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The novel antipsychotic drugs

More than 40 years ago, the first effective antipsychotic drugs were introduced, beginning a revolution in the treatment of schizophrenia and other psychotic disorders. These drugs, still known as "conventional" or "typical" antipsychotics, suppress delusions and hallucinations and greatly reduce the risk of bizarre and destructive behavior. Because of drug treatment, today most schizophrenic patients can avoid being confined to psychiatric hospitals for their protection or for treatment.

But the conventional drugs are unsatisfactory in many ways. They have serious limitations and side effects, and most people who take them remain unable to lead normal lives. So some patients, families, and physicians were hoping for a second revolution when a new class of antipsychotic medications came into use a little more than 10 years ago. The new drugs apparently had less serious side effects and might help some patients who did not respond to the older medications.

Five of these second-generation drugs are now available in the United States: clozapine, risperidone, olanzapine, quetiapine, and ziprasidone (*see table, page 5*). They are still called "novel" or "atypical" drugs, although they have been available so long and are so widely used that neither of these adjectives is entirely accurate. Almost everyone regards the new drugs as an improvement on the old ones, but they have drawbacks of their own and seem unlikely to generate that second revolution.

Side effects

Patients often pay a high price in side effects for the relief provided by conventional antipsychotics. They may become drowsy and constipated. Their mouths may become uncomfortably dry and their vision blurred. They may become dizzy and fall when they move from a lying or sitting to a standing position because of blood rushing away from the head (orthostatic hypotension). Most of these drugs also raise levels of the hormone prolactin, which can cause breast development in men, disturbances of the menstrual cycle in women, inappropriate production of breast milk, and sexual problems in both sexes.

The most serious side effect of conventional antipsychotics is difficulty in coordinating body movements. An early problem is extrapyramidal symptoms, so called because of the brain system involved. These are of three kinds:

- **Acute dystonia:** twitching, muscle spasms
- **Parkinsonism:** trembling and muscle rigidity resembling Parkinson's disease—stiff posture, hesitant arm and leg movements, a shuffling walk, an expressionless face
- **Akathisia:** an irresistible feeling of restlessness that causes fidgeting and pacing

These symptoms, especially akathisia, can make patients so uncomfortable that they stop taking the drug. The solution is to lower the dose, which can raise the risk of psychosis, or prescribe antiparkinsonian medications such as benztropine (Cogentin), which don't always work and have side effects of their own.

Extrapyramidal symptoms often go away after a few months, but then another movement disorder may appear—tardive ("belated") dyskinesia. Its symptoms include sucking motions, grimacing, lip-smacking, and jerky and writhing (choreoathetoid) movements of the neck and arms. About one third of patients in long-term treatment with conventional antipsychotics develop at least a mild form of tardive dyskinesia. In severe cases, it can be disfiguring or socially incapacitating. It often persists even when the patient stops taking the drug. There is no reliable treatment.

Novel drugs

Side effects are not the only reason for dissatisfaction with conventional drugs. Sadly, they are of little use in treating some of the most important schizophrenic symptoms. "Positive" symptoms—delusions, hallucinations, and chaotic thinking—usually succumb to the drugs. "Negative" or "deficit" symptoms, often

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Antipsychotic drugs

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more persistent and disabling, do not respond. These deficits include lack of energy and initiative, emotional inexpressiveness and unresponsiveness, social withdrawal, limited speech, slowed thought processes, and apparent inability to feel pleasure.

One advantage of the novel drugs was obvious from the start: they rarely caused movement disorders. Later it appeared that they gave patients some relief from negative symptoms, and it looked as though they might be helpful for the 20%–30% who did not respond to conventional drugs or could not tolerate their side effects. The promise has been partly fulfilled, but the novel drugs also have serious side effects, and now experts are questioning how much more effective they are.

Novel drugs: side effects

Weight gain (see *Harvard Mental Health Letter,* December 2000) may be the most serious drawback of the novel drugs (ziprasidone is a possible exception, although information on that recently introduced drug is limited). Like the extrapyramidal symptoms caused by the older drugs, weight gain is a serious side effect that portends even more serious long-term consequences. And like extrapyramidal symptoms, it can make people stop using the drug and relapse.

Patients taking clozapine, olanzapine, or risperidone may put on as much as a pound a week in the first two months — the equivalent of consuming 500 extra calories a day. Weight gain may slow after that, but it doesn't stop. In one study, patients on olanzapine gained 26 pounds in a year. More than half of people who continue to take these drugs become obese — 20% or more above the healthy weight range. The resulting problems are familiar: arthritis, high blood pressure, coronary artery disease, strokes, and some cancers. (Patients also gain weight on conventional antipsychotics, but usually not nearly as much.)

One of the most dangerous consequences of obesity is Type 2 diabetes, in which the body becomes resistant to insulin, and loses the capacity to control blood sugar levels. The ensuing circulatory problems may cause kidney failure, heart disease, stroke, blindness, or limb damage requiring amputation. Most people with Type 2 diabetes eventually need to take insulin shots. In a Veterans Administration study of nearly 40,000 schizophrenic patients reported this year, researchers found a significantly higher rate of diabetes among those under age 60 — and especially among those under 40 — if they were taking one of the novel drugs. In another study, nearly 40% of patients taking clozapine for five years developed diabetes.

Independent of weight gain, these drugs may alter blood sugar regulation. Several can cause ketoacidosis, an acute condition that arises when insulin is so inefective that the body can't break down fats. Fats accumulate in the blood, causing high blood pressure, dehydration, nausea, and sometimes a coma.

Making the comparison

Several advantages are claimed for the novel drugs. They have fewer short-term side effects and do more to relieve negative symptoms, improving patients' judgment and initiative. Therefore patients are more likely to continue taking the drugs and less likely to relapse. And because they suffer less from side effects and negative symptoms and relapse less often, they will have a better overall quality of life.

The evidence confirms some of these claims, although not always strongly. For example, in a 1998 study, 40% of patients taking haloperidol and only 25% of those taking risperidone relapsed within a year. A 1999 meta-analysis of 30 clinical trials of clozapine (mostly short-

term) indicated that it was modestly more effective than conventional drugs in relieving symptoms and preventing relapse. Most studies did not measure patients' quality of life or social functioning, but those that did showed little advantage for clozapine.

As research accumulates, the advantages of the new drugs sometimes seem less impressive. In a meta-analysis of 52 clinical trials involving more than 12,000 patients, four novel antipsychotic drugs (all except ziprasidone) were compared with conventional drugs, mainly haloperidol and chlorpromazine (Thorazine). Clozapine and olanzapine, although not risperidone and quetiapine, produced a statistically greater improvement in symptoms and lower treatment dropout rates than conventional drugs. But the differences were modest. Few studies lasted longer than three months, and the ones that did gave inconsistent results. In trials that used a low dose of conventional drugs, novel drugs had no advantage.

In a recent study based on pharmacy records, researchers found that in the first six months, patients taking novel antipsychotic drugs went without medication for an average of four days a month, compared with seven days a month for those taking conventional drugs. But after a year the difference had disappeared, and those taking the novel drugs were actually more likely to need hospitalization.

One of the latest studies, published this year, compared clozapine, olanzapine, and risperidone with haloperidol in a three-month clinical trial. The novel drugs were somewhat superior, but the authors dismiss the difference as "slight and debatable." That debate continues.

Although it's hardly the only way to judge the value of a drug, a calculation of economic costs and benefits can provide some guidance. The novel drugs cost more, and clozapine, possibly the most effective, is especially expensive because it requires frequent periodic blood tests. In compensation, patients are less likely to need hospitalization. The balance probably favors novel drugs. Canadian researchers found that switching from a conventional drug to risperidone reduced the number of hospital admissions by 60% and saved nearly $5,000 per patient per year. But another study indicated that for patients who are rarely hospitalized, clozapine cost an extra $2,300 per patient per year. No studies have factored in the long-term costs of obesity and diabetes. This debate, too, will continue.

New directions

The average time between a person's first psychotic symptoms and the first use of antipsychotic drugs is a year. That delay may slow recovery and make the long-term prognosis worse. After prolonged or repeated psychotic episodes, a satisfactory personal and social life becomes increasingly difficult to recover, and each psychotic episode may heighten the brain's vulnerability to further psychosis and deterioration. So most psychiatrists believe antipsychotic drug treatment should begin as early as possible.

But physicians have been reluctant to prescribe conventional drugs at the earliest sign of psychotic illness, because they are concerned about movement disorders. They do not want to risk irreversible tardive dyskinesia in a person who may not even be schizophrenic. The novel drugs, of course, do not present that risk to the same extent. Patients undergoing a first episode of schizophrenia also seem to tolerate the novel drugs better and are less likely to stop taking them. Some researchers have begun to give the drugs on an experimental basis to genetically vulnerable kin of schizophrenic patients who show what may be early signs of the disorder.

The oldest of the novel drugs has been available in the United States for only 12 years. Medical researchers still have a great deal to learn about them — for example, how long they will remain effective, and which types of schizophrenia and schizophrenic patients will respond best. More long-term studies and more careful comparisons between novel and conventional drugs are needed. Meanwhile, the novel drugs will probably go on gradually replacing their rivals on prescription pads and pharmacy shelves — not a revolutionary but an evolutionary change in the treatment of schizophrenia.

References

Buckley, P. F. "New Antipsychotic Agents: Emerging Clinical Profiles," *Journal of Clinical Psychiatry* (1999): Vol. 60, Suppl. 1, pp.12–17.

Keefe, R.S.E., et al. "Do Novel Antipsychotics Improve Cognition? A Report of a Meta-Analysis," *Psychiatric Annals* (November 1999): Vol. 29, No. 11, pp. 623–29.

Kramer, T. "The Dopamine System Stabilizers," *Medscape Psychiatry & Mental Health Journal* (2002): Vol. 7 No. 1.

McEvoy, J.P. et al. "The Expert Consensus Guideline Series: Treatment of Schizophrenia," *Journal of Clinical Psychiatry* (1999): Vol. 60, Suppl. 11.

Richelson, R. "Receptor Pharmacology of Neuroleptics: Relation to Clinical Effects," *Journal of Clinical Psychiatry* (1999), Vol. 60, Suppl. 10, pp. 5–14.

Volavka, J. et al. "Clozapine, Olanzapine, Risperidone, and Haloperidol in the Treatment of Patients with Chronic Schizophrenia and Schizoaffective Disorder," *American Journal of Psychiatry* (February 2002): Vol. 159, No. 2, pp. 255–62.

Wahlbeck, K. et al. "Evidence of Clozapine's Effectiveness in Schizophrenia: A Systematic Review and Meta-Analysis of Randomized Trials," *American Journal of Psychiatry* (July 1999): Vol. 156, No. 7, pp. 990–99.

How antipsychotic drugs work

Conventional and novel antipsychotics work differently. The older drugs are dopamine antagonists, occupying and blocking the dopamine D2 receptor, a docking site on nerve cells for the neurotransmitter dopamine. Reducing dopamine has a therapeutic effect in the brain's limbic system, which governs emotional responses. (People with schizophrenia may have an excess of dopamine D2 receptors in that region.) The same blocking action in the extrapyramidal system, part of a circuit controlling body movements, causes parkinsonism and tardive dyskinesia.

The novel drugs have a much lower affinity for the dopamine D2 receptor, which explains why they don't cause extrapyramidal symptoms. How they relieve psychotic symptoms is less clear. Their actions vary, targeting other dopamine receptors as well as serotonin, norepinephrine, and other neurotransmitters. The effects of clozapine, in particular, are scattered among several types of receptors.

All of the novel drugs act much more strongly at a serotonin receptor site, the 5HT2 receptor, than at dopamine receptors. Some scientists think that explains their therapeutic powers. The theory is that the drugs keep dopamine activity within a normal range. When serotonin receptors are blocked, neurons elsewhere in the brain release more dopamine. Dopamine receptors adjust by responding less, and that causes other neurons to release serotonin. Serotonin receptors adjust in turn, and eventually, if all goes well, the system settles into a stable balance.

Another way to moderate the effects of dopamine is to occupy receptors with a drug that displaces the neurotransmitter while performing a weak imitation of its effects. This kind of drug is called an agonist-antagonist or partial agonist. If dopamine levels are high, it functions as an antagonist—a less active substitute that excludes dopamine. If dopamine levels are low, it serves as the opposite, an agonist, because it has some dopamine-like activity.

When a conventional antagonist blocks dopamine receptors, neurons that release dopamine immediately begin to produce more in order to compensate. Eventually they slow production, creating a new balance with just enough dopamine activity. But this balance takes time to establish and is not always stable. In the extrapyramidal system, a nearly total dopamine blockade may continue, causing movement disorders.

A partial agonist does not create that problem, because of its own dopamine-like activity. And when it occupies receptors, neurons that release dopamine do not immediately produce more, because there is less need to compensate. In theory, the system can stabilize at a lower level more quickly and reliably.

A new class of antipsychotic drugs is based on this principle, and the first of these drugs, aripiprazole, will probably win FDA approval next year. So far, it seems to be about as effective as the older novel drugs and may have fewer side effects — no weight gain, for example. But the risks and benefits of partial agonists will not become clear until more patients have taken them for longer periods of time.

New approaches to treating psychosis

Medical researchers looking for better ways to treat negative symptoms are considering new possibilities. Glutamate is the brain's chief excitatory neurotransmitter, the messenger that directs neurons to continue propagating a nerve impulse. It acts in the main pathways that connect the seat of thinking and planning in the cerebral cortex to the centers of emotion and memory in the limbic system and temporal lobes.

According to one theory, the brain malfunction in schizophrenia originates in this pathway, when receptors for glutamate malfunction. One result is the negative or deficit schizophrenic symptoms. Another result is excessive dopamine activity in the limbic region, which causes the delusions and hallucinations suppressed by today's antipsychotic drugs. The psychotic symptoms, then, are not fundamental to schizophrenia but only a particularly painful and troublesome byproduct of the disorder. As one piece of evidence for this theory, today's drugs are not specific treatments for schizophrenia. They curb psychotic symptoms and calm agitation from many causes, including mania, dementia, and drug-induced psychoses.

If this picture is right, attacking schizophrenia at its origin in the cerebral cortex would relieve negative as well as positive symptoms and revolutionize the lives of schizophrenic patients. But indiscriminate glutamate activity would only flood nerve cells and poison them. Instead, scientists are looking for drugs that act selectively at particular glutamate receptors. They are especially interested in a type of receptor that works in coordination with another neurochemical, N-methyl-D-aspartate (NMDA). Some researchers have tried to treat schizophrenic symptoms by stimulating glutamate to activate NMDA receptors. They have seen some improvement in a few experiments. Although practical use of such findings is a long way off, they may represent the future of research on the treatment of schizophrenia.

Antipsychotic drugs: The pros and cons

Drug	Advantages	Side Effects
Conventional (more than 20 drugs)	• Well known. Proven effective for positive symptoms • Cause less weight gain and diabetes than novel drugs • Some can be injected for gradual absorption with effects lasting up to a month	• Constipation, dry mouth, blurred vision, dizziness • Movement disorders • Rise in prolactin levels • Little effect on negative symptoms
Clozapine (Clozaril), approved 1990	• May be most effective, especially for negative symptoms and cognitive deficiencies • Does not raise prolactin levels • Does not cause movement disorders • May lower the risk of alcohol and drug abuse	• Agranulocytosis[1] (in at least 1% of patients) • Drowsiness, dizziness, drooling • Seizures (in 1%–5% of patients) • Muscle weakness • Weight gain • Diabetes • Rapid withdrawal may lead to psychosis
Risperidone (Risperdal), approved 1993	• Probably outperforms conventional drugs • No seizures or drooling • Movement disorders uncommon	• Dizziness, drowsiness, dry mouth, rapid heartbeat • Some movement disorders at high doses • Weight gain • Diabetes
Olanzapine (Zyprexa), approved 1996	• Probably outperforms conventional antipsychotics • Overall low rate of side effects • Does not raise levels of prolactin • No seizures or drooling • Movement disorders uncommon • Can be injected for gradual absorption with effects lasting up to a month	• Dizziness, drowsiness, dry mouth • Substantial weight gain • Diabetes
Quetiapine (Seroquel), approved 1997	• Similar to risperidone and olanzapine, but little risk of dry mouth or dizziness	• Drowsiness • Substantial weight gain • Diabetes • Occasional movement disorders • See note below[2]
Ziprasidone (Geodon), approved 2001	• No movement disorders • Apparently little weight gain (more data needed) • May be helpful for depression and anxiety	• Headaches, nausea, drowsiness, dizziness, rash • See note below[3]

Notes

[1] Agranulocytosis is a drastic fall in the white blood cell count that creates a risk of fatal infection. White cell count returns to normal in 2–3 weeks when the drug is withdrawn. FDA requires weekly blood tests that considerably raise cost and inconvenience. Clozapine is usually recommended only for patients who have not responded to at least two other antipsychotic drugs.

[2] Cataracts have been reported when quetiapine is given to animals at high doses, and the manufacturer recommends periodic eye examinations. So far no cataracts have developed in human beings.

[3] Ziprasidone can slow electrical conduction through the heart. For most patients, this is not a problem. Heart monitoring by electrocardiogram is recommended for older patients and those with heart disease or a family history of sudden heart attack death.