Treatments for chronic psychosis

Carol A. Tamminga, MD; Adrienne C. Lahti, MD

Psychosis is a mental condition characterized by hallucinations, delusions, and thought disorder; it spans diagnostic entities that respond to similar therapeutic approaches. Psychosis has no fully described tissue pathology, as yet, but is still identified and assessed symptomatically. The first generation of antipsychotic drugs was developed in the middle of the 20th century. The second generation of drugs arrived in the 1990s. This new group of antipsychotic drugs has potent therapeutic actions on the positive symptoms of psychosis with far fewer side effects, especially motor effects. However, each of the new drugs has its own characteristic clinical and pharmacological features that affect individual patient response. Understanding these individual drug characteristics can promote optimal drug choice and use in conditions of chronic psychosis.

Psychosis is an illness of the brain in which thoughts are disordered and reality distortions occur, like hallucinations and delusions.[1-3] These symptoms characteristically manifest themselves within different diagnostic categories. The diagnoses in which psychosis often occurs are schizophrenia, characterized by a lifelong mental psychotic condition, bipolar disorder, in which primarily affect disturbance occurs (mania or depression), and dementia, in which loss of cognitive capacity can be confounded by paranoia and thought disorder. Other conditions, like drug abuse, alcoholism, Parkinson's disease, and Huntington's chorea, are associated with psychotic symptoms, less frequently and usually in a transient fashion.

The treatment of psychotic symptoms is the same in all diagnostic categories, namely administration of antipsychotic drugs.[4] Not all the symptoms of each of these illnesses can be treated by antipsychotic drugs alone, eg, the cognitive dysfunction in schizophrenia is minimally affected by haloperidol, wich has little effect on the affective dysregulation in bipolar disorder.[5] However, hallucinations, delusions, and thought disorder are treated similarly across the diagnoses, although different dose levels, schedules, and durations are used. Antipsychotic drugs are characterized by the common mechanism of action of blockade of dopamine receptors. There exist first- and second-generation antipsychotic drugs. The first-generation drugs are characterized by predominant dopaminergic blockade, while the second generation of antipsychotic drugs involve more prominently dopaminergic and serotonergic blockade. Clinically, the second-generation drugs have few or no parkinsonian side effects. Consequently, the second generation of drugs is now more widely used than the first, and likely to take over the market for treatment of psychosis.[6]

The antipsychotic properties of these drugs were discovered serendipitously in the early 1950s by Delay and Deniker, who reported the selective antipsychotic action of chlorpromazine.[7] After the mechanism of action was identified as dopamine/aminergic receptor blockade,[8,9] many newer drugs were developed, selectively designed to block dopamine and other receptors.[10] These are now referred to as the first-generation antipsychotics. These drugs were all developed on the basis of dopamine recep-

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

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

tor blockade, either pure dopamine (eg, haloperidol) or mixed aminergic receptor antagonist (eg, fluphenazine). However, all have potent antidopaminergic actions and hence show parkinsonism and often cardiovascular side effects along with their primary antipsychotic actions. The first second-generation antipsychotic was clozapine.[11] This drug is an old drug, not a new one, and although it has the serious side effect of agranulocytosis, it has several positive clinical properties, like no motor side effects and uniquely potent antipsychotic actions. When these properties were documented by Kane et al in 1988[11] in a multisite controlled study for registration in the USA, these new drug effects became targets for drug development, producing a second generation of antipsychotic drugs. The second-generation drugs were developed and introduced in the 1990s. This new group of antipsychotics have been more broadly tested and have clear clinical advantages; they have thus been widely used. The first generation of drugs is often represented by haloperidol, but is actually composed of drugs with high affinity (eg, haloperidol) and low affinity (eg, chlorpromazine) at the dopamine D_2 receptor. The low-affinity drugs have cardiovascular side effects, and were therefore soon abandoned in favor of high-potency compounds like haloperidol. Now, the second-generation compounds are replacing haloperidol and its congeners because of their lack of motor side effects.[12] It is only the remaining economic advantages of the first-generation drugs that still compel their use. While the second-generation drugs have the common advantage of low or no motor side effects, they are neurochemically and pharmacologically distinct from each other, and probably have distinct clinical characteristics as well.

Chronic psychoses

The chronic psychoses are brain diseases where psychotic symptoms present themselves as a significant part of the illness picture and require treatment. Within each distinct illness, psychosis may be a varying part of the symptomatic picture, with schizophrenia showing consistent and prolonged psychosis and dementia showing more transient symptoms. However, whenever they present themselves, the symptom configurations require treatment because of their intrusive and absorbing nature, and because of their morbidity and even mortality.

Schizophrenia is a lifelong psychotic illness that is also characterized by cognitive and affective dysfunctions; it affects 1% of the population worldwide. The core of disease definition is psychosis. There exist many different manifestations of schizophrenia with the predominant symptoms being psychotic, cognitive, or affective (negative symptoms).[13,14] This is an illness where most affected persons do not return to any normal existence, even with the available treatments. Only perhaps 10% of affected persons return to normal health and less than 20% return to work. New treatments are essential. It appears as though the available drugs primarily target positive psychotic symptoms, and not cognitive dysfunction or negative symptoms. However, each and every treatment approach is helpful. Persons with schizophrenia require medication throughout their entire lives. About 20% of them do not respond to antipsychotic medications at all and are candidates for clozapine.

Bipolar illness has a lifetime prevalence of 1.3% to 1.6%, with a 10% to 20% mortality rate due to suicide.[15] Psychosis is prevalent, nearly ubiquitous, during manic episodes, most often requiring antipsychotic treatment. All the second-generation drugs are effective and have far less motor side effects than haloperidol. The second-generation drugs appear to have similar efficacies, but different side effects, particularly weight gain.[16] Use of antipsychotic treatments along with mood stabilizers for the treatment of acute mania has become routine.

In dementia, psychosis and other severe behavioral disturbances like agitation, wandering, self-mutilation, and assaultiveness all occur. Antipsychotic treatments at very low doses (relative to schizophrenia) have been used successfully to treat these psychotic and behavioral symptoms.[17] Whether the behavioral disturbances are clinical manifestations of psychosis or based on another cerebral physiology, they are mitigated with antipsychotic drugs. While the first-generation drugs are effective even in small doses, they are accompanied by motor side effects. Thus, the use of second-generation drugs is clearly indicated and effective in the elderly demented patient, and are accompanied by manageable side effects.

Antipsychotic drugs: individual characteristics

Haloperidol

Haloperidol is the prototypical first-generation antipsychotic. Until the 1990s, haloperidol was the most widely used antipsychotic for the treatment of any psychosis.

Its potent antipsychotic action along with little sedation, despite its considerable motor side effects, has sustained its worldwide use. Those same characteristics have recommended its ongoing use, along with its economic advantage.

Receptor affinity and animal pharmacology

The pharmacology of haloperidol is extensively and well documented because the drug is the usual comparator compound in animal research and was also used, for a time, in human experiments. Haloperidol has a high affinity for the D_2 family of dopamine receptors. It has little D_1 receptor affinity, but does possess modest affinity for the α_1 adrenoceptor and serotonin (5-hydroxytryptamine) receptor 5-HT_2,[18] but the latter may not be manifest at clinically relevant dose levels. Haloperidol defined the animal pharmacological actions of an antipsychotic drug: it inhibits conditioned avoidance responding; it blocks apomorphine- and amphetamine-induced motor behaviors; and it induces catalepsy in animal preparations.[19] It elevates dopamine metabolites, homovanillic acid (HVA) and dihydrophenylacetic acid (DOPAC), in rat dorsal and ventral striatum with acute administration; it stimulates Fos protein expression throughout rat striatum and the limbic forebrain with acute administration[20]; and it causes depolarization blockade in the A9 and the A10 groups of dopamine neurons with subchronic administration.[21] Also, chronic treatment in the rat upregulates dopamine receptor number throughout striatum, modifies γ-aminobutyric acid $GABA_A$ receptor binding in substantia nigra and alters $GABA_A$ receptor density in rat thalamus.[22] Since many of these pharmacological characteristics are now linked to the undesirable motor side effects of antipsychotics, these are not characteristically targeted in drug development today.

Efficacy in chronic psychoses

The antipsychotic efficacy of haloperidol in schizophrenia was established in comparative trials in the early 1960s.[10] However, it was not until recently that a placebo-controlled trial with a range of doses was completed with this drug.[23] In this schizophrenia trial, doses of 4, 8, and 16 mg/day were tested against placebo in a multicenter efficacy trial. The results showed haloperidol to be a highly effective antipsychotic drug in this dose range and there was no relationship between drug dose and clinical response across this dose range. This lack of detection of a relationship between dose and clinical response across a usual clinical dose range suggests the lack of sensitivity of large multicenter drug trials.

Haloperidol was used in the treatment of acute mania long before clinical trials verified its action in that psychotic condition. It is effective in managing the psychosis at doses used in schizophrenia. However, motor side effects are problematic and clinical use has been largely taken over by second-generation compounds.

Similarly, in dementia, haloperidol was previously used in the treatment of psychosis long before clinical trials verified the efficacy or the drug dose. Efficacy was apparent, even at very low drug doses, up to 4 mg/day. Overt psychotic symptoms respond as well as aggressive/agitated behaviors. However, the frequency and severity of the motor side effects have limited drug use.[24] Moreover, the very high incidence of drug-induced dyskinesias (40% per year)[25] further drove clinicians from the use of this drug. While behaviorally effective, motor side effects have effectively limited drug use in this condition.

Recent in vivo human imaging analysis of regional drug action with haloperidol shows that the drug affects neuronal metabolism and/or regional cerebral blood flow (rCBF) in the striatum, thalamus, middle frontal cortex, and anterior cingulate cortex (ACC).[26] Within the ACC, drug action does not correct the abnormal task-activated rCBF patterns in schizophrenia, but it appears to more closely "normalize" rCBF in the frontal cortex *(Figure 1)*. The rCBF pattern changes with haloperidol are consistent with the clinical actions and side-effect profile of the drug (Lahti et al, personal communication).

Drug side effects and human pharmacokinetics

Haloperidol produces significant parkinsonism and akathisia in a large number of subjects even at very low dose levels. In a controlled multicenter trial that evaluated 4 to 16 mg/day dose levels, the motor side effects were evident at the lowest dose, suggesting that motor side effects are inevitable, even at very low clinical doses. However, other side effects produced by many of the first-generation antipsychotic drugs, like cardiovascular effects, anticholinergic actions, and hematological changes, are no particular problem with haloperidol. The compound fails to alter the QT interval on electrocardiography (ECG), a measure of cardiac repolarization

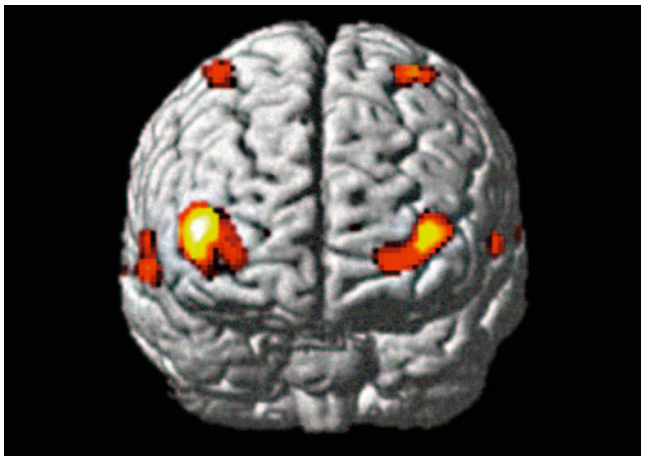

Figure 1. Statistical parametric map derived from ^{15}O-labeled water positron emission tomography (PET) scans rendered onto three-dimensional standard brain displayed in the frontal coronal view. This map indicates the difference in regional cerebral blood flow (rCBF) obtained when the same schizophrenic volunteers (SVs) were scanned, first medication-free, and then again after treatment with haloperidol during performance of a cognitive task. During the task, the haloperidol-treated SVs show rCBF changes in the frontal cortex, bilaterally, compared with when they are medication-free.

time. Little weight gain has been documented with haloperidol. Haloperidol has only one minor metabolite (reduced haloperidol) and both parent and metabolite are easy to analyze. Haloperidol's half-life in humans is 12 to 22 h in a mixed population and 12.2±2.6 h in "good" metabolizers. In our hands (N=10), the time to maximum concentration (T_{max}) is 5±2 h, its distribution half-life is 1.3±0.03 h; peak plasma level after 10 mg oral concentrate (C_{max}) is 12.3±6.7 ng/mL and elimination half-life is 21.7±20 h (unpublished data). Treatment studies from multiple laboratories indicate that drug concentrations of 4 to 16 ng/mL form the therapeutic range for the drug.[27]

Clozapine

Clozapine was first marketed in the early 1960s, but its use was severely restricted due to the acute agranulocytosis seen in Finland and the associated deaths. However, despite this, the early use of the drug suggested its unique antipsychotic actions; these were demonstrated in the 1988 study by Kane et al.[11] Since then, use in persons with psychosis unresponsive to other drugs has been strongly advocated and the clinical outcomes have been broadly positive. In some countries, eg, China, clozapine has been used as a first-line drug because of its outstanding clinical actions.[28] The clinical actions of the drug have an associated human physiology, which is consistent with its unique actions (see below).

Receptor profile and animal pharmacology

Clozapine has a broad affinity for many central nervous system (CNS) receptors. It has measurable affinity not only for D_1 and D_2 dopamine receptor families (D_1, D_2, D_3, and D_4), but also for the serotonin (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, and 5-HT_7) receptors. In addition, it has significant affinity for the α_1 and α_2 adrenergic, cholinergic, and histamine sites.[18] Although the affinity of clozapine for these sites overall is low, clinical doses are relatively high, giving clozapine a broad but low-affinity blockade of many CNS receptors in the clinical situation. As predicted by this receptor profile, clozapine blocks animal behaviors and neurochemical changes induced by dopaminergic, serotonergic, cholinergic, and noradrenergic agents.[29] In addition, clozapine has distinctive regional actions in animal brain: it activates c-fos mRNA only in limbic cortex and not in the dorsal striatum[20]; moreover, it affects dopamine cell bodies by producing depolarization blockade only in the A10 neuronal group (mesolimbic) and not in the A9 group (nigrostriatal).[21] These data are consistent with the clinical actions and the lack of motor side effects that are characteristic of clozapine.

Efficacy in chronic psychoses

In schizophrenia, clozapine has been demonstrated to have a unique and superior antipsychotic action. This was first demonstrated in those 20% of severely ill schizophrenics who are treatment resistant, but has been extended to all partially responsive persons with schizophrenia. This is to say that 35% to 50% of treatment-resistant patients treated with clozapine demonstrate a response to the drug.[11] This response is characterized by a decrease in positive and negative symptoms and an improvement in cognitive function. Moreover, the response is greater than to any other first- or second-generation antipsychotic.

In psychotic affective conditions, clozapine shows clear efficacy. However, characteristically, treatment in normal mania is not extended; moreover, other antipsychotics show efficacy, thus the "nonresponder" status is

rarely reached. Weight gain is a greater problem in mood disorders than in schizophrenia, possibly only because of the intact self-perception of the patient group, and clozapine is burdened with this side effect. Consequently, clozapine is not recommended as a first-line drug in this area.

Clozapine has also been effective in dementia with psychosis. Although side effects are substantial, with agranulocytosis being more frequent, improvement is roughly "moderate to marked," even at low doses (100-150 mg/day). However, anticholinergic side effects can limit use. However, if an indication for clozapine is established, it can be effective and safely used in the elderly with psychotic and/or severe behavioral disorders, provided there is careful monitoring.

Clozapine is the recommended treatment in the levodopa (L-DOPA)–induced psychosis of Parkinson's disease, where it characteristically fails to worsen the parkinsonian symptoms. Psychotic symptoms have become more common today with the introduction of L-DOPA treatment. Moreover, mild psychotic symptoms, if left untreated, have a tendency to worsen.[30] Clozapine is generally effective and well tolerated in psychotic symptoms accompanying late-stage Parkinson's disease, including sleep, motor, and sensory disturbances, and is a first-line treatment.[31]

In vivo imaging studies with clozapine suggest a potential mechanism for the superior clinical antipsychotic action, namely that in humans, clozapine has the same focused and "normalizing" action on limbic cortical function as the drug shows in animal model studies. First, clozapine has a greater activating effect on neuronal activity in the ACC and the middle frontal cortex than do other antipsychotics (specifically haloperidol) *(Figure 2A)*. However, clozapine also has a "normalizing" action on the behavior of the ACC during performance of a task that utilizes the ACC *(Figure 2B)*.

Drug side effects and human pharmacokinetics

Clozapine has a multitude of serious as well as incidental side effects, all of which affect patient use. Given the serious nature of the side effects, it is indeed surprising that the drug is used at all, and the fact that it is, is a testimony to its superior clinical efficacy. The drug was first noted to produce agranulocytosis after several deaths

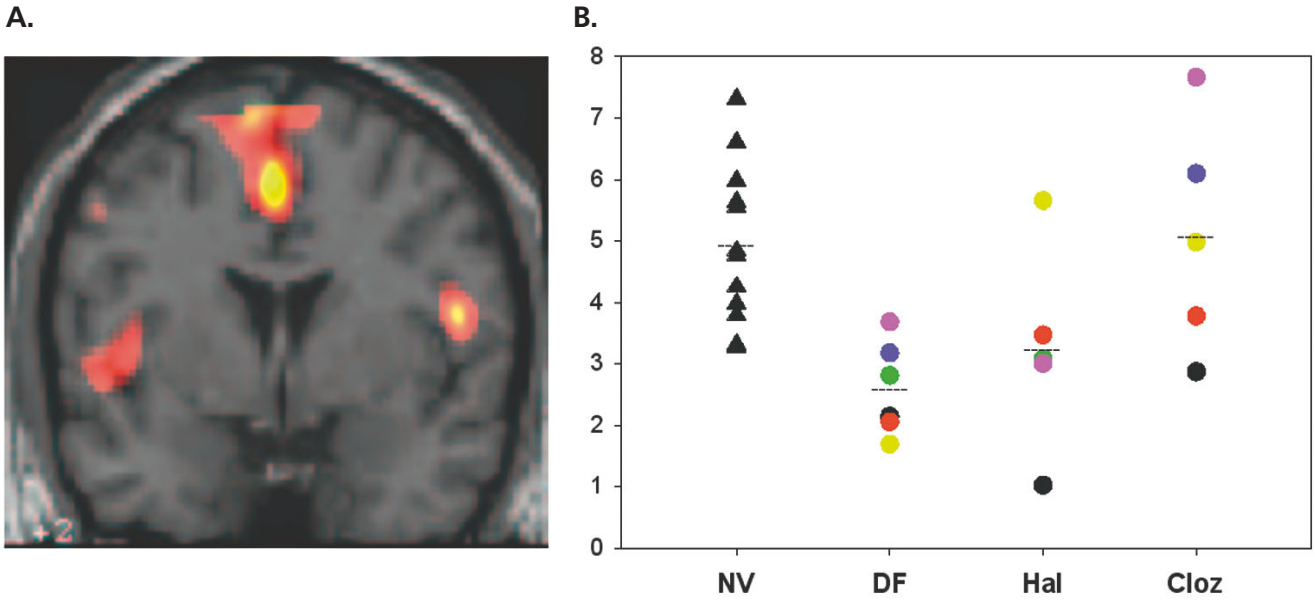

Figure 1. A. Coronal statistical parametric map derived from ^{15}O-labeled water positron emission tomography (PET) scans indicating the difference in regional cerebral blood flow (rCBF) between clozapine-treated and haloperidol-treated schizophrenic volunteers (SVs). Clozapine has a greater activation effect in the anterior cingulate cortex (ACC) compared with haloperidol. **B.** Individual rCBF changes in ACC activation during performance of a cognitive task in drug-free (DF), haloperidol-treated (Hal), and clozapine-treated (Cloz) SVs. Values for the normal group (NV) are provided for reference. Clozapine, but not haloperidol, shows a "normalizing" action on the activation of the ACC during performance of a cognitive task compared with drug-free SVs. Colors are coded such that the same color always identifies the same volunteer.

occurred in a Finnish hospital in the 1960s. The action of clozapine in suppressing granulocyte production in the marrow was described and its incidence gradually tabulated over time, now known to be 0.5% to 1% with a mortality rate of 3% to 15%. Currently, clozapine use is restricted in the USA to those psychotic persons who fail to respond to other drugs. Its use is also accompanied by required blood counts, most frequent (weekly) in the first 6 months of treatment. In addition, clozapine causes weight gain, hypotension, tachycardia, arrhythmias, sialorrhea, sedation, and seizures in addition to the putatively more serious agranulocytosis. In reality, it is these "lesser" side effects that most often cause drug discontinuation. However, clozapine fails to cause acute or chronic motor side effects to any notable extent.
Clozapine has several major metabolites, at least two of which have CNS activity, norclozapine and desmethylclozapine. Too little is known about the actions and kinetics of clozapine and its metabolites. After a single dose of clozapine (200 mg), T_{max} is 3±1.5 h and C_{max} is 386±249 ng/mL. Its elimination half-life is approximately 10.3±2.9 h and its mean half-life is 17.4±7.7 h. Plasma concentrations are linear with dose.

Risperidone

Risperidone was designed on the basis of the clinical observation that haloperidol combined with a pure serotonin antagonist showed fewer motor side effects than haloperidol alone.[32] Risperidone contains both the antidopaminergic and the antiserotonergic components of the two distinct test drugs. Risperidone was the first drug rationally designed to affect both the dopamine and the serotonin systems, where the antiserotonergic actions are more potent than the antidopaminergic actions. Although clozapine possesses these properties, it was not designed as such. In the clinical development of risperidone, the advantages of this kind of drug target were delineated and their clinical end points developed.

Receptor profile and animal pharmacology

Risperidone has high affinity for the D_2 dopamine receptor family and for the 5-HT_{2A} and 5-HT_7 receptors. The drug also has high affinity for the α_1 and α_2 adrenoceptors, but moderate affinity for the 5-HT_{2C} and histamine H_1 receptors.[18] The major active metabolite of risperidone, 9-OH-risperidone, has the same affinity profile. Thus, the drug has antidopaminergic and antiserotonergic characteristics in animal models of drug action, with greater antiserotonergic than antidopaminergic actions. It entirely lacks anticholinergic properties. Risperidone increases dopamine turnover in frontal and olfactory cortex to a greater extent than it does in striatum.[19] Moreover, risperidone only produces catalepsy in rats at high dose levels. Consistent with these behavior actions is the tendency of risperidone to only activate c-*fos* mRNA in the ventral, not dorsal striatum. However, the drug produces depolarization blockade in A9 as well as A10 dopamine neurons, without the selectivity shown by clozapine. Preclinically, the animal profile is mixed with respect to whether or not motor side effects would be predicted in human use.

Efficacy in chronic psychoses

Risperidone was first tested in a multicenter, multidose, international study in the psychosis of schizophrenia.[33] Data from this trial indicated that the drug was surely antipsychotic and potently so, but that the best dose was in the lower dose range, around 6 mg/day, which was confirmed in further studies. Current drug use studies suggest that the doses of risperidone currently prescribed are biphasic, with one peak around 2 to 5 mg/day and another peak at doses above 8 mg/day. The lower dose range is not associated with parkinsonism and only low levels of akathisia, whereas the higher dose range has haloperidol-like levels of motor side effects. Early use with risperidone suggested that the drug might have some positive effects on cognitive dysfunction in schizophrenia. In in vivo ligand studies in humans, the occupancy of striatal dopamine receptors remains below 70% within the low dose range, while occupancy of cortical serotonin receptors is higher by about 20%, in the range of 80% to 95%.[34] This is characteristic of the second-generation antipsychotics and is consistent with their animal pharmacology.
Risperidone was one of the first second-generation antipsychotics with low motor side effects, especially at low dose levels, to also have a good side-effect profile. Hence, the drug was used extensively, and then studied, in the psychosis of the elderly, then an area of great medical need. In an early report,[35] risperidone was found to be "safe and effective" for psychosis in the elderly, with hypotension being a use-limiting side effect. Later controlled trials confirmed and extended

these early observations.[36] An extensive development program has demonstrated the drug to be effective and well tolerated in many fragile patients[37] at doses of 0.5 to 1.5 mg/day.[38] Risperidone is widely used in the elderly when an antipsychotic is required; the low anticholinergic characteristics are positive for the elderly.

Drug side effects and human pharmacokinetics

Risperidone is not free of motor side effects in its higher doses (above 6 mg/day). Whereas at dose levels below 4 to 6 mg/day motor side effects are at placebo levels, at the higher doses sometimes needed in treated individuals, especially schizophrenic patients, parkinsonism and akathisia occur and they can do so at the same intensity as with haloperidol. However, because this is such a common, if not usual, side effect, treatments and compensations exist for it and its presence does not rule out risperidone use. In addition, risperidone causes some weight gain; its potency in this area is less than several of the other second-generation antipsychotics, for reasons that remain obscure, but the effect is greater than haloperidol and considerably less than clozapine. Risperidone not only elevates plasma prolactin, but also causes galactorrhea, particularly in women; this has become a significant side effect, even though its frequency is low.
With respect to pharmacokinetics, risperidone is metabolized by the CYP2D6 liver isoenzyme system to its primary metabolite, 9-OH-risperidone. This metabolite is active, and retains all of the pharmacological characteristics of the parent compound. Thus, in kinetic studies, the levels of both risperidone and 9-OH-risperidone need to be taken into account. After a single 1-mg dose of risperidone, T_{max} is 1 h for risperidone and 3 h for 9-OH-risperidone. The half-life of risperidone is 3.6 h, whereas that for 9-OH-risperidone is 22 h. Kinetics are dose-proportional up to 10 mg. Because the excretion of 9-OH-risperidone is renally dependent, its kinetics are relatively independent of the rate of liver metabolism and its half-life remains 20 to 22 h. In renally impaired individuals and in the elderly, metabolism and excretion are reduced.[39]

Olanzapine

Olanzapine is an antipsychotic with a broader receptor profile than risperidone and was developed to mimic the pharmacology of clozapine. Olanzapine affects the dopamine D_2 receptor, several serotonergic and noradrenergic receptors, and selectively the muscarinic M_1 cholinergic receptor. It has greater serotonergic than dopaminergic binding across its whole clinical dose range (not just the lower clinical dose range like risperidone) and causes placebo-level motor side effects at all clinically effective doses. Other unanticipated side effects with olanzapine (eg, weight gain) have tended to dampen otherwise strong enthusiasm for the drug, especially in some psychotic diagnoses.

Receptor profile and animal pharmacology

Olanzapine was developed to have a receptor affinity profile similar to clozapine. Hence olanzapine has a broad profile, including blockade of the D_1 and D_2 families and potent blockade of the 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, M_1, H_1, and α_1 receptors.[40] It differs from clozapine receptor profile in the overall level of affinity for the 5-HT_{1A} receptor (higher for clozapine), α_2 blockade (higher for clozapine), and in the spectrum of activity at the M_1 to M_4 receptors (more restricted for olanzapine). These differences are relatively minor in the overall picture and, in many ways, it is surprising that olanzapine is not more similar to clozapine. However, this drug was evaluated carefully prior to clinical development and found to lack any effects of bone marrow effects, and hence no agranulocytosis.
Olanzapine has both antidopaminergic and antiserotonergic actions in animal models, but has a higher antiserotonergic potency, like the second-generation antipsychotics. Olanzapine produces depolarization blockade in the A10 but not in the A9 dopamine neurons,[41] like clozapine, and fails to affect c-*fos* activity in the dorsal striatum.[42] With chronic treatment, olanzapine causes mild dopamine receptor upregulation in striatum in the rat, but significantly less than haloperidol. Olanzapine fails to produce dystonias in neuroleptic-sensitized *Cebus* monkeys[43] and fails to produce vacuous chewing movements in chronically treated rats,[44] both suggesting that olanzapine will not produce tardive dyskinesias in humans. Moreover, the clinical data are so far consistent with this.

Efficacy in chronic psychoses

Olanzapine has a potent antipsychotic action in schizophrenia, bipolar disorder, and psychosis associated with dementia. Olanzapine was the second drug approved for

psychosis in psychotic disorders directly after risperidone. The drug was studied in four large placebo-controlled trials in schizophrenia.[45,46] Results from all studies were consistent and reported significantly greater antipsychotic activity than placebo on both positive and negative symptoms and equivalent activity to haloperidol on positive symptoms. These data suggested that olanzapine is better than haloperidol on negative symptoms. However, whether this outcome is an effect on primary or secondary symptoms has been argued. Olanzapine has been compared with chlorpromazine in treatment-resistant patients and been found to be equivalent.[47] Although other equivalence studies (rather than difference studies) have been done and found supportive, the definitive study was negative. That olanzapine might lack such a pivotal characteristic of clozapine, despite its very close structure and pharmacology, was surprising and has been puzzling for identifying the critical mechanism for clozapine action in schizophrenia.

Olanzapine has been tested in randomized controlled, multicenter, clinical trials in mania. The drug is effective in treating mania and was the first of the second-generation compounds to receive an indication in this area.[48] Treatment was rather short in these trials (3 weeks), but, when needed in clinical practice, often extends for longer, eg, 6 months, but it is not characteristically chronically administered in mania unlike in schizophrenia.

For the psychotic and behavioral symptoms that accompany dementia, olanzapine has also undergone testing in controlled multicenter trials. Doses in the lower range (5-10 mg/day) were effective and well tolerated.[49] Side effects included somnolence and gait disturbance, but no measurable interference with cognitive function. Olanzapine is safe and effective for agitation and psychosis in elderly demented persons.

Drug side effects and human pharmacokinetics

The motor side effects with olanzapine are remarkably and significantly diminished from those appearing with haloperidol.[45] This result is consistent across all clinical studies. Parkinsonism and akathisia are absent at recommended dose levels, though mild akathisia and a low level of anticholinergic medication use can be detected at higher dose levels. Other side effects with olanzapine are generally mild, except for weight gain. Mild somnolence and dizziness have been noted. The weight gain is clear and appears to be cumulative over time. Metabolic abnormalities of carbohydrate metabolism leading to diabetes have been reported. They were initially thought to be secondary to the weight gain, but are now suspected to be independent. No cardiac effects, blood dyscrasias, serious liver toxicity, or lasting prolactin elevations have been noted.

Olanzapine has two primary metabolites, 4-*N*-desmethylolanzapine and 10-*N*-glucuronide olanzapine, both of which seem to be behaviorally inactive. The parent compound has weak affinity for several different hepatic isoenzyme systems, including CYP2D6, CYP1A2, CYP3A4, and CYP2C19. This suggests that minimal drug–drug interactions occur with olanzapine, because so many routes of degradation exist. The half-life of olanzapine is long (31 h; range 21-54 h) and the T_{max} is 5 h. Gender influences drug metabolism, in that females metabolize the drug more slowly and consequently have higher plasma levels at fixed dose levels.

Quetiapine

Quetiapine was developed to mimic the receptor profile and the pharmacology of clozapine. As such, it has very weak affinity for both the dopamine and the serotonin receptors and a broad profile at the other receptors; it still has a higher serotonin than dopamine receptor affinity. Early on, drug potency was questioned probably because the recommended dose levels were not high enough. Side effects appear to be mostly clozapine-like, except for the agranulocytosis, which none of the new drugs displays. Nor have any of the new drugs yet demonstrated unique antipsychotic actions. Side effects are very low.

Receptor profile and animal pharmacology

Quetiapine has a very broad receptor affinity profile, with significant but weak attraction to the D_1 and D_2 family of dopamine receptors, to the 5-HT_{1A}, 5-HT_{2A}, 5-HT_6, and 5-HT_7 families of serotonin receptors, and to the α_1 and α_2 noradrenergic and H_1 receptors without muscarinic affinity.[18] These affinities are low, but in the range of those of clozapine. Quetiapine increases dopamine metabolites in striatum with acute administration, but fails to upregulate D_2 dopamine receptors with chronic treatment. The c-*fos* upregulation pattern produced by quetiapine resembles clozapine. Quetiapine blocks dopamine- and serotonin-induced animal behaviors in laboratory testing and fails to induce catalepsy at clinically relevant doses.[50]

Efficacy in chronic psychoses

Quetiapine has a significantly greater antipsychotic action than placebo according to several controlled trials at doses of 150 to 750 mg/day.[51] Moreover, it has actions equivalent to haloperidol and risperidone on positive and negative symptoms. Several studies also document a positive effect of quetiapine on cognitive dysfunction in schizophrenia, especially attention and working memory. This effect will need to be documented as a distinct action from the antipsychotic effects, and such studies are now under way.
Quetiapine has been tested in mania, but not in multisite controlled trials. Nonetheless, in open clinical use, quetiapine seems to have the usual antipsychotic action in mania as reported for other agents.[52] Moreover, it is safe and apparently effective in adolescent mania.[53] In the area of behavioral disruption/agitation in dementia, quetiapine requires further study with systematic evaluation. However, because other agents have been tested and found effective in the psychosis and agitation of the elderly with dementia, quetiapine has been similarly applied. Open results indicate that the drug is effective and well tolerated in elderly dementia and should be further and rigorously tested.[54]

Drug side effects and human pharmacokinetics

Quetiapine has a benign side-effect profile. It fails to induce motor side effects in excess of placebo. No akathisia is apparent. Reported side effects include sedation, somnolence, and headache. Mild weight gain does occur, but at lower levels than with clozapine. The report of cataracts in animals developing during drug treatment have failed to show extension to humans, and hence no cataract risk currently exists for humans and slit-lamp examinations are not necessary.
The plasma half-life of quetiapine is approximately 6 h. The kinetics are linear up to 600 mg. Drug clearance is reduced in the elderly, and so lower doses should be used in this population.

Ziprasidone

Ziprasidone is a drug designed to have a high ratio of serotonin ($5\text{-}HT_2$) to dopamine receptor affinity. In addition, it has some unique properties, one of which is to block serotonin and norepinephrine reuptake blockade; this is a rather potent action on the reuptake proteins, though related advantages have not been adequately explored as yet. Its approval by the Food and Drug Administration (FDA) was delayed because the drug was shown to produce QTc prolongation, consistent with potential cardiac arrhythmias. Additional studies were required for ziprasidone to rule out added cardiac risk. A large study has been carried out on the effect of ziprasidone on QT duration. The results showed a mild prolongation, but without any worsening with a metabolic inhibitor. Overall safety of the drug has been confirmed in a large data set.

Receptor profile and animal pharmacology

Ziprasidone has a high affinity for the D_2 dopamine receptor family, for all the serotonin receptor families, for α_1, but not α_2, adrenoceptors, and for the 5-HT and norepinephrine reuptake proteins. It has the highest ratio of serotonin to dopamine affinity of any of the second-generation antipsychotics. Moreover, it appears to have agonist action at the $5\text{-}HT_{1A}$ receptor (as does clozapine), whereas it is an antagonist at all other receptors.
Behaviorally, ziprasidone potently inhibits dopamine- and serotonin-mediated behaviors. It inhibits conditioned avoidance response in rats. It decreases spontaneous locomotor activity and causes catalepsy at very high doses (probably no longer clinically relevant).

Efficacy in chronic psychoses

Ziprasidone is a highly effective antipsychotic drug in the dose range of 80 to 160 mg/day compared with placebo and with active comparators; its effects on positive and negative symptoms are equivalent to haloperidol (R. O'Connor et al, personal communicaction) Because of the unique receptor and reuptake-protein binding profile, broader effects were postulated for ziprasidone other than merely effects on psychosis. This profile predicts antidepressant and possibly cognition-enhancing characteristics. No extraordinary clinical actions have yet been detected. However, these evaluations are ongoing, and signal detection is low due to the complex symptom picture and the confounding of cognitive change with psychosis improvement. Therefore, clinicians should expect clear indications for schizophrenia subtypes to develop.

Studies of ziprasidone in mania and in psychotic/agitated dementia are ongoing, but not yet published. Because all of the other antipsychotics have efficacy in these psychotic diagnoses, the probability is great that ziprasidone will be found to be effective as well. Perhaps in nonschizophrenic psychoses, it will be easier to demonstrate a cognitive or affective action of ziprasidone.

Drug side effects and human pharmacokinetics

Ziprasidone has no dose-related motor side effects that can be distinguished from placebo, and it produces no weight gain even over time. The latter side-effect advantage may be particularly important in persons with abnormal glucose handling with other drugs. Some akathisia has been noted. Other side effects are benign, except for one. Ziprasidone prolongs the QT interval on ECG by approximately 15 to 20 ms. This prolongation could be associated with torsades de pointes (a ventricular arrhythmia). There was an exhaustive study carried out to document the effect of ziprasidone on cardiac parameters, particularly the QT duration, relative to other antipsychotics and, repeated using metabolic inhibitors. The composite QT prolongation characteristics of the following drugs, thioridazine, ziprasidone, risperidone, quetiapine, olanzapine, and haloperidol, were 36, 16, 8, 6, 4, and -2 ms, respectively.
The study showed that, with a metabolic inhibitor, there was no worsening of this QT prolongation with ziprasidone. Moreover, with a very large clinical database, including several cases of overdose with QT monitoring, showed no increased incidence of adverse events, even all-cause mortality. The increases in QT length are mild and no increase in overall mortality with drug use has been shown. Consequently, despite the QT prolongation, no adverse cardiac events have been linked to ziprasidone. Thus, the drug has been approved by the FDA with minimal restriction and is being successfully marketed. Its freedom from weight gain as a side effect and its potential for antidepressant actions due to its reuptake protein blockade should be advantageous for this antipsychotic.

Pipeline compounds and novel approaches

Many antipsychotic drugs remain in development. Some are pharmacologically similar to current compounds, being potent D_2 dopamine and 5-HT_2 serotonin receptor antagonists. Despite pharmacological similarities, clinical activity differences in efficacy and particularly in side-effect profiles do become apparent with clinical use. Consequently, there still exists room for new or second-generation antipsychotic drug development.
However, drugs acting through novel mechanisms to produce a putative antipsychotic action are also being developed and tested. Aripiprazole (a partial dopamine agonist) has been shown to have equivalent efficacy to other antipsychotics and has a more benign side-effect profile than D_2 blockers. Iloperidone and sertindole are being prepared for regulatory review. OSU6162 and ACR-16 are two chemical congeners of each other developed by Arvid Carlsson and called dopaminergic "stabilizers" because they reduce dopaminergic function when elevated and elevate dopaminergic function in hypodopamine situations.
Moreover, in some categories (glutamatergic drugs, nicotinic agonists, muscarinic-1 antagonists, and metabotropic agents), glutamatergic antipsychotic drug strategies are being subjected to evaluation first in animal models, and then in human studies. Clinicians look forward to having novel antipsychotics potentially targeted at disease pathophysiology.

Summary and conclusions

The state of therapeutic agents for psychosis is broad today and rather full of opportunity for patients. Whereas there was a long "dry" period in drug development for psychosis throughout the whole of the 1980s, research and development laboratories have turned their attention to entirely more creative antipsychotic strategies. Suddenly, a wave of new second-generation drugs were able to stand up to clinical development and now clinicians have several at least equally efficacious treatments with far fewer side effects. Even now, new ideas and hypotheses exist for drug treatment of chronic psychosis, promising a hopeful future. ❑

Tratamientos para las psicosis crónicas

La psicosis es una condición mental que se caracteriza por alucinaciones, delirios y trastornos del pensamiento e incluye varios cuadros clínicos que responden a estrategias terapéuticas similares. Hasta la fecha la psicosis no tiene descrita completamente una patología tisular; sin embargo, está bien identificada y evaluada sintomáticamente. La primera generación de fármacos antipsicóticos fue desarrollada a mediados del siglo XX. La segunda generación de fármacos apareció en la década de los '90. Este nuevo grupo de fármacos antipsicóticos tiene acciones terapéuticas potentes sobre los síntomas positivos de la psicosis con bastantes menos efectos secundarios, especialmente a nivel motor. Sin embargo, cada uno de los nuevos fármacos tiene sus propias características clínicas y farmacológicas que afectan la respuesta individual de los pacientes. La comprensión de estas características individuales de los fármacos puede facilitar una elección óptima de ellos y su utilización en casos de psicosis crónicas.

Traitement de la psychose chronique

La psychose est une maladie psychique caractérisée par la présence d'hallucinations, d'idées délirantes, et de perturbations de la pensée. Le terme de psychose recouvre toute une gamme d'entités diagnostiques qui répondent à des approches thérapeutiques similaires. Aucun stigmate organique n'a pu être décrit de façon définitive pour cette maladie, dont le diagnostic et l'évaluation du degré de sévérité reposent encore uniquement sur des critères symptomatiques. La première génération de médicaments antipsychotiques a vu le jour vers le milieu du XX^{e} siècle, suivie d'une seconde génération dans les années 90. Ce nouveau groupe de substances antipsychotiques est doté d'effets thérapeutiques puissants vis-à-vis des symptômes positifs de la psychose, tout en bénéficiant d'effets secondaires moins nombreux, en particulier en ce qui concerne ceux relatifs à la motricité. Chacun de ces nouveaux produits n'en possède pas moins ses particularités cliniques et pharmacologiques qui influent sur la réponse individuelle des patients au traitement. Une bonne connaissance de ces particularités permettra de déterminer de façon optimale quel médicament choisir et comment le prescrire dans le cadre de la psychose chronique.

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