TABLE 371-14 *Antipsychotic Agents*

Name	Usual PO Daily Dose, mg	Side Effects	Sedation	Comments
TYPICAL ANTIPSYCHOTICS				
Low-potency				
Chlorpromazine (Thorazine)	100–600	Anticholinergic effects; orthostasis; photosensitivity; cholestasis; QT prolongation	+ + +	EPSEs usually not prominent; can cause anticholinergic delirium in elderly patients
Thioridazine (Mellaril)	100–600			
Mid-potency				
Trifluoperazine (Stelazine)	2–15	Fewer anticholinergic side effects; fewer EPSEs than with higher potency agents	+ +	Well tolerated by most patients
Perphenazine (Trilafon)	4–32		+ +	
Loxapine (Loxitane)	20–250	Frequent EPSEs	+ +	
Molindone (Moban)	50–225	Frequent EPSEs	0	Little weight gain
High potency		No anticholinergic side effects; EPSEs often prominent		Often prescribed in doses that are too high; long-acting injectable forms of haloperidol and fluphenazine available
Haloperidol (Haldol)	0.5–10		0/+	
Fluphenazine (Prolixin)	1–10	Frequent EPSEs	0/+	
Thiothixene (Navane)	2–20	Frequent EPSEs	0/+	
NOVEL ANTIPSYCHOTICS				
Clozapine (Clozaril)	200–600	Agranulocytosis (1%); weight gain; seizures; drooling; hyperthermia	+ +	Requires weekly WBC
Risperidone (Risperdal)	2–6	Orthostasis	+	Requires slow titration; EPSEs observed with doses >6 mg qd
Olanzapine (Zyprexa)	10–20	Weight gain	+ +	Mild prolactin elevation
Quetiapine (Seroquel)	350–700	Sedation; weight gain; anxiety	+ + +	Bid dosing
Ziprasidone (Geodon)	40–60	Orthostatic hypotension	+/++	Mimimal weight gain; increases QT interval
Aripiprazole (Abilify)	10–30	Nausea, anxiety, insomnia	0/+	Mixed agonist/ antagonist

Note: EPSEs, extrapyramidal side effects; WBC, white blood count.

etiology. The mechanism of action involves, at least in part, blockade of dopamine receptors in the limbic system and basal ganglia; the clinical potencies of traditional antipsychotic drugs parallel their affinities for the D_2 receptor, and even the newer "atypical" agents exert some degree of D_2 receptor blockade. All neuroleptics induce expression of the immediate-early gene c-*fos* in the nucleus accumbens, a dopaminergic site connecting prefrontal and limbic cortices. The clinical efficacy of newer atypical neuroleptics, however, may involve D_1, D_3, and D_4 receptor blockade, α_1- and α_2-noradrenergic activity, and/or altering the relationship between $5HT_2$ and D_2 receptor activity, as well as faster dissociation of D_2 binding.

Conventional neuroleptics differ in their potency and side-effect profile. Older agents, such as chlorpromazine and thioridazine, are more sedating and anticholinergic and more likely to cause orthostatic hypotension, while higher potency antipsychotics, such as haloperidol, perphenazine, and thiothixene, are more likely to induce extrapyramidal side effects. The model atypical antipsychotic agent is *clozapine*, a dibenzodiazepine that has a greater potency in blocking the $5HT_2$ than the D_2 receptor and a much higher affinity for the D_4 than the D_2 receptor. Its principal disadvantage is a risk of blood dyscrasias. Unlike other antipsychotics, clozapine does not cause a rise in prolactin level. Approximately 30% of patients have a better response to these agents than to traditional neuroleptics, suggesting that they will increasingly displace the older-generation drugs. Clozapine appears to be the most effective member of this class and has demonstrated superiority to other atypical agents in preventing suicide; however, its side-effect profile makes it most appropriate for treatment-resistant cases. *Risperidone*, a benzisoxazole derivative, is more potent at $5HT_2$ than D_2 receptor sites, like clozapine, but it also exerts significant α_2 antagonism, a property that may contribute to its perceived ability to improve mood and increase motor activity. Risperidone is not as effective as clozapine in treatment-resistant cases but does not carry a risk of blood dyscrasias. *Olanzapine* is similar neurochemically to clozapine but has a significant risk of inducing weight gain. *Quetiapine* is distinct in having a weak D_2 effect but potent α_1 and histamine blockade. Ziprasidone causes minimal weight gain and is unlikely to increase prolactin, but may increase QT prolongation. Aripiprazole also has little risk of weight gain or prolactin increase but may increase anxiety, nausea, and insomnia as a result of its partial agonist properties.

Conventional antipsychotic agents are effective in 70% of patients presenting with a first episode. Improvement may be observed within hours or days, but full remission usually requires 6 to 8 weeks. The choice of agent depends principally on the side-effect profile and cost of treatment or on a past personal or family history of a favorable response to the drug in question. Atypical agents appear to be more effective in treating negative symptoms and improving cognitive function. An equivalent treatment response can usually be achieved with relatively low doses of any drug selected, i.e., 4 to 6 mg/d of haloperidol, 10 to 15 mg of olanzapine, or 4 to 6 mg/d of risperidone. Doses in this range result in >80% D_2 receptor blockade, and there is little evidence that higher doses increase either the rapidity or degree of response. Maintenance treatment requires careful attention to the possibility of relapse and monitoring for the development of a movement disorder. Intermittent drug treatment is less effective than regular dosing, but gradual dose reduction is likely to improve social functioning in many schizophrenic patients who have been maintained at high doses. If medications are completely discontinued, however, the relapse rate is 60% within 6 months. Long-acting injectable preparations are considered when noncompliance with oral therapy leads to relapses. In treatment-resistant patients, a transition to clozapine usually results in rapid improvement, but a prolonged delay in response in some cases necessitates a 6- to 9-month trial for maximal benefit to occur.

Antipsychotic medications can cause a broad range of side effects, including lethargy, weight gain, postural hypotension, constipation, and dry mouth. Extrapyramidal symptoms such as dystonia, akathisia, and akinesia are also frequent with traditional agents and may contribute to poor compliance if not specifically addressed. Anticholinergic and parkinsonian symptoms respond well to trihexyphenidyl, 2 mg bid, or benztropine mesylate, 1 to 2 mg bid. Akathisia may respond to beta blockers. In rare cases, more serious and occasionally life-threatening side effects may emerge, including ventricular arrhythmias, gastrointestinal obstruction, retinal pigmentation, obstructive jaundice, and neuroleptic malignant syndrome (characterized by hyperthermia, autonomic dysfunction, muscular rigidity, and elevated creatine phosphokinase levels). The most serious adverse effects of clozapine are agranulocytosis, which has an incidence of 1%, and induction of seizures, which has an incidence of 10%. Weekly white blood cell counts are required, particularly during the first 3 months of treatment.