Antipsychotics

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Introduction

- Antipsychotic drugs = Neuroleptics= Major tranquilizers
- Drugs that are primarily used to treat schizophrenia
- They can also be used for other psychotic states including manic states with psychotic symptoms such as grandiosity, paranoia and hallucinations

Introduction

- Use of antipsychotics involves benefits of alleviating psychotic symptoms and the risk of troubling adverse effects
- Antipsychotic drugs are not curative and do not eliminate the chronic thought disorder
- These drugs decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment

Introduction

- Psychosis: a mental disorder caused by brain dysfunction
- Schizophrenia: Type of chronic psychosis characterized by:
  - Delusions
  - Hallucinations (often in the form of voices)
  - Thinking or speech or behavior disturbances
  - Negative symptoms such as avolition or ambivalence
  - Schizophrenia is a chronic and disabling disorder
  - Occurs in 1% of population
  - It has a genetic component
- Biochemical abnormalities include dysfunction of the mesolimbic or mesocortical dopaminergic neuronal pathways.
- Associated with D2 type of dopamine receptor

Introduction

- The positive symptoms of psychosis include hallucinations, delusions, disorganized speech, and disorganized or agitated behavior.
- These positive psychotic symptoms are found individually, and occasionally together, in all psychotic disorders and are typically responsive to pharmacotherapy.
- Schizophrenia patients also suffer from negative symptoms (apathy, avolition, diminished expression, reduced social drive) and cognitive deficits.

Diagnostic criteria

- At least two of the characteristic symptoms:
  - Delusions
  - Hallucinations
  - Disorganized thoughts and speech
  - Grossly disorganized behavior
  - Negative symptoms (blunted affect, anhedonia, avolition, apathy, social isolation, poor hygiene, poor memory, impaired attention and poor cognition)
- Deterioration in function
- Duration at least 6 months

Antipsychotic drugs

- Affect dopamine by blocking dopamine receptors
- First generation antipsychotics are classified as either:
  - low potency
  - high potency
- This is based on their affinity to dopamine receptors which affects the incidence of side effects

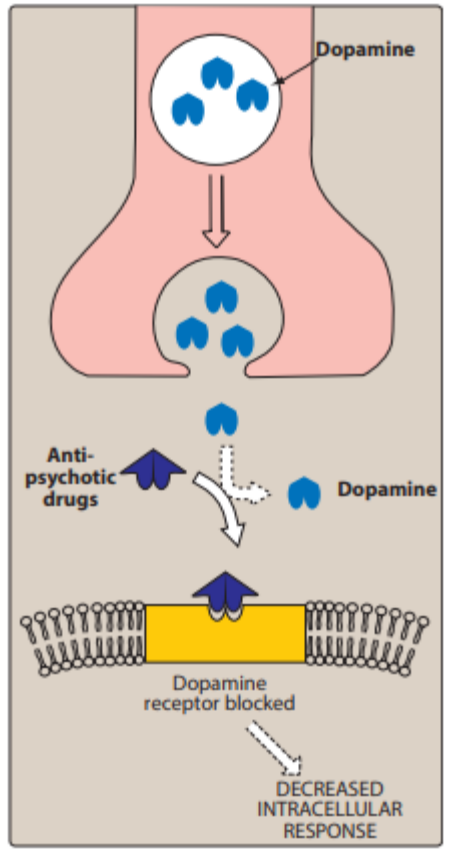


Figure 11.2
Dopamine-blocking actions of antipsychotic drugs.

Antipsychotic drugs

- Low potency
  - Chlorpromazine
  - Thioridazine
- High potency
  - Haloperidol
  - Fluphenazine
  - Loxapine
  - Perphenazine
  - Pimozide
  - Prochlorperazine
  - Thiothixene
  - Trifulperazine

First generation antipsychotics

- Also called conventional, typical or traditional antipsychotics
- Competitive blockers of D2 receptors
- Associated with movement disorders, especially the ones with stronger binding to dopamine receptors
- No drug is clinically more effective than the other

Second generation antipsychotics

- Aripiprazole
- Brexpiprazole
- Lurasidone
- Paliperidone
- Iloperidone
- Risperidone
- Ziprasidone
- Asenapine
- Cariprazine
- Olanzapine
- Pimavanserin
- Quetiapine
- Clozapine

Second generation antipsychotics

- Preferred to minimize the risk of debilitating movement disorders associated with first generation
- Efficacy is equivalent to and occasionally exceeds, that of the first-generation
- No differences in therapeutic efficacy among second- generation drugs
- Individual patient response and comorbid conditions must often be considered in drug selection
- Second-generation antipsychotics are not interchangeable because patients may respond differently to each drug

Second generation antipsychotics

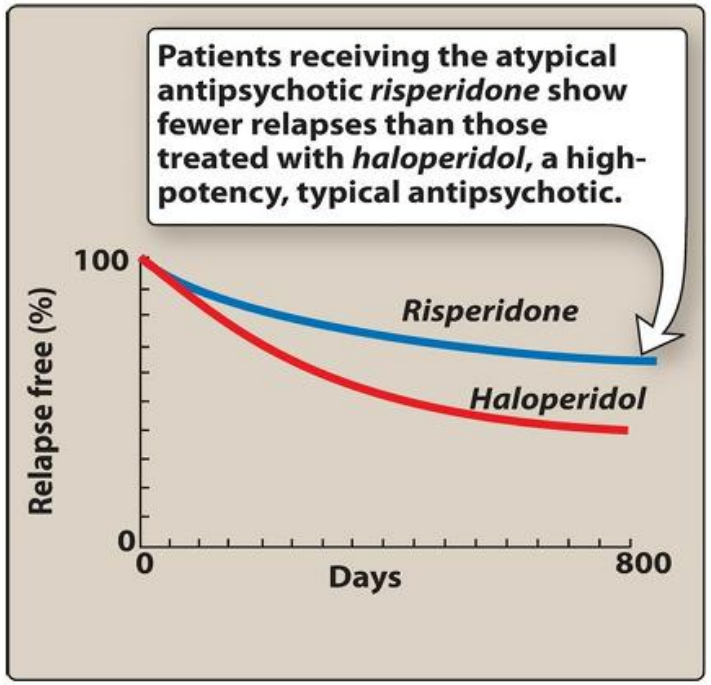


Figure 11.7 Rates of relapse among patients with schizophrenia after maintenance therapy with either *risperidone* or *haloperidol*.

Second generation antipsychotics

- 20% of patients with schizophrenia will have an insufficient response to all first- and second generation antipsychotics and clozapine has shown to be effective for these patients
- **Clozapine** use is limited to refractory patients because of serious side effects:
  - Bone marrow suppression
    - frequent monitoring of white blood cell counts is required due to risk of severe agranulocytosis
  - Seizures
  - Cardiovascular side effects
  - Constipation that can progress to severe bowel complications

Second generation antipsychotics

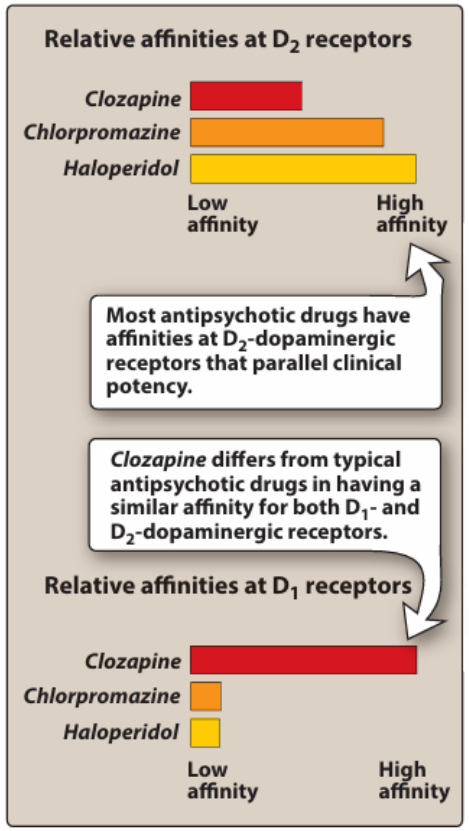


Figure 11.3
Relative affinity of *clozapine*, *chlorpromazine*, and *haloperidol* at D_1 and D_2 dopaminergic receptors.

Second generation antipsychotics

- Also referred to as atypical antipsychotics
- Have fewer EPS than first generation drugs
- Associated with a higher risk of metabolic side effects like diabetes, hypercholesterolemia and weight gain
- Block both dopamine and serotonin receptors

Antipsychotics: actions

- The antipsychotic actions are due to **blockade at dopamine and/or serotonin receptors**
- Many of these agents also **block cholinergic, adrenergic, and histaminergic receptors** causing adverse effects
    - Antipsychotic actions
    - Extrapyramidal effects
    - Antiemetic effects
    - Anticholinergic effects
    - Other effects

Antipsychotics

1. Antipsychotic actions:

- All antipsychotics can reduce the hallucinations and delusions associated with schizophrenia (“positive” symptoms) by blocking dopamine receptors in the mesolimbic system of the brain
- The “negative” symptoms, such as blunted affect, anhedonia, apathy, impaired attention, and cognitive impairment are not as responsive to therapy, particularly with the first-generation
- Many second-generation agents, such as clozapine, ameliorate the negative symptoms
- All of the drugs also have a calming effect and reduce spontaneous physical movement without depressing the intellectual functioning of the patient
- The antipsychotic effects take several days to weeks

Antipsychotics

2. Extrapyramidal effects:

- Dystonias (sustained contraction of muscles leading to twisting, distorted postures)
- Parkinson-like symptoms
- Akathisia (motor restlessness)
- Tardive dyskinesia (involuntary movements of the tongue, lips, neck, trunk, and limbs)
- Occur with chronic treatment due to blocking of dopamine receptors in the nigrostriatal pathway
- The second-generation antipsychotics exhibit a lower incidence of these symptoms

Antipsychotics

3. Antiemetic effects:

- Most antipsychotic drugs have antiemetic effects that are mediated by blocking D2-dopaminergic receptors of the chemoreceptor trigger zone of the medulla
- Older antipsychotics, prochlorperazine, haloperidol, are used for nausea due to cancer chemotherapy
- Olanzapine (SGA) may be effective for the prevention of both acute and delayed nausea and vomiting due to chemotherapy.
- Second-generation antipsychotic drugs are not used as antiemetics

Antipsychotics

4. Anticholinergic effects:

- Some antipsychotics particularly thioridazine, chlorpromazine, clozapine, and olanzapine produce anticholinergic effects, including blurred vision; dry mouth
- This anticholinergic property may actually assist in reducing the risk of EPS with these agents
- Clozapine is an exception, it increases salivation; confusion; and inhibits gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention

Antipsychotics

5. Other effects

- Blockade of α-adrenergic receptors causing orthostatic hypotension
- In the pituitary, antipsychotics block D2 receptors, leading to an increase in prolactin release
- Second-generation antipsychotics are less likely to produce prolactin elevations
- Sedation occurs with drugs that are potent antagonists of the H1-histamine receptor, including chlorpromazine, olanzapine, quetiapine, and clozapine
- Sexual dysfunction may also occur

Antipsychotics

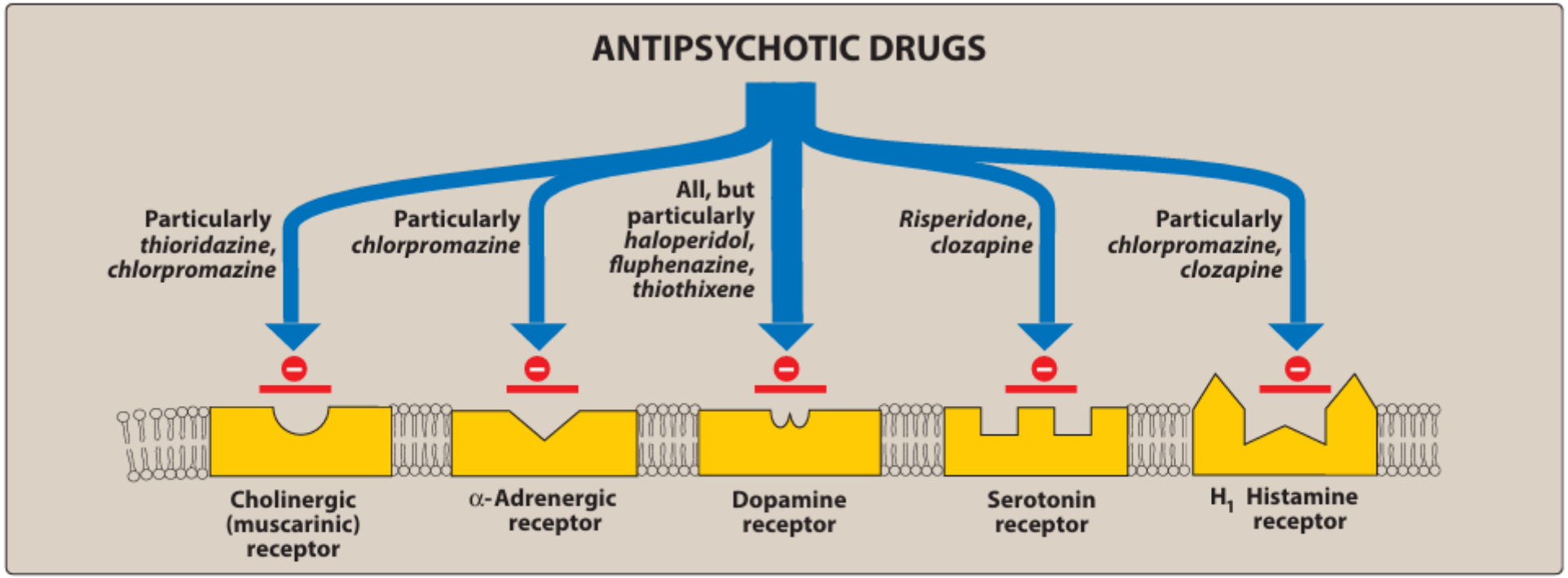


Figure 11.4

Antipsychotic drugs block at dopaminergic and serotonergic receptors as well as at adrenergic, cholinergic, and histamine-binding receptors.

Antipsychotics Therapeutic uses

1. **Treatment of schizophrenia:**
   - Antipsychotics are the only efficacious pharmacological treatment for schizophrenia.
   - The first-generation antipsychotics are generally most effective in treating the positive symptoms of schizophrenia.
   - The atypical antipsychotics with 5-HT2A receptor–blocking activity may be effective in many patients who are resistant to the traditional agents, especially in treating the negative symptoms of schizophrenia.
2. **Prevention of severe nausea and vomiting:**
   - Older antipsychotics like prochlorperazine are useful in the treatment of drug-induced emesis (e.g. chemotherapy)
   - Olanzapine, SGA, may be effective for the prevention of both acute and delayed nausea and vomiting due to chemotherapy

Antipsychotics Therapeutic uses

3. Used as tranquilizers to manage agitated and disruptive behavior secondary to other disorders
   - Risperidone and aripiprazole are approved for management of the disruptive behavior and irritability secondary to autism
4. Many antipsychotic agents are approved for the management of the manic and mixed symptoms associated with bipolar disorder.
   - Lurasidone, cariprazine, and quetiapine are indicated for the treatment of bipolar depression.
5. Some antipsychotics (aripiprazole, brexpiprazole, and quetiapine) are used as adjunctive agents with antidepressants for treatment-refractory depression.
6. Used in combination with narcotic analgesics for treatment of chronic pain with severe anxiety
7. Chlorpromazine is used to treat intractable hiccups (baclofen and gabapentin are preferred)

Antipsychotics

- Metabolized by the cytochrome P450 system in the liver: CYP2D6, CYP1A2, and CYP3A4
- Some metabolites are active
- Can be administered orally
- Some are available as are long-acting injectable (LAI) formulations (fluphenazine, haloperidol, risperidone, paliperidone, aripiprazole, olanzapine)
    - These formulations usually have a therapeutic duration of action of 2-4 weeks, with some having a duration of 6- 12 weeks, or even 6 months.
    - Often used to treat outpatients and individuals who are nonadherent with oral medications.

Antipsychotics Adverse effects

1. Extrapyramidal side effects:
   - due to blockade of dopamine receptors
   - The maximal risk of movement disorders is time and dose dependent
   - Administration of a beta blocker such as propranolol or an anticholinergic drug, such as benztropine minimizes EPS especially dyskinesia

Antipsychotics Adverse effects

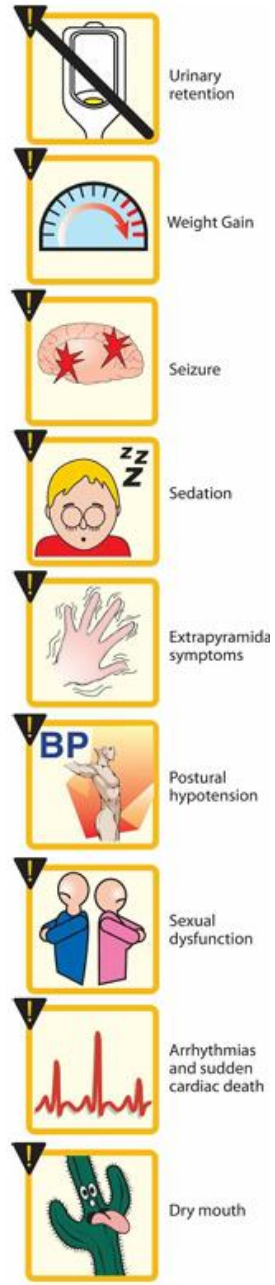
2. Tardive dyskinesia:
   - Due to long-term treatment with antipsychotics
   - Involuntary movements
   - A prolonged holiday from antipsychotics may cause the symptoms to diminish or disappear
   - Can be irreversible
   - Caused by an increased number of dopamine receptors that are synthesized as a compensatory response to long-term dopamine-receptor blockade causing excess movement in the patient
   - Valbenazine and deutetrabenazine are inhibitors of the vesicular monoamine transporter and they are indicated for the management of tar dive dyskinesia.

Antipsychotics Adverse effects

3. Neuroleptic malignant syndrome: (Potentially fatal)
   - Muscle rigidity, fever, altered mental status , unstable blood pressure, tachycardia
   - Treatment necessitates discontinuation of the antipsychotic agent and supportive therapy, administration of dantrolene or bromocriptine may be helpful

Antipsychotics Adverse effects

4. Drowsiness occurs due to CNS depression and antihistaminic effects
5. Antimuscarinic activity produces dry mouth, urinary retention, constipation
6. Blocking α-adrenergic receptors results in orthostatic hypotension. (Chlorpromazine, clozapine)
7. The antipsychotics depress the hypothalamus, affecting thermoregulation and causing amenorrhea, galactorrhea, gynecomastia, infertility, and impotence
8. Weight gain
9. Hyperglycemia and hypercholesterolemia (second- generation antipsychotics); Glucose and lipid profiles should be monitored
10. Can cause QT prolongation, especially thioridazine
11. Clozapine causes agranulocytosis



Antipsychotics Adverse effects

TYPE	MECHANISM	MANIFESTATIONS
Autonomic nervous system	Muscarinic cholinoceptor blockade	Loss of accommodation, dry mouth, difficulty in urinating, constipation
	α-Adrenoceptor blockade	Orthostatic hypotension, impotence, failure to ejaculate
Central nervous system	Dopamine receptor blockade	Parkinson's syndrome, akathisia, dystonia
	Super-sensitivity of dopamine receptors	Tardive dyskinesia
	Muscarinic blockade	Toxic confusional state
Endocrine system	Dopamine receptor blockade resulting in hyperprolactinemia	Amenorrhea–galactorrhea, infertility, impotence
Other	Possibly combined H_1 and 5-HR_2 blockade	Weight gain

Figure 11.6
Adverse pharmacologic effects of antipsychotic drugs and their mechanism.

Antipsychotics

- Patients who have had two or more psychotic episodes, secondary to schizophrenia, should receive maintenance therapy for at least 5 years, and some experts prefer indefinite therapy
- Low doses of antipsychotic drugs are not as effective as higher-dose maintenance therapy in preventing relapse
- The rate of relapse may be lower with second generation drugs
- **Relapse rates with LAIs may be lower than with oral agents**

DRUGS	ORAL DOSE (mg)	EXTRAPY-RAMIDAL EFFECTS[1]	AUTONOMIC EFFECTS (HYPOTENSIVE)	SEDATION	METABOLIC SIDE EFFECTS			INCREASED PROLACTIN
					Weight gain	Lipid	Glucose	
Conventional or first-generation drugs:								
Alipathic phenothiazines								
Chlorpromazine	100–600	++	+++	+++	+	+++	++	++
Triflupromazine	5–30	++	+++	+++	+			
Piperidine phenothiazines								
Thioridazine[2]	100	+	+++	+++		–	–	++
Mesondazine	50	+	+++	+++	+			
Piperzine phenothiazines								
Trifluoperazine	5–30	+++	++	++	+	–	–	++
Fluphenazine[3]	2.5–15	+++	++	++	+			
Butyrophenones								
Haloperidol	2–10	+++	+	+	+	–	–	++
Other related drugs								
Loxapine	15–50	+++	++	++	–	–	–	++
Atypical or second-generation drugs:								
Clozapine[4]	200–600	±	++	+	+++	+++	+++	+
Olanzapine[1,3]	5–20	±	+	++	+++	+++	+++	+
Quetiapine[3]	200–600	±	++	++	++	+	±	+
Risperidone[3,5]	4–8	++	+	+	+	±	±	++
Ziprasidone[6]	120–160	±	±	±	±	–	–	+
Third-generation drug:								
Aripiprazole	10–20	±	+	±	±	–	–	+

[1]Excluding tardive dyskinesia.
[2]Cardiotoxicity.
[3]Depot form (long-acting injectables) available.
[4]Start at a low dose with monitoring blood counts as it may cause agranulocytosis in ~2% patients
[5]Little extrapyramidal effects at low doses.
[6]QTc prolongation.

Figure 11.7
Potency and selected adverse effects of representative conventional and atypical antipsychotic drugs.

DRUG	ADVANTAGES	DISADVANTAGES
First generation:		
Chlorpromazine	Generic inexpensive	Many adverse effects, especially moderate-to-high potential for extrapyramidal syndrome, orthostasis, and sedation; moderate-to-high potential for weight gain
Thioridazine	Slight extrapyramidal syndrome, generic drug	800 mg/d limit, no parenteral form, cardiotoxicity
Fluphenazine	Depot form also available (enanthate, decanoate); effect lasts for 2 to 3 weeks, especially in noncompliant patients; least expensive	Oral formulation has high potential for EPS; low potential for weight gain, sedation, orthostasis, or muscarinic adverse events; weight gain Increased tardive dyskinesia
Thiothixene	Parenteral form also available Decreased tardive dyskinesia	Uncertain
Haloperidol	Parenteral form also available; long-acting injection administered every 4 weeks; low potential for antiadrenergic (orthostasis) or antimuscarinic adverse events, weight gain, or sedation	Severe extrapyramidal syndrome
Second generation:		
Loxapine	No weight gain	Uncertain
Clozapine	May benefit treatment-resistant patients; little extrapyramidal toxicity	May cause agranulocytosis in up to 2% of patients, dose-related lowering of seizure threshold; risk of myocarditis; high potential for sialorrhea, weight gain, antimuscarinic effects, orthostasis, and sedation
Risperidone	Broad efficacy; little or no extrapyramidal system dysfunction at low doses; low-to-moderate risk of weight gain, orthostasis, and sedation; long-acting injection administered every 2 weeks (expensive); also used in BPAD	Extrapyramidal system dysfunction and hypotension with higher doses
Olanzapine	Effective against negative as well as positive symptoms; little or no extrapyramidal system dysfunction; low potential for orthostasis; also approved for BPAD; long-acting injection administered every 2 to 4 weeks	Weight gain; dose-related lowering of seizure threshold
Quetapine	Similar to olanzapine, perhaps less weight gain; also approved for BPAD and as an adjunctive treatment for depression	May require high doses if there is associated hypotension; short t½ and twice-daily dosing
Ziprasidone	Minimal weight gain, parenteral form available; less potential for EPS; used in BPAD	QT prolongation; therefore contraindicated in patients with cardiac arrhythmia
Asenapine	Low potential for EPS, weight gain, sedation, orthostasis; also approved for BPAD; available as sublingual formulation	Uncertain
Third generation:		
Aripiprazole	Lower weight gain liability, sedation, and antimuscarinic effects; long half-life; novel mechanism; also approved for BPAD, autistic disorders in children and as an adjunctive treatment for depression	Uncertain, novel toxicities possible

BPAD = bipolar affective disorder.

Figure 11.8
Summary of representative antipsychotic drugs commonly used to treat schizophrenia.