most consistent and scientifically supported etiological theory of schizophrenia, the primary antipsychotic action of antipsychotics may be envisioned by postsynaptic dopamine blockade.

Dopamine is actually blocked in three areas in the brain, giving three distinct actions common to all antipsychotics.

Dopamine Blockade in the Mesolimbic System

The limbic system and its midbrain connections are the seat of emotion and behavior. Specifically, it is dopamine blockade in this locality that is thought to act against the symptoms of schizophrenia.

Dopamine Blockade in the Nigrostriatal System

Dopamine of the extrapyramidal system is likewise blockaded by all antipsychotics. Decreased dopamine transmission in the substantia nigra causes parkinsonism, similar to idiopathic dopamine degeneration in the substantia nigra of elderly people, which causes primary Parkinson's disease. Typical symptoms include rest tremor, masked facies, shuffling gait, and muscular rigidity. Other extrapyramidal effects of antipsychotics, such as akathisia and acute dystonia, are thought to be due to diminished dopamine transmission in the striatum. The acute dystonias include acute spasms of muscle groups occurring early (hours to days) in treatment. Examples are spasm of neck muscles (torticollis), of extraocular muscles (oculogyric phenomenon), of the masticatory muscles (trismus), and of the back muscles (opisthotonos). Clinical observation suggests that the less-sedating piperazine phenothiazines more often cause dystonias. In contrast, the more-sedating aliphatics, like chlorpromazine, tend to cause parkinsonism.

In recent years, much attention has been focused on late-appearing choreoathetoid movements of the tongue, mouth, and extremities, known as tardive dyskinesia. The social and cosmetic undesirability of these movements is underscored by the knowledge that the syndrome is irreversible in many cases, even after the medications are withdrawn. Theoretically, tardive dyskinesia is opposite to parkinsonism and the dystonias because too much striatal dopamine, not too little, is its cause.

Initially, postsynaptic dopamine blockade by antipsychotic medications decreases striatal dopamine. However, years of denervation lead to two compensatory mechanisms. First, new receptors grow de novo postsynaptically. Second, feedback

loops cause increased presynaptic dopamine release. The net result is increasing dopamine activity that eventually overcomes drug blockade and results in a high dopamine state in the striatum. When dopamine activity becomes excessive in the caudate nucleus, the choreoathetosis of tardive dyskinesia results. Dopamine inhibits the caudate, which itself is an inhibitory nucleus. Excessive dopamine inhibition of the caudate causes disinhibition of movements normally suppressed, with resulting choreoathetosis. This resembles the choreoathetosis of Huntington's disease, in which idiopathic caudate degeneration similarly disinhibits normally suppressed movements.

The situation in the striatal disorders is actually more complicated because it is not absolute dopamine deficiency or excess that causes the extrapyramidal signs; rather, it is a change in the dopamine-acetylcholine ratio. Thus, if the cholinergic system is diminished to the same extent as the dopaminergic system, as by benztropine (Cogentin), parkinsonism and dystonias will not occur. Likewise, if the cholinergic system can be enhanced by physostigmine, cholinergic activity temporarily rises to match the enhanced dopamine activity of tardive dyskinesia, and the choreoathetosis transiently disappears. In this light, anticholinergic drugs worsen the low acetylcholine-high dopamine balance and worsen tardive dyskinesia.

Dopamine Blockade in the Tuberoinfundibular System

Dopamine, blocked in these tracts in the hypothalamus, causes the well-known rise in prolactin induced by all antipsychotic drugs. Since dopamine causes tonic inhibition of prolactin, blocking dopamine allows dysinhibition and tonic release of prolactin. This results in galactorrhea, gynecomastia, amenorrhea, and the libidinal disturbances well known with antipsychotics.

Anti-H_1 Histaminic

The most striking feature of the low-potency antipsychotics, such as chlorpromazine (Thorazine) and thioridazine (Mellaril)—the feature that earned the antipsychotics the dubious title of tranquilizers—is their sedative effect. It has recently been proposed that the sedative action of tricyclic antidepressants is due to their H_1 antihistaminic action.[2] The tricyclic antidepressants are structurally very similar to the phenothiazines. They were, in fact, originally synthesized in an attempt to find a more effective phenothiazine.

It should be appreciated that phenothiazines are true antihistamines.[3] They are one of the five basic structural classes of antihistamic drugs, the prototype in general clinical use being promethazine (Phenergan). Promethazine is identical to chlorpromazine except that the three-carbon bridge between the tricyclic B-ring nitrogen and the amine side chain moiety is replaced by a two-carbon bridge in the nonpsychoactive antihistamine promethazine. The three-carbon bridge is necessary for antipsychotic activity, occurring in all of the psychoactively efficacious phenothiazines.

The necessary structure for antihistaminic activity is a substituted ethylamine.[3] The phenothiazine structure, with the tricyclic ring linked to the side-chain ethylamine, is a perfect example of this antihistamine structure. How H_1 antihistamines depress the central nervous system and cause sedation is not understood from a structure activity viewpoint,[3] but it is well established that they do cause sedation, as anyone with hayfever knows. Thus, by recognizing that phenothiazines, the prototype antipsychotics, are antihistamines, their sedative action can easily be appreciated and conceptualized.

Anti-Alpha Adrenergic

The adrenergic blocking action of antipsychotics is well documented as causing orthostatic hypotension. The low-potency antipsychotics, such as chlorpromazine (Thorazine) and thioridazine (Mellaril), are especially potent in this activity and in causing orthostasis.[4] Since alpha receptor stimulation causes vascular smooth muscle constriction, blocking these receptors causes dilatation of the peripheral vasculature and consequent pooling of blood with orthostasis.

This specific alpha blockade is the reason why epinephrine should never be used to treat a patient who is hypotensive from antipsychotic drug administration. Being both an alpha and a beta stimulator, epinephrine will do little to reverse already blocked alpha receptors but will stimulate beta receptors. This will result in paradoxical worsening

of the hypotension, since beta stimulation dilates the "fright-or-flight" skeletal muscle vasculature, resulting in increased peripheral pooling. A specific alpha adrenergic stimulator like metaraminol (Aramine) or norepinephrine (Levophed) will reverse the alpha blockade without danger of beta mediated skeletal muscle blood pooling.

Other common pressor agents are poor choices in neuroleptically induced hypotension. Dopamine (Intropin) is most useful when the primary problem is low cardiac output, especially with associated oliguria. This specificity results from its positive inotropic and renal vasodilating actions, respectively. Since alpha adrenergic activity becomes prominent only at high dosages, its usefulness is minimal in neuroleptic induced hypotension, which is of the low systemic vascular resistance type. Dopamine is also less effective because dopamine receptors are already blocked by the offending antipsychotic drug. Of course, giving dopamine poses the additional risk of inducing exacerbation of the psychosis. Dobutamine (Dobutrex) is likewise a poor choice for antipsychotic drug induced hypotension. This synthetic catecholamine works by beta-1 mediated, positive inotropic action. It is specifically useful where cardiac decompensation secondary to decreased contractility is the problem. As with epinephrine, neuroleptic induced hypotension may actually become worse with dobutamine because its beta-2 action, although minor, may be enough to dilate skeletal muscle vasculature.

It used to be taught that the alpha blocking action of phenothiazines was the reason for their antipsychotic action. Although alpha receptors may have subsidiary roles in treating psychosis, it has been demonstrated that the strength of dopamine blockade specifically correlates with clinical antipsychotic activity.[5]

Antimuscarinic

The muscarinic cholinergic receptor, innervating smooth muscle and glands, is blocked by all known antipsychotic drugs. Well-known atropinic side effects result, with dry mouth, constipation, and blurred vision being the most common and bothersome. (The blurred vision is due to blockade in cholinergically mediated ciliary muscle and resulting cycloplegia.) In elderly men with prostatic hypertrophy, urinary retention may become a problem.

The low-potency drugs, such as chlorpromazine and thioridazine, have much more anticholinergic activity than do the high-potency drugs.[6] Adding antiparkinsonian anticholinergic drugs such as benztropine (Cogentin) increases the muscarinic blockade. A patient may slip into an anticholinergic state, manifested by the additional signs of decreased bowel sounds; dry, warm skin; pupillary dilation; and even paralytic ileus and atropine-type delirium.

Miscellaneous Effects

There are numerous less common, less important, or idiosyncratic effects of antipsychotics not proved to be mediated by any of the "anti-fours." These simply must be memorized by rote and include allergic cholestatic jaundice, agranulocytosis, corneal and lens deposits, pigmentary retinopathy (especially with high dosages of thioridazine), blue-grey pigmentation of skin exposed to sunlight, and quinidinelike effects on the heart.

Implications for Treatment

Clearly, since antipsychotics are employed to treat schizophrenia and similar psychoses, drugs acting specifically to treat the behavioral symptoms without producing side effects would be most elegant. From a review of the "anti-fours," antidopamine activity limited to the mesolimbic area of the brain would give specific antipsychotic activity. A drug approaching this specificity is known and has been marketed in Europe under the generic name clozapine. Its idiosyncratic high incidence of agranulocytosis makes it impractical, however.

The high-potency antipsychotics are the most specific dopamine blockers available. They have far less antihistaminic, anti-alpha adrenergic, and anticholinergic activity than do the low-potency drugs such as the aliphatic phenothiazine, chlorpromazine, and the piperidine, Thioridazine. Nevertheless, their dopamine blockade is not limited to the mesolimbic system; so they cause prolactin

Table 2. Commonly Used High-Potency Antipsychotics

Pharmacological Class	Generic Name	Trade Name	Dose Equivalents (chlorpromazine =100)[9]	Usual Daily Dosages (by mouth)
Phenothiazine piperazines	Fluphenazine	Prolixin	1-2	5-50 mg
	Trifluoperazine	Stelazine	5-10	5-40 mg
	Perphenazine	Trilafon	10	4-64 mg
Butyrophenone	Haloperidol	Haldol	2-5	5-60 mg
Thioxanthene	Thiothixene	Navane	5	5-60 mg
Dihydroindolone	Molindone	Moban	?	50-225 mg

release (tuberoinfundibular dopamine blockade) and a high incidence of extrapyramidal side effects (nigrostriatal dopamine blockade, which requires cholinergic blockade to restore the dopaminergic-cholinergic ratio). Anticholinergics can be added, if necessary, to restore the dopaminergic-cholinergic ratio and reverse extrapyramidal effects. Since the high-potency antipsychotics cause little antihistaminic sedation and antiadrenergic hypotension, and since the extrapyramidal side effects are so easily reversible, they are probably the most useful antipsychotic drugs available (Table 2). They include the piperazine phenothiazines (fluphenazine [Prolixin], perphenazine [Trilafon]), the butyrophenone haloperidol (Haldol), the dihydroindolone (Molindone), and the thioxanthene thiothixene (Navane). On the other hand, as chlorpromazine is associated with a high incidence of antihistaminic sedation, causes antiadrenergic hypotension, and has low antidopaminergic potency, thereby exposing the body to excessive numbers of milligrams of the drug,[7] and as its use results in a high incidence of idiosyncratic side effects, such as jaundice,[3,7,8] skin pigmentation,[3,8] lens deposits,[3] and agranulocytosis,[3,7] it might be prudent to use more potent drugs whenever possible. Recent thinking also contradicts the traditional view that sedating drugs are best for the agitated patient: "A myth exists in psychiatry that hyperexcitable patients respond best to chlorpromazine because it is a sedating phenothiazine . . . that belief has never been proven true."[8]

Summary

By conceptualizing actions of all antipsychotics as fitting into one of four major antagonistic categories, the "anti-fours," one can quickly and rationally appreciate the major actions of the antipsychotics.

References

1. Snyder SH, Banerjee SP, Yamamura HL, et al: Drugs, neurotransmitters, and schizophrenia. Science 184:1243, 1974

2. Richelson E: Tricyclic antidepressants and neurotransmitter receptors. Psychiatr Ann 9:186, 1979

3. Gilman AG, Goodman LS, Gilman A (eds): The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan, 1980

4. Bernstein JG: Clinical Psychopharmacology. Littleton, Mass, PSG Publishing, 1978, p 122

5. Seeman P, Lee T: Antipsychotic drugs: Direct correlation between clinical potency and presynaptic actions on dopamine neurons. Science 188:1217, 1975

6. Snyder SH, Greenberg D, Yamumura HL: Antischizophrenic drugs and brain cholinergic receptors. Arch Gen Psychiatry 31:58, 1974

7. Zavodnick S: Comparison of neuroleptics. In Ayd FJ (ed): Haloperidol Update. Baltimore, Ayd Medical, 1980, pp 15-30

8. Freedman AM, Kaplan HI, Sadock BJ (eds): Comprehensive Textbook of Psychiatry III, ed 3. Baltimore, Williams & Wilkins, 1980, p 2261

9. Klerman GL: Neuroleptics: Too many or too few? In Ayd FJ (ed): Rational Psychopharmacology and the Right to Treatment. Baltimore, Ayd Medical, 1975, pp 6-8