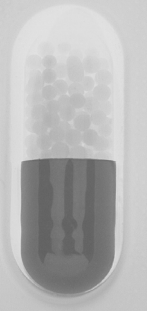


Second-Generation Antipsychotics



Abilify (aripiprazole)
Clozaril (clozapine)
Geodon (ziprasidone)
Risperdal and Risperdal Consta (risperidone)
Seroquel (quetiapine)
Symbyax (Zyprexa [olanzapine] and Prozac [fluoxetine] combination)
Zyprexa and Zyprexa Zydis (olanzapine)

The **second-generation antipsychotics**, also commonly known as *atypical* antipsychotics, are among the most significant medicines developed in the past decade for the treatment of severe mental disorders such as schizophrenia, schizoaffective disorder, and mania. These agents are *atypical* because they are significantly different, both in structure and pharmacology, from the older, *typical* antipsychotic medications such as Thorazine (chlorpromazine), Mellaril (thioridazine), and Haldol (haloperidol). Having multiple mechanisms of action in the brain, the second-generation antipsychotics have wider applications than just for the treatment the “positive” symptoms of psychosis (e.g., hallucinations, delusions, bizarre behavior, disorganized speech). These medicines have proven to be highly effective for treating **negative symptoms** of schizophrenia, which are characterized by emotional and social withdrawal, flat affect, lack of spontaneity, inability to feel pleasure, attention impairment, and other restrictions in thought, speech, and behavior. Several of these new antipsychotic medications have been approved by the U.S. Food and Drug Administration (FDA) for treating acute mania (Geodon, Risperdal, Seroquel, and Zyprexa), and Abilify will soon follow. Zyprexa (olanzapine) has also been indicated for long-term treatment (maintenance treatment) of bipolar disorder. Thus most clinicians view second-generation antipsychotics not merely as antipsychotic medications but also as **psychotropic agents**, which are effective in treating a wide spectrum of mental disorders.

Clozaril (clozapine), the oldest of the second-generation antipsychotics, has been in use in Europe for more than 30 years. At one time, Clozaril held great promise for treatment of schizophrenia, but that hope was dashed when the drug was reported in the mid-1970s to cause **agranulocytosis**, a life-threatening condition in which white blood cells are fatally diminished. When deaths were reported from Clozaril-induced agranulocytosis, the drug was withdrawn from general use. Clozaril was not made available in the United States until the late 1980s, but the FDA restricted its use, requiring close monitoring conditions and reserving the drug for treatment-resistant schizophrenia unresponsive to conventional antipsychotics. Clozaril was the prototype of the second-generation antipsychotics, and the renewed interest in such agents spurred the development of new antipsychotic agents with similar properties but without the risk of agranulocytosis. In a little more than a decade after the introduction of Clozaril in this country, Risperdal, Zyprexa, Seroquel, Geodon, and Abilify were developed.

How Antipsychotics Work

How antipsychotic drugs work may be explained by the *dopamine receptor antagonist hypothesis*. **Dopamine** is a *neurotransmitter*, a chemical produced by brain cells (neurons) that enables neurons to communicate with each other. Dopamine is released by one neuron into the space between that neuron and the next neuron and attaches to specific surface sites on the next neuron called **receptors**. The interaction of the neurotransmitter on the receptors results in very specialized activities coded in the neuron, and it ultimately generates an electrical impulse that is transmitted down the nerve cell. At the end of the nerve terminal, the electrical impulse effects further release of dopamine, and the process continues. This form of communication between neurons is called **neurotransmission**. In specific areas of the brain, excessive dopamine neurotransmission may produce the psychotic symptoms (e.g., hallucinations, delusions, bizarre behavior) characteristic of schizophrenia and more severe cases of bipolar disorder. Drugs such as amphetamine and cocaine, for example, are known to increase dopamine release. In excessive amounts, these drugs induce psychotic symptoms not unlike schizophrenia.

Psychotic symptoms commonly seen in schizophrenia and other mental disorders, such as bipolar disorder, dementia, and drug-induced psychosis, include delusions, hallucinations, disorganized speech, and bizarre, agitated, or catatonic behavior. These symptoms are also commonly called the **positive symptoms of psychosis** due to the excessive and overt nature of their clinical presentation.

Antipsychotics work principally by blocking, or antagonizing, the action of dopamine at its receptors, decreasing the chemical signals that drive such psychotic behavior. In effect, antipsychotics decrease neurotransmission by blocking dopamine from binding to the receptors. Excessive dopamine activity in selected areas of the brain may be the underlying cause of psychosis. Both conventional and second-generation antipsychotics are dopamine antagonists and are therefore effective in treating positive symptoms. In areas of the brain where antipsychotics have no therapeutic benefits, they may induce side effects.

There is a significant difference between the second-generation antipsychotics and the conventional antipsychotics in that the former also block the receptors of another neurotransmitter, **serotonin**. The action of serotonin is closely coupled with dopamine, and it has important influences on dopamine release in different areas of the brain. Serotonin antagonism is the defining feature of the second-generation antipsychotics and is the most important property that distinguishes these agents from conventional antipsychotics. In addition, the second-generation antipsychotics have low propensity to induce **extrapyramidal symptoms** (EPS) and have efficacy for negative symptoms. The second-generation antipsychotics are sometimes called **serotonin-dopamine antagonists**.

Advantages of the Second-Generation Antipsychotics

In the past decade, second-generation antipsychotics have essentially replaced the older, conventional antipsychotics. The primary reason for this is that the second-generation antipsychotics are much better tolerated than their older counterparts. The second-generation agents are associated with a substantially lower risk of EPS and **tardive dyskinesia** (TD). EPS are acute-onset movement disorders characterized by muscular rigidity, tremors, shuffling movement, restlessness, and muscle spasms resulting in abnormal posture. TD is a delayed-onset condition that consists of abnormal involuntary movements usually involving the tongue and mouth and sometimes the arms and trunk. EPS and TD are substantial risks with conventional antipsychotics. Patients frequently cannot, and will not, tolerate the side effects of antipsychotics, and this becomes problematic if long-term treatment is needed. With their more favorable side effect profile, the newer antipsychotics are better tolerated, and patients are more likely to take them consistently.

The other distinguishing advantage of the second-generation antipsychotics is that they are superior in treating negative symptoms. In areas of the brain where emotion and cognition are affected by the balance of serotonin and dopamine, the dual action of the second-generation agents resets this important balance when it has been altered. In patients with mental disorders such as schizophrenia, the balance of these neurotransmitters is disturbed, and patients may manifest negative symptoms.

For more information about a particular second-generation antipsychotic medication, refer to the hand-out for that medication.