**Antipsychotic Drugs**

**I. OVERVIEW**

The antipsychotic drugs (also called neuroleptics or major tranquilizers) are used primarily to treat schizophrenia, but they are also effective in other psychotic states, including manic states with psychotic symptoms such as grandiosity, paranoia, and hallucinations, and delirium. The use of antipsychotic medications involves a difficult trade-off between the benefit of alleviating psychotic symptoms and the risk of wide variety of troubling adverse effects. Antipsychotic drugs are not curative and do not eliminate the chronic thought disorder, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment.

**II. SCHIZOPHRENIA**

Schizophrenia is a particular type of psychosis (that is, a mental disorder caused by some inherent dysfunction of the brain). It is characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances. This mental disorder is a common affliction, occurring in about 1 percent of the population. The illness often initially affects people during late adolescence or early adulthood and is a chronic and disabling disorder. Schizophrenia has a strong genetic component and probably reflects some fundamental biochemical abnormality, possibly a dysfunction of the mesolimbic or mesocortical dopaminergic neuronal pathways.

**III. ANTIPSYCHOTIC DRUGS**

The antipsychotic drugs are divided into first- and second-generation agents. The first-generation drugs are further classified as “low-potency” or “high-potency,” not to indicate the drugs’ clinical effectiveness, but rather to indicate their affinity for the dopamine D2 receptor, which, in turn, influences the adverse effect profile of the drug.

1. **First-generation antipsychotics**

The first-generation antipsychotic drugs (also called conventional, typical, or traditional antipsychotics) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competi- tive blocking of D2 dopamine receptors. First-generation antipsy- chotics are more likely to be associated with movement disorders, particularly for drugs that bind tightly to dopaminergic neurorecep tors, such as haloperidol, and less true of medications that bind weakly, such as chlorpromazine. No one drug is clinically more effective than another.

1. **Second-generation antipsychotic drugs**

The second generation antipsychotic drugs (also referred to as “atypi- cal” antipsychotics) have fewer extrapyramidal symptoms (EPS) than the first-generation agents, but are associated with a higher risk of met- abolic side effects, such as diabetes, hypercholesterolemia, and weight gain. The second-generation drugs appear to owe their unique activ- ity to blockade of both serotonin and dopamine (and, perhaps, other) receptors.

**1. Drug selection:** Current antipsychotic therapy commonly comprises second-generation agents to minimize the risk of debilitating move- ment disorders associated with the first-generation drugs that act primarily at the D2 dopamine receptor. All of the second-generation antipsychotics exhibit an efficacy that is equivalent to, and occa- sionally exceeds, that of the first-generation antipsychotic agents. However, consistent differences in therapeutic efficacy among the individual second-generation drugs have not been established, and individual patient response and comorbid conditions must often be used as a guide in drug selection. Further, second-generation antipsychotics should not be considered interchangeable because patients may respond differently to each drug in this class.

**2. Refractory patients**: Approximately 20% of patients with schizo- phrenia will have an insufficient response to all first- and second- generation antipsychotics. For these patients, clozapine has shown to be an effective antipsychotic with minimal risk of EPS. However, its clinical use is limited to refractory patients because of serious side effects. Clozapine can produce bone marrow suppression, seizures, and cardiovascular side effects. The risk of severe agranulocytosis necessitates frequent monitoring of white blood cell counts.

**C. Mechanism of action**

**1. Dopamine receptor–blocking activity in the** brain: All of the first- generation and most of the second-generation antipsychotic drugs block dopamine receptors in the brain and the periphery (Figure 13.2). The clinical efficacy of the typical antipsychotic drugs correlates closely with their relative ability to block D2 receptors in the mesolim- bic system of the brain. The actions of the antipsychotic drugs are antagonized by agents that raise synaptic dopamine concentrations (for example, levodopa and amphetamines) or mimic dopamine at post-synaptic binding sites (for example, bromocriptine).

**2. Serotonin receptor–blocking activity in the brain**: Most of the second-generation agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly 5-HT2A receptors. Thus, clozapine has high affinity for D1, D4, 5-HT2, muscarinic, and α-adrenergic receptors, but it is also a weak dop- amine D2-receptor antagonist (Figure 13.3). Risperidone [ris-PEAR-ih- dohn] blocks 5-HT2A receptors to a greater extent than it does D2 receptors, as does olanzapine [oh-LANZ-ih-peen]. The second-gen- eration antipsychotic aripiprazole [a-rih-PIP-ra-zole] is a partial ago- nist at D2 and 5-HT1A receptors as well as a blocker of 5-HT2A recep- tors. Quetiapine [qwe-TY-ih-peen] blocks D2 receptors more potently than 5HT2A receptors but is relatively weak at blocking either recep- tor, and its low risk for EPS may also be related to the relatively short period of time it binds to the D2 receptor.

**B. Actions**

The antipsychotic actions of antipsychotic drugs appear to refl ect a blockade at dopamine and/or serotonin receptors. However, many of these agents also block cholinergic, adrenergic, and histaminergic receptors (Figure 13.4). It is unknown what role, if any, these actions have in alleviating the symptoms of psychosis. The undesirable side eff ects of these agents, however, are often a result of actions at these other receptors.

1**. Antipsychotic actions**: All of the antipsychotic drugs can reduce the hallucinations and delusions associated with schizophrenia (the so-called “positive” symptoms) by blocking dopamine receptors in the mesolimbic system of the brain. The “negative” symptoms, such as blunted aff ect, anhedonia (not getting pleasure from nor- mally pleasurable stimuli), apathy, and impaired attention, as well as cognitive impairment, are not as responsive to therapy, particu- larly with the fi rst-generation antipsychotics. Many second-genera- tion agents, such as clozapine, ameliorate the negative symptoms to some extent. All of the drugs also have a calming eff ect and reduce spontaneous physical movement. In contrast to the central nervous system (CNS) depressants, such as barbiturates, the antipsychotics do not depress the intellectual functioning of the patient as much, and motor coordination diffi culties are minimal. The antipsychotic eff ects usually take several days to weeks to occur, suggesting that the therapeutic eff ects are related to secondary changes in the cor- ticostriatal pathways.

2. **Extrapyramidal eff ects**: Dystonias (sustained contraction of muscles leading to twisting, distorted postures), Parkinson-like symptoms, akathisia (motor restlessness), and tardive dyskinesia (involuntary movements of the tongue, lips, neck, trunk, and limbs) occur with chronic treatment. Blocking of dopamine receptors in the nigrostriatal pathway probably causes these unwanted movement symptoms. The second-generation antipsychotics exhibit a lower incidence of these symptoms.

3. **Antiemetic eff ects**: With the exception of aripiprazole, most of the antipsychotic drugs have antiemetic eff ects that are mediated by blocking D2-dopaminergic receptors of the chemoreceptor trigger zone of the medulla. (See p. 357 for a discussion of emesis.) Figure 13.5 summarizes the antiemetic uses of antipsychotic agents, along with the therapeutic applications of other drugs that combat nau- sea. [Note: The second-generation antipsychotic drugs are not used as antiemetics.]

4. **Anticholinergic eff ects:** Some of the antipsychotics, particularly thi- oridazine, chlorpromazine, clozapine, and olanzapine, produce anti- cholinergic eff ects, including blurred vision; dry mouth (the excep- tion is clozapine, which increases salivation); confusion; and inhibi- tion of gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention. This anticholinergic property may actually assist in reducing the risk of EPS with these agents.

5. **Other eff ects:** Blockade of α-adrenergic receptors causes ortho- static hypotension and light-headedness. The antipsychotics also alter temperature-regulating mechanisms and can produce poikilo- thermia (condition in which body temperature varies with the envi- ronment). In the pituitary, antipsychotics block D2 receptors, leading to an increase in prolactin release. Second-generation antipsychot- ics are less likely to produce prolactin elevations. Sedation occurs with those drugs that are potent antagonists of the H1-histamine receptor, including chlorpromazine, olanzapine, quetiapine, and clo- zapine. Sexual dysfunction may also occur with the antipsychotics due to various receptor-binding characteristics.

C. **Therapeutic uses**

**1. Treatment of schizophrenia**: The antipsychotics are considered to be the only effi cacious treatment for schizophrenia. Not all patients respond, and complete normalization of behavior is seldom achieved. The fi rst-generation antipsychotics are most eff ective in treating positive symptoms of schizophrenia (delusions, hallucina- tions, thought processing, and agitation). The newer agents with 5-HT2A receptor-blocking activity may be eff ective in many patients who are resistant to the traditional agents, especially in treating the negative symptoms of schizophrenia (social withdrawal, blunted emotions, ambivalence, and reduced ability to relate to people). However, even the second-generation antipsychotics do not consis- tently improve the negative symptoms of schizophrenia more than the older agents do.