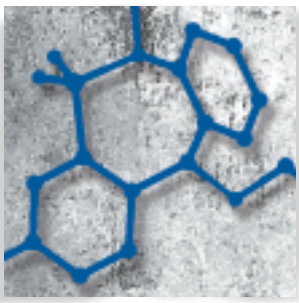
Treatment mechanisms: traditional and new antipsychotic drugs

Carol A. Tamminga, MD



The first generation of antipsychotic drugs was discovered in the 1960s and 1970s. These agents were effective in treating psychosis, but were accompanied by significant side effects, including severe parkinsonism and akathisia. Second-generation antipsychotics were introduced in the 1990s. These drugs have at least equal efficacy to their predecessors, but far fewer side effects. Some data suggest a broader efficacy profile. Clozapine remains the only superior antipsychotic in terms of the magnitude of psychotic symptom reduction. Clinical and animal studies are consistent in suggesting that the antipsychotic component of antidopaminergic treatments is initiated by dopamine receptor blockade in the striatum and that the signal is transmitted to the neocortex through the established basal ganglia–thalamo–cortical neuronal circuits. Other neurotransmitter actions (eg, antiserotonergic) can be exerted locally, in the neocortex. Defining tissue targets of drug action may suggest additional strategies for developing new antipsychotic drugs.

Several different classes of antipsychotic medications have been reliably shown to reduce active psychotic symptoms in schizophrenia and other psychoses[1]; all these drugs block the D_2 family of dopamine receptors. Unfortunately, the drug action is accompanied by side effects, which have inevitably limited their use. The first antipsychotic drug, chlorpromazin, was discovered serendipitously by Delay and Deniker,[2] who were testing preanesthetic agents in schizophrenia for their "calming" action. Shortly after their discovery, a mechanism of action was proposed,[3] and subsequently many similar drugs were synthesized and marketed; these are called traditional or first-generation antipsychotics. Between 1975 and 1990, almost no new drug discovery occurred in schizophrenia. Then, in the 1990s, a second generation of antipsychotic drugs was developed—drugs with at least the same, possibly greater, antipsychotic action, but with significantly reduced motor side effects.[4] The loss of motor side effects has produced a generation of medications far better tolerated by psychotic patients, and thus critically improving compliance. These second-generation drugs still possess the ability to block the D_2 family of dopamine receptors, but have broader receptor affinity profiles, particularly affinity at the serotonin–2 (5-hydroxytryptamine–2 [5-HT_2]) receptors.

The mechanism of the antipsychotic action of these drug families certainly involves blockade of the D_2 dopamine receptor. However, the mechanism whereby the brain translates this primary antidopaminergic action into a reduction in psychosis remains unclear. Moreover, the additional new "ingredients" of action in the second-generation drugs also remain obscure, although 5-HT_2 receptor antagonism has been often invoked.[5] Recently, new technologies have been applied to human brain research to address these important questions, and the

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Author affiliations: Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Md, USA

Address for correspondence: Carol A. Tamminga, Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Box 21247, Baltimore, MD 21228, USA
(e-mail: ctamming@mprc.umaryland.edu)

results have been supplemented by data from new directions in animal pharmacology.
This paper will review the new antipsychotic agents, and then propose an overall mechanism of antipsychotic action. This "working" hypothesis of antipsychotic drug action is itself testable using contemporary techniques of human brain imaging.

Drug actions and side effects: traditional and new drugs

The first antipsychotic to be discovered and developed was chlorpromazine. Very soon after the initial reports of its selective antipsychotic action, it was tested and applied around the world in psychotic patients.[1] The drug was responsible for "emptying out" mental hospitals worldwide. Today's clinicians may underappreciate the potency of chlorpromazine in those neuroleptic-naive individuals: the average symptom diminution was 80% or more. Although a potent antipsychotic, the drug has significant motor, sedative, and cardiovascular side effects; consequently, its use in schizophrenia has gradually diminished over the years.
After chlorpromazine, dozens of antipsychotics were developed. All were characterized by dopamine receptor blockade and catalepsy (in rats) or parkinsonism (in humans). Gradually, the compounds became purer dopamine receptor antagonists, without other monoaminergic, cholinergic, or histaminergic blockade. Haloperidol is a typical example of these newer agents, which still acted predominantly via D_2 dopamine receptor blockade. It was introduced in the 1960s, and soon became the most widely used antipsychotic drug. Haloperidol had the same antipsychotic potency as chlorpromazine, but lacked several of its more significant side effects, including cardiovascular side effects, and much of its sedative effect.
The efficacy of haloperidol was established in controlled trials in the 1960s, and it was used by clinicians thereafter over a wide dose range, often up to hundreds of milligrams per day. Pharmacokinetic studies suggested that its active antipsychotic dose range was 4 to 16 mg/day.[6] However, a random assignment dose–response trial with haloperidol was not carried out until the early 1990s. This dose–response study compared doses of 0, 4, 8, and 16 mg/day.[7] The results showed a significant difference only between placebo and the 8 mg/day and 16 mg/day doses, but no differences between any of the doses either statistically or in overall magnitude of response. None of the items of the Brief Psychiatric Rating Scale (BPRS) had a linear dose–response relationship, not even the positive symptom scores. Moreover, parkinsonism and akathisia were significantly present with the 4 mg/day dose, and remained at a maximal score at all higher dose levels. These results demonstrate that haloperidol is a potent antipsychotic and has significant motor side effects, even at its lowest threshold of antipsychotic dose (4 mg/day).
Clozapine was the first of the "new" antipsychotics, even though it was not new at all at the time of its introduction to the US market. It was marketed in Europe in the 1970s, and its widespread European inpatient use allowed the detection of its most serious side effect, agranulocytosis. The clinical use of clozapine led to the hypothesis that it was a superior antipsychotic, which was tested by Kane et al in a controlled trial.[8] Their initial study, carried out in fully treatment-resistant schizophrenic individuals, was followed up by a clozapine vs haloperidol comparison in schizophrenic "partial" responders. In both studies, the data show that clozapine has a significantly greater antipsychotic action than chlorpromazine or haloperidol in schizophrenic individuals. Clozapine remains the only antipsychotic whose efficacy has been demonstrated to be superior to other agents in the antipsychotic class.
Unfortunately, in addition to the serious side effect of agranulocytosis (which can be successfully managed by weekly plasma monitoring), clozapine also has a diverse array of additional side effects, some of which are serious, others merely bothersome. These include tachycardia, hypotension, sedation, seizures, akathisia, drooling, and significant weight gain. The disincentives to clinical use produced by these many side effects are significant, but the drug is still used around the world, indicating its superior efficacy. Most psychiatrists would agree that clozapine is underutilized in the US, given its superior antipsychotic efficacy.
Four new antipsychotics have since followed clozapine to market. With these, there has been an attempt to reduce motor side effects and increase treatment efficacy. To some extent, this has been achieved with the new antipsychotics; most prominently, they lack motor side effects. The approval of the new compounds by the US Food and Drug Administration (FDA) (first risperidone, then olanzapine, quetiapine, and finally ziprasidone) fails to recognize the significant number of drugs that nearly reached general approval, but failed for safety or effi-

cacy reasons. This list includes drugs like remoxipride, which caused aplastic anemia; sertindole, which prolongs the QT interval on the electrocardiogram; and M100907, which failed because of reduced efficacy. These failures illustrate some of the risks involved in developing a successful antipsychotic. The difficulty in the development of drugs for schizophrenia is primarily due to the lack of a pathophysiologic understanding of the illness and, consequently, the lack of a known drug target. Animal testing to help focus drug candidate choices is not usually helpful because of the obvious difficulties in modeling psychosis. Nonetheless, it is an area of the highest medical need and, for that reason, pharmaceutical companies continue to invest in antipsychotic drug development. It is fortunate that each new drug candidate introduced to the market to date has provided additional advances in patient response and has been widely used.

Risperidone, the first drug to market after clozapine, is predominantly a D_2 dopamine receptor antagonist and a 5-HT_2 receptor antagonist at clinical doses. It was shown to be effective against placebo with an antipsychotic response comparable to that of haloperidol. In several studies, greater efficacy is apparent at a lower dose (<6 mg/day). This initial observation by Marder et al[9] preceded several later reports showing the same phenomenon in "naturalistic" studies, that low daily dose averages are 4 to 4.5 mg/day.[10] At these dose levels, risperidone's motor side effects are minimal, although they do increase at daily doses above 6 mg/day. Risperidone has been widely prescribed and well received. Galactorrhea secondary to elevated prolactin levels is one of its major side effects and a moderate weight gain is apparent. Risperidone has been studied in psychosis of dementia and found to be therapeutic at the lower dose range of 1 to 2 mg/day.

Olanzapine was approved in the US approximately a year after risperidone. The drug has a broad receptor affinity profile, similar to that of clozapine, except for a generally higher receptor affinity at each site. Its antipsychotic action tested against haloperidol is at least comparable, with both drugs showing significantly better effects than placebo.[11] With respect to its therapeutic action, olanzapine has broader effects than a traditional compound like haloperidol, with some antianxiety, antidepressant, and arguably antinegative symptom actions as well.[12] Olanzapine has been tested in the psychosis of bipolar illness and found to be therapeutic. Olanzapine's side effects are mostly benign, with no parkinsonism, mild akathisia, and no blood dyscrasias or prolactin elevations. Significant weight gain and its consequences, including adult-onset diabetes and hyperlipidemia, are its most significant side effects.

Quetiapine was the third new antipsychotic to be approved worldwide for psychosis. This low affinity but broad spectrum compound (like clozapine) is an effective antipsychotic.[13] Worldwide use has been relatively low, despite its efficacy and attractive side-effect profile: "placebo-level" parkinsonism and akathisia with no prolactin elevation but moderate weight gain. Moreover, quetiapine has been studied in the psychosis of dementia with oral reports of good activity.[14,15] Ziprasidone is due to be released onto the US market in early 2001. Efficacy and side-effect data for this promising compound are forthcoming.

Amisulpride is an antipsychotic available in several European countries, but not yet in the US. Its antipsychotic efficacy has been demonstrated, together with a low, but not "placebo" level, motor side-effect profile. Several studies have suggested an antinegative symptom profile for this drug. Such a unique characteristic has not yet been rigorously demonstrated, but repeatedly suggested in the literature.

Even beyond these compounds, the industrial pipelines for new antipsychotics are not dry.[16] Newer drugs are being tested in all stages of trials: phases 1 through 4. Currently, all the compounds under study block D_2 dopamine receptors, but additional novel strategies are also being evaluated, like partial dopamine agonists[17] and indirect-acting *N*-methyl-D-aspartate (NMDA)–sensitive glutamate agonists.[18] The discovery of a disease mechanism will catapult the discovery process ahead. Currently, discovery efforts are tending to focus on the different mechanisms for the positive, negative, or cognitive manifestations of schizophrenia.[19]

Evidence for mechanism(s) of action

Human

Basic to a full understanding of the biology of the mental dysfunction in psychosis and the therapeutic action of these drugs in psychosis is the concept of the brain as a set of overlapping distributed neural systems, each of which utilizes particular brain regions as needed to fulfill their circuit function. The best understood set of these distributed systems has been identified using motor out-

puts, since motor end points can be most easily measured in experimental situations.[20,21] One set of distributed systems governing aspects of motor function is made up of parallel, segregated neuronal circuits that project from the frontal cortex, supplementary motor area (SMA), to the basal ganglia, and then on to the thalamus, and thereafter return to the SMA. The frontal projections begin in the neocortex, synapse in the caudate/putamen, and then split into two pathways, an indirect pathway through the globus pallidus (ultimately inhibitory) and a direct pathway to the substantia nigra (ultimately facilitatory), which both pass into the substantia nigra pars reticulata and from there to the specific nuclei of the thalamus. The segregated pathways project from the thalamus back to their specific regions of the frontal cortex, presumably carrying a subcortically modified neuronal signal back from the basal ganglia to the frontal cortex.

D_2 dopamine receptors, the putative site of action of antipsychotic drugs, reside in very high concentrations in the caudate and the putamen. Antipsychotic drugs are believed to exert their primary therapeutic action here in the basal ganglia. Yet, a mechanism to transmit this action in the basal ganglia back to the neocortex, particularly the frontal cortex, would "deliver" such a basal ganglia action to the neocortical brain areas, those presumably affected by schizophrenia. The transmission of this "D_2-receptor-modified" message through the basal ganglia and thalamus, then back to frontal cortex, is the mechanism that we have proposed to mediate the therapeutic action of these drugs in humans.

Indeed, we have tested this hypothesis in our clinical laboratory with patient volunteers using regional functional imaging techniques with fluorodeoxyglucose (FDG) and positron emission tomography (PET) or regional cerebral blood (rCBF) flow with and without antipsychotic drugs. Simply stated, schizophrenic volunteers received a fixed dose of haloperidol (0.3 mg/kg/day) for 30 days; and then an FDG/PET scan was done. The volunteers then received the same dose of placebo (matched pill number) with a repeat FDG/PET after the second period of 30 days. Computer subtractions were done between the group-average "on drug" scan and its "off drug" counterpart, showing the regions where haloperidol increased and decreased neuronal activity. Haloperidol had the following actions in these volunteers: (i) it increased neuronal activity in the caudate/putamen (presumably a disinhibition); (ii) it increased neuronal activity in the thalamus (presumably associated with a diminished inhibitory reticulothalamic signal); (iii) it decreased anterior cingulate neuronal activity (presumably secondary to reduced activity in the thalamocortical excitatory afferent pathway); and (iv) it decreased middle frontal cortical activity (ie, the same explanation as for [iii]).[22] The "explanations" (given in parentheses above) represent the interpretation we have made of the functional data to shed light on the question of the neural mechanism of antipsychotic drug action. We propose that the disinhibition that haloperidol (or any D_2 dopamine receptor antagonist) produces in the caudate/putamen is transmitted through the basal ganglia and thalamus to ultimately inhibit key areas of the neocortex. These PET findings have been replicated in our laboratory using rCBF,[23] and the data are entirely consistent.

These results are consistent with many of the functional imaging results from other laboratories doing similar kinds of studies.[24,25]

Animals

Experiments in our laboratory over the last few years have involved the administration of traditional and new antipsychotic drugs to laboratory rats for subchronic time periods (6 months) for the purpose of examining critical neurotransmitter systems in the central nervous system (CNS) regions (the basal ganglia–thalamocortical neural circuit) and their alteration with chronic drug treatment. We postulated that the neurochemical marker for D_2 dopamine receptor blockade (D_2 upregulation) and the "transmitted" signals through this system would both vary between the traditional and new drugs. We measured D_2 dopamine receptor density in rat caudate, $GABA_A$ (GABA: gamma-aminobutyric acid) receptor density and D_1 dopamine receptor density in rat substantia nigra, and $GABA_A$ receptor density and glutamic acid decarboxylase (GAD) mRNA expression in rat thalamus. With haloperidol, all these "markers" significantly changed in each region, implying a potent drug action in the caudate/putamen and a strong transmitted signal through the rest of the basal ganglia to the thalamus and thereafter to the cortex.[26] These data are direct evidence from the experimental animal of the idea of a transmitted antipsychotic action through the basal ganglia and the thalamus to the cortex. With the new antipsychotics, these neurochemical changes were milder and not as broad, but always involved the basal ganglia and the thalamus. While the dopaminergic component of antipsy-

chotic drug action is putatively mediated through these defined neural circuits, other transmitter-specific components of drug action (eg, antiserotonergic or antiadrenergic) are likely produced directly in the neocortex.

Working hypothesis and conclusion

It is our current hypothesis that both traditional and new antipsychotic drugs exert the dopaminergic component of their action in the caudate/putamen and that this action is transmitted through the basal ganglia–thalamo–cortical system to the frontal cortex where the pivotal therapeutic action is delivered. Other neurotransmitter influences are most likely exerted in all parts of this circuit, in both the basal ganglia and the cortex.
Given this hypothesis, the obvious proposition is to modulate the circuit's activity at other neurochemical sites in the circuit. This proposition may underlie the putative therapeutic actions of glutamatergic[27] and GABAergic[28] compounds in schizophrenia. ❑

Mecanismos de tratamiento: fármacos antipsicóticos tradicionales y nuevos

La primera generación de fármacos antipsicóticos se descubrió en los años '60 y '70. Estos agentes fueron efectivos para el tratamiento de la psicosis, pero se acompañaron de significativos efectos laterales, que incluyeron parkinsonismo severo y acatisia. La segunda generación de antipsicóticos se introdujo en los '90. Estos fármacos son tan efectivos como sus predecesores, pero con mucho menos efectos secundarios. Algunos datos sugieren un perfil de eficacia mayor. La clozapina se mantiene como el único antipsicótico superior, en términos de la magnitud de la reducción de los síntomas psicóticos. Tanto estudios clínicos como en animales son consistentes al sugerir que el componente antipsicótico de los tratamientos antidopaminérgicos se inicia por el bloqueo del receptor de dopamina en el estriado y que la señal se transmite al neocórtex a través del circuito neuronal ganglio basal-tálamo-cortical. Las acciones sobre otros neurotransmisores (ej. antiserotoninérgica) se pueden ejercer localmente en el neocórtex. El definir tejidos blanco para la acción de fármacos puede sugerir estrategias adicionales para el desarrollo de nuevos fármacos antipsicóticos.

Mécanismes thérapeutiques : molécules traditionnelles et nouveaux antipsychotiques

La première génération de médicaments antipsychotiques a été découverte dans les années 60 et 70. Ces produits étaient efficaces dans le traitement des psychoses mais leurs effets secondaires, dont un syndrome extra-pyrimidal sévère et une akathisie, étaient importants. Les antipsychotiques de seconde génération sont apparus dans les années 90. D'efficacité comparable aux précédents, leurs effets indésirables se sont révélés bien moins importants. Certaines données ont suggéré un profil d'efficacité plus large. La clozapine est le seul à induire une réduction plus importante des symptômes psychotiques. Les études cliniques et chez l'animal se rejoignent sur l'origine probable de la composante antipsychotique des traitements antidopaminergiques : blocage des récepteurs dopaminergiques dans le striatum et transmission du signal au néocortex au travers des circuits neuronaux cortico-thalamo-ganglions de la base. D'autres actions neurotransmettrices (antisérotoninergiques par exemple) peuvent s'exercer localement dans le néocortex. La définition de nouvelles cibles tissulaires pour l'action médicamenteuse pourrait constituer d'autres stratégies de développement des nouvelles molécules antipsychotiques.

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