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ANTIPSYCHOTIC DRUGS

INTRODUCTION

Information about antipsychotic drugs and developments in the treatment of psychosis is rapidly expanding. The advent of newer second-generation antipsychotics in the wake of clozapine represents the first significant advances in the pharmacologic treatment of schizophrenia and related psychotic disorders, and second-generation antipsychotics have become first-choice agents for acute and maintenance therapy for these illnesses.

There is growing evidence that most of the new medications can offer advantages over conventional neuroleptics; these include fewer extrapyramidal symptoms, lower risk of tardive dyskinesia, reduced cognitive impairment, and possible improvement in negative symptoms. Treatment successes have contributed to the increased use of newer antipsychotic agents and have also allowed psychiatrists to expand clinical expectations. In addition, these second-generation drugs are being used increasingly for various conditions beyond schizophrenia, as happened with the conventional antipsychotics.

PHARMACOLOGY

The first-generation antipsychotic agents are equally effective in the treatment of psychotic symptoms of schizophrenia, although they vary in potency and their propensity to induce various side effects. All have a high affinity for dopamine

D_2 receptors. In addition, all produce extra-pyramidal symptoms (EPS), including parkinsonism, dystonia, akathisia, are associated with a substantial risk of tardive dyskinesia (TD), and increase serum prolactin concentration in the usual clinical dose range. First-generation agents are usually classified into three groups: phenothiazines, butyrophenones (e.g., haloperidol), and others (e.g., thiothixene, molindone, and loxapine), based on their structure.

Second-generation antipsychotic drugs are characterized by the following criteria:

- few or no EPS; significant reduction in tardive dyskinesia liability compared to first-generation antipsychotics
- expanded spectrum of therapeutic efficacy
- less prolactin elevation

There is a continuum of typical and atypical effects in atypical drugs rather than several dichotomous groups.

Chemistry

Antipsychotic drugs bind to numerous neurotransmitter receptor subtypes, including those of dopamine, norepinephrine, epinephrine, acetylcholine, serotonin, and histamine. They act to antagonize the endogenous ligands at these receptors. Both therapeutic and extrapyramidal side effects can be attributed to the antagonism of dopamine at D_2 receptors, with actions at the other neuroreceptors associated with various other side effects.

The typical antipsychotics have been described as being of high (e.g., haloperidol), low (e.g., chlorpromazine), and mid (e.g., loxapine) potency on the basis of their degree of affinity for D_2 receptors and their therapeutic dose range. Atypical antipsychotics are characterized by generally lower affinities for D_2 receptors and relatively greater affinities for serotonin (5-hydroxytryptamine) 5-HT_{2A} receptors in particular, but also for noradrenergic receptors (α_1 and α_2), muscarinic acetylcholine receptors, histamine, and other dopamine (DA) subtype receptors. Aripiprazole is currently the only antipsychotic that acts as a partial agonist at D_2 and 5-HT_{1A} receptors as well as an antagonist at the 5-HT_{2A} and D_2 receptors, and these properties are believed to account for its therapeutic effects. It has no appreciable activity at

muscarinic receptors and modest affinity for alpha-1 adrenergic and histamine H_1 receptors.

Mechanism of Action

The therapeutic actions of antipsychotic drugs are generally attributed to antagonism of DA receptors, particularly the D_2 subtype. Atypical antipsychotics, with their lower D_2 receptor affinities and broader spectrum of pharmacologic properties, also antagonize 5-HT_{2A} receptors, giving possible therapeutic advantages and a superior motor side effect profile. At this point it is unclear what clinical effects 5-HT_{2A} antagonism confers, other than mitigating the adverse effect of striatal D_2 antagonism, and propensity to cause EPS. The low EPS liability of aripiprazole is at least in part related to its partial agonist activity at the D_2 receptor. Its D_2 antagonist activity is broadly comparable with that of haloperidol and chlorpromazine, but it clearly has weaker cataleptogenic activity. Furthermore, chronic treatment with aripiprazole is associated with much less upregulation of striatal D_2 receptors compared with haloperidol.

What has been established is that as a consequence of their different pharmacologic profile, the atypical drugs have a much wider separation of the dose-response curves of therapeutic antipsychotic action and extrapyramidal side effects.

Pharmacokinetics

Antipsychotic agents are rapidly absorbed from the gastrointestinal tract and undergo extensive first pass metabolism. They are highly lipophilic, which results in ready transport across the blood-brain barrier. Antipsychotics are metabolized by the cytochrome P450 enzyme system. The isozyme systems predominantly involved are CYP2D6, CYP1A2, CYP3A4, and CYP2C19, and medications that inhibit or compete for these substrates can increase antipsychotic blood levels. After undergoing various degrees of metabolism, antipsychotic drugs and their metabolites are glucuronidated in the liver and excreted by the kidney in the urine or in feces.

The average plasma half-life of the antipsychotics as a family is approximately 20 to 24 hours, allowing for once-daily dosing. Aripiprazole and its active metabolite dehydro-aripiprazole have exceptionally long half-lives of 75 and 94

hours respectively and steady state concentrations are achieved after 14 days. Some drugs have shorter half-lives (e.g., quetiapine: 6 to 12 hours; ziprasidone: 4 to 10 hours), which suggests twice-daily administration. However, with repeated dosing the pharmacodynamic effects may extend beyond the period suggested by pharmacokinetic parameters, allowing the consolidation of dosing to once daily.

Among the second-generation antipsychotics, olanzapine (5–10 mg initial dose) and ziprasidone (10–20 mg initial dose) are available in a parenteral form for acute use in agitated patients, giving the benefits of a more rapid onset of action and the ability to bypass the extensive first-pass metabolism that these agents undergo.

Several of the antipsychotic drugs (three in the United States: haloperidol and fluphenazine decanoate, and Risperidone – Risperdal Consta) are available in long-acting injectable preparations for intramuscular administration. This allows for less fluctuation in plasma level compared to oral formulations, bypasses first-pass metabolism, and can improve patient compliance.

Recommended dosages for second-generation antipsychotic agents are shown in Table 1-1.

INDICATIONS FOR USE OF ANTIPSYCHOTIC DRUGS

Antipsychotic agents are effective for treating nearly every medical and psychiatric condition where psychotic symptoms or aggression are present. They are currently used routinely in the management of psychosis and/or agitation associated with:

- Schizophrenia and Schizoaffective Disorder
- Acute manic and mixed episodes of bipolar disorder
- Major depression with psychosis
- Delusional disorder
- Delirium
- Dementia
- Mental retardation
- Developmental disorders (e.g., Autism)
- Huntington's disease
- Tourette's syndrome
- Substance-induced psychoses (psychostimulants, phencyclidine, levodopa, steroids)

■ **TABLE 1-1.** Antipsychotic Drugs, Doses, Forms, and Costs

DRUG CLASS	THERAPEUTIC DOSE RANGE: USUAL ORAL DAILY DOSE (mg/d)	THERAPEUTIC EQUIVALENT ORAL DOSE (mg/d)	FORMS	HALF-LIFE (h)
First-generation antipsychotics				
Perphenazine	8–64	10	Tablets (2, 4, 8, 16 mg) Concentrate (16 mg/5 ml) Injectable solution (5 mg/ml)	9
Chlorpromazine	200–1,000	100	Tablets (10, 25, 50, 100, 200 mg) Concentrate (30, 100 mg/ml) Gel Caps (30 mg) Spansules (30, 75, 150 mg) Injectable solution (25 mg/ml) Rectal suppositories (25 mg)	23–37
Haloperidol	2–20	2	Tablets (0.5, 1, 2, 5, 10, 20 mg) Concentrate (2 mg/ml) Injectable solution (5 mg/ml)	24
Second-generation antipsychotics				
Risperidone	2–8	1–2	Tablets (0.25, 0.5, 1, 2, 3, 4 mg) Concentrate (1 mg/ml) M-tabs (0.5, 1, 2 mg) rapidly disintegrating tablets Risperdal Consta long-acting injectable (25, 37.5, 50 mg) q 2 wk)	Parent 3 Metabolite 24

■ TABLE 1-1. (Continued)

DRUG CLASS	THERAPEUTIC DOSE RANGE: USUAL ORAL DAILY DOSE (mg/d)	THERAPEUTIC EQUIVALENT ORAL DOSE (mg/d)	FORMS	HALF-LIFE (h)
Ziprasidone	80–200	20	Capsules (20, 40, 60, 80 mg)	4–10
			Injectable solution 20 mg/ml	
Clozapine	25–600	50	Tablets (25, 100 mg)	8–12
Olanzapine	5–30	2.5–5	Tablets (2.5, 5, 7.5, 10, 15, 20 mg)	27
			Zydis (5, 10, 15, 20 mg) rapidly disintegrating tablets	
			Injectable solution 5 mg/ml	
Quetiapine	150–800	50–100	Tablets (25, 50, 100, 200, 300, 400 mg)	7
Aripiprazole	10–30	5–10	Tablets (5, 10, 15, 20, 30 mg)	75–96
			Oral solution 1 mg/ml	
Long-acting preparations				
Fluphenazine decanoate	12.5–50 q 2–4 wk	12.5–50	Injectable solution (25 mg/ml)	2–3 wk
Haloperidol decanoate	50–300 q 3–4 wk	50–300	Injectable solution (100 mg/ml)	3 wk
Risperdal Consta	25–50 mg q 2 wk	25, 37.5, 50 mg	Microspheres in fixed dose vials; 2 ml	3–6 days

The development of second-generation antipsychotics has been a major clinical advance for the treatment of schizophrenia. At present, these drugs are used as the first-line treatment for schizophrenia, and are being used increasingly for various conditions beyond schizophrenia. The low incidence of EPS and TD associated with second-generation agents is highly beneficial in several neuropsychiatric conditions.

DRUG SELECTION AND INITIATION OF TREATMENT
Drug Selection for the Treatment of Schizophrenia

In choosing an antipsychotic agent for the treatment of an episode of schizophrenia, the clinician should be guided by the patient's history. The following tests should be performed:

- a complete physical examination including weight
- a review of symptoms
- routine blood chemistry including fasting blood glucose and lipid profile
- complete blood cell count
- electrocardiogram

Once any medical or neurologic causes of the symptoms have been ruled out, the clinician should consider the following questions:

- Is this a psychotic episode consistent with schizophrenia?
- Have affective syndromes such as mania and depression with psychotic features been ruled out?
- Is this the patient's first episode?
- Is there a history of prior antipsychotic treatment response?
- How well was the antipsychotic tolerated?
- Were there prominent side effects?
- Did the patient ever previously have EPS or TD?
- Does the patient have a history of neuroleptic malignant syndrome?
- What symptoms (positive or negative) are predominant in the episode?

- Is there a history of non-compliance, and, if so, has the patient had a trial of depot preparations?
- If there have been antipsychotic trials that have failed, were the trials of an adequate dose and of an adequate duration?
- Does the patient meet the criteria for treatment resistance?
- Does the patient have a history of cardiac conduction delay?
- Does the patient have any prior history of blood dyscrasias?
- Does the patient have normal hepatic and renal functions?
- Is the patient medically debilitated?

### TREATMENT INITIATION AND DOSE TITRATION

Once the questions above are answered, the clinician should select an antipsychotic medication and initiate the treatment trial. The algorithm from the practice guidelines for schizophrenia developed by the American Psychiatric Association may be useful for drug selection (Figure 1-1).

Selection of an agent in emergency settings for the management of the gross agitation, excitement, and violent behavior associated with psychosis might be based on clinical symptoms, differences in efficacy or side effects of candidate drugs, or, more pragmatically, the formulation of a drug as it affects route of administration, onset, and duration.

There is now a considerable amount of clinical experience with atypical antipsychotics in acute emergency situations, and they have come to replace first-generation antipsychotics as the agents of choice when treatment is initiated. Olanzapine and ziprasidone are available in short-acting formulations for intramuscular administration; risperidone and aripiprazole are available as oral solutions; and olanzapine and risperidone are available as rapidly disintegrating oral tablets. These various formulations provide tremendous flexibility to the clinician in choosing the optimal medication and method of administration based on clinical considerations.

The use of oral second-generation antipsychotics and benzodiazepines in combination is the most common medication strategy in psychiatric emergency settings. It is best to avoid combining antipsychotics in favor of sequential trials of monotherapy with different antipsychotics. Because most patients with schizophrenia will require long-term treatment with antipsychotics it is imperative that, in addition to short-term treatment goals of control of behavioral dysregulation
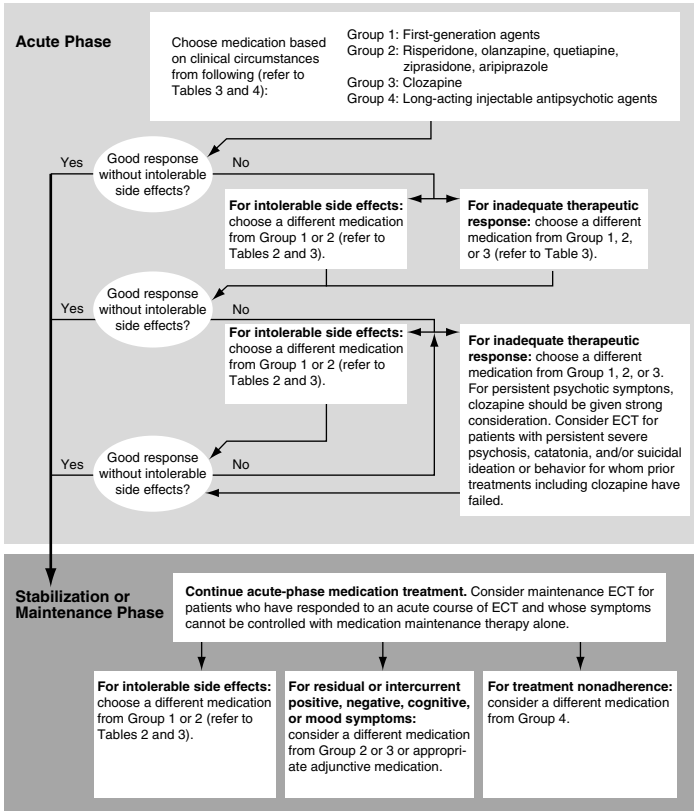
FIGURE 1-1. Somatic Treatment of Schizophrenia. Also refer to Table 1-1 and the following: First episode–Group(G) 2; Persistent suicidal ideation or behavior–G3; Persistent hostility and aggressive behavior–G3; Tardive dyskinesia–G2 all group 2 drugs may not be equal in their lower or no tardive dyskinesia liability and G3; History of sensitivity to extrapyramidal side effects–G2 except higher doses of risperidone; History of sensitivity to prolactin elevation–G2 except risperidone; History of sensitivity to weight gain, hyperglycemia, or hyperlipidemia–G2 ziprasidone or aripiprazole; Repeated nonadherence to pharmacological treatment–G4 (taken from the Practice Guidelines for the Treatment of Patients with Bipolar Disorder, Second Edition from the American Psychiatric Association Practice Guidelines for the Treatment of Psychiatric Disorders Compendium, Copyright 2004).

and psychotic symptom resolution, clinicians consider long-term side effect profiles of the available treatment options with the goal of minimizing long-term side effect burden. Ziprasidone and aripiprazole may be specifically indicated in patients who are intolerant of the side effects that can occur in greater frequency with some of the second-generation drugs, such as weight gain and alterations in glucose and lipid metabolism, as they do not produce these effects to any significant degree.

One can safely escalate the dose of second-generation antipsychotics more rapidly than is usual in outpatient settings to achieve target doses typically utilized for the treatment of schizophrenia. Once behavioral control is achieved, benzodiazepines should be discontinued and the patient should be maintained on the atypical antipsychotic alone. The dose recommendations for second-generation antipsychotic drugs are summarized in Table 1-2.

The anti-aggressive characteristics of clozapine are well established in chronically psychotic patients; however clozapine initiation is contraindicated in the psychiatric emergency setting because of its serious potential side effects, including seizures and agranulocytosis.

On the rare occasion that a physician elects to use a first-generation antipsychotic during the first few days of treatment, "rapid neuroleptization" should be avoided as there is no evidence for increased efficacy and risk of side effects is greater at higher doses. If a low-potency agent is chosen, the recommendation is to begin with a low dose such as chlorpromazine, 50 mg twice a day, and to titrate slowly so that the difficulties associated with orthostatic hypotension can be reduced. If a high-potency agent such as haloperidol is chosen, the recommendation is also to begin a course of prophylactic antiparkinsonism medication such as benztropine, 1 mg twice a day, to decrease the incidence of EPS side effects. The initial dose of antipsychotic should be titrated to between 5 and 10 haloperidol equivalents or 200 to 400 chlorpromazine equivalents. At this time, the only groups of patients in which the first-generation antipsychotics are clearly preferable are those who have a history of good response to these agents with minimal side effects.

After initiating treatment and titrating to a standard dose of antipsychotic, the clinician, patient, and family must wait for the antipsychotic to take effect. Because patients are acutely

■ **TABLE 1-2.** Recommended Dosages for Second-Generation Antipsychotic Agents

	HALF-LIFE (hr) (MEAN)	STARTING DOSE (TOTAL mg/day)	AVERAGE DOSE RANGE (mg/day)		AVERAGE MAINTENANCE DOSE (mg/day)	ROUTES OF ADMINISTRATION
			FIRST EPISODE	RECURRENT EPISODE		
Clozapine	10–105 (16)	25–50	150–300	400–600	400	Oral
Risperidone	3–24 (15)	1–2	2–4	3–6	3–6	Oral, depot
Olanzapine	20–70 (30)	5–10	10–20	15–30	10–20	Oral, IM
Quetiapine	4–10 (7)	50–100	300–600	500–800	400–800	Oral
Ziprasidone	4–10	40–80	80–120	120–200	120–160	Oral, IM
Zotepine	12–30 (15)	50–100	75–150	150–450	75–300	Oral
Amisulpride	8–20 (12)	50–100	50–300	400–800	400–800	Oral
Aripiprazole	(75–96)	10–15	10–30	15–30	15–30	Oral

Source: Adapted from McEvoy JP, Scheifler PL, Frances A (1999) The expert consensus guideline series: Treatment of schizophrenia. *J Clin Psychiatr* 60, 1–80; Burns MJ (2001) The pharmacology and toxicology of atypical antipsychotic agents. *J Clin Toxicol* 39, 1–14; Worrel JA, Marken PA, Beckman SE, et al. (2000) Atypical antipsychotic agents: A critical review. *Am J Health Syst Pharm* 57, 238–255.

ill, there is often a tremendous temptation and external pressure to increase the dose of the antipsychotic in the hope that the patient's condition will improve more rapidly. Despite this hope, there is little, if any, clinical evidence that a higher dose of antipsychotic is in any way advantageous; in fact, it will only increase the likelihood of side effects. During this difficult time it may be necessary to add sedating medications such as short-acting benzodiazepines (e.g., lorazepam) to help the patient maintain control until the antipsychotic has started to work.

TREATMENT EVALUATION AND DRUG SWITCHING

If the first-episode patient has failed to respond to a 6-week trial of an antipsychotic, the clinician should evaluate possible non-compliance with medication, the likelihood of a partial response or a complete nonresponse to treatment. If there was no response, a change to a second antipsychotic from a new family is recommended. If one of the newer agents was not the clinician's first choice, it should be used at this point in the decision tree.

If a patient has already discontinued use of a medication, then the new treatment is selected and initiated as described above. However, if the patient is undergoing maintenance drug treatment and drugs are to be electively switched in the hope of achieving a better therapeutic response or alleviating drug side effects, then the goal is to switch medications without destabilizing the patient.

Medication changes should be performed by a concurrent slow tapering of the initial antipsychotic while the second antipsychotic is being slowly titrated. The specific rate of cross-titration depends on the dose of the old medication and the relative stability of the patient. In general, the higher the dose and the more unstable the patient, the longer and more gradual the cross-titration schedule. Although this varies, a rule of thumb is to cross-titrate by yoked increments and decrements of 25% every 2 to 5 days. Adjunctive medications should be adjusted or tapered accordingly.

If the patient is judged to be a partial responder to the antipsychotic trial, then the clinician may consider the addition of an agent for augmentation. At this point, it is again important for the clinician to re-evaluate the presence of affective symptoms. If there is significant depressive symtomatology in

the clinical presentation, then the addition of an antidepressant may be warranted. If the presence of mood symptoms is consistent with a manic episode, the addition of a mood stabilizer such as lithium as an augmentation strategy may be clinically useful.

Treatment During the Resolving Phase If a particular antipsychotic medication has improved the acute symptoms it should be continued at the same dose for the next six months before a lower maintenance dose is considered for continued treatment. Rapid dose reduction or discontinuation of the medications during the resolving phase may result in relatively rapid relapse. It is essential to continue to assess side effects present in the acute phase and modify treatment to minimize their negative impact, and to re-evaluate the necessity of any adjunctive therapies used in the acute phase.

If the decision has been made to switch to a long-acting depot antipsychotic agent, this can often be achieved during this phase. This is also a good time to educate the patient and family regarding the course and outcome of schizophrenia, as well as factors that influence the outcome such as drug compliance.

MAINTENANCE TREATMENT

The goals of treatment during the stable or maintenance phase are to maintain symptom remission, to prevent psychotic relapse, to implement a plan for rehabilitation, and to improve the patient's quality of life.

Current guidelines recommend that first-episode patients should be treated for one to two years; however, 75% of patients will experience relapses after their treatment is discontinued. Patients who have had multiple episodes should receive at least five years of maintenance therapy. Patients with severe or dangerous episodes should probably be treated indefinitely.

Gradual dose reduction to identify the minimum effective dose for the patient can be attempted in this phase, although relapse rates are excessively high when doses are reduced to about 10% of the acute dose.

Antipsychotics have been proven to be effective in reducing the risk of psychotic relapse in maintenance therapy for schizophrenia. In the stable phase of illness, antipsychotics can reduce the risk of relapse to less than 30% per year.

Without maintenance treatment, 60–70% of patients relapse within one year and almost 90% relapse within two years. These results indicate that antipsychotic medications are effective in preventing relapse in most stabilized patients. There is also strong evidence that patients who relapsed while on antipsychotic medications had episodes that were less severe than patients not on antipsychotic drugs.

As atypical drugs have fewer EPS side effects, patients on these compounds may be less likely to be non-compliant with treatment and may thereby decrease their risk of relapse. It has also been suggested that in addition to fewer side effects, atypical drugs may have inherently greater prophylactic efficacy than typical drugs and therefore be better for patients with an increased risk of relapse.

TREATING TREATMENT RESISTANCE

Treatment resistance is generally defined as a failure of two prior drug trials of 4–6 weeks duration. Although most definitions of treatment resistance focus on the persistence of positive symptoms, there is growing awareness of the problems of persistent negative symptoms and cognitive impairments, which may have an important impact on level of functioning, psychosocial integration, and quality of life.

Approximately 10 to 15% of patients with first-episode schizophrenia are resistant to drug treatment, and between 25% and 50% of long-term patients will have severe, persistent symptoms including psychosis.

Only clozapine has consistently demonstrated efficacy for psychotic symptoms in well-defined treatment refractory patients; the mechanism responsible for this therapeutic advantage remains uncertain. Serum levels of 350 μg/mL or greater have been associated with maximal likelihood of response. Depending on the type of residual symptom, augmentation strategies include adding another antipsychotic, anticonvulsants, benzodiazepines, and cholinergic agonists may prove useful.

Since the approval of clozapine, attention has shifted to a greater focus on the use of other second-generation antipsychotics for managing treatment resistance in schizophrenia. Both olanzapine (15–25 mg/day) and clozapine (200–600 mg/day) were shown to be similarly effective in reducing

overall psychotic symptoms in treatment-resistant patients clinically eligible for treatment with clozapine. Some preliminary reports suggest that higher doses of olanzapine may be more effective; however, dosage issues of olanzapine have not yet been adequately addressed in more controlled conditions. There are also several recent reports of beneficial effects of quetiapine in treatment-resistant patients with schizophrenia.

Given the risk of agranulocytosis, the burden of side effects, and the requirement of white blood cell monitoring, the second-generation agents (risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) should be tried in almost all patients before proceeding to clozapine. Many clinicians express the impression that certain patients do respond preferentially to a single agent of this class.

SCHIZOAFFECTIVE DISORDER AND VIOLENT PATIENTS

Among the specific therapeutic effects claimed for atypical drugs is their ability to alleviate mood symptoms associated with the psychotic disorder. Although this has not been definitively proved, preliminary results indicate that mood symptoms may selectively abate with atypical drugs. This evidence suggests that patients with schizoaffective disorder, residual mood symptoms (e.g., postpsychotic depression), a history of, or current, suicidal behavior, and violent behavior may benefit most from treatment with an atypical drug as compared to a conventional antipsychotic agent.

ADJUNCTIVE TREATMENTS

For patients who are unresponsive to antipsychotic agents, including clozapine, and for patients who are responsive but have substantial residual symptoms, the question is what further options exist. Adjunctive medications as indicated in the algorithm (other than electroconvulsive therapy) have been used extensively but without any empiric data to demonstrate their efficacy. These adjuncts include anticonvulsants, lithium, antidepressants, benzodiazepines, and cholinesterase inhibitors.

Effects of Antipsychotic Agents on Symptoms of Schizophrenia

The clinical profile of second-generation antipsychotic agents on the symptoms of schizophrenia are summarized in Table 1-3.

■ TABLE 1-3. Clinical Profile of Second-Generation Antipsychotic Drug Efficacy

DRUG	CLOZAPINE	RISPERIDONE	OLANZAPINE	QUETIAPINE	ZIPRASIDONE	SERTINDOLE	AMISULPRIDE	ARIPIPRAZOLE	ILOPERIDONE
Clinical effect									
Psychotic symptoms	+++	+++	+++	++	++	+++	+++	+++	+++
Negative symptoms	+	+	+	+	+	++	++	++	++
Cognitive symptoms	++	++	++	+	?	?	?	++	?
Mood symptoms	+++	++	+++	+++	++	++	++	++	?
Refractory symptoms	+++	++	++	++	?	?	++	?	?

+ to +++, weakly to strongly active; ?, questionable to unknown activity.

Source: Adapted from Dawkins K, Lieberman JA, Lebowitz BD, et al. (1999) Antipsychotics: Past and future. National Institute of Mental Health Division of Services and Intervention Research Workshop (July 14, 1998). *Schizophr Bull* 25, 395–404, with permission from Oxford University Press.

Positive Symptoms Antipsychotic agents have a specific effect on positive symptoms of schizophrenia including hallucinations, delusions, and thought disorder. Approximately 30% of patients with acutely exacerbated psychotic symptoms have little or no response to conventional antipsychotics, and up to 50% of patients have only a partial response to medication. Although the proportion of patients who improve and the magnitude of therapeutic effects vary greatly, second-generation antipsychotics appear to be at least as effective for psychotic symptoms as conventional drugs.

Negative Symptoms Studies of the early course of illness have shown that about 70% of schizophrenics develop primary negative symptoms such as affective blunting, emotional withdrawal, poverty of speech, anhedonia, and apathy, before the onset of positive symptoms. Negative symptoms may represent core features of the illness, and may be associated with poor outcome and prolonged hospitalization for patients.

Negative symptoms can be divided into three components that are usually difficult to distinguish:

- primary or deficit – enduring negative symptoms
- primary – non-enduring negative symptoms
- secondary negative symptoms that may be associated with psychotic symptoms, EPS, depression, and environmental deprivation

Conventional antipsychotics are generally less effective against negative than positive symptoms of schizophrenia; thus, the efficacy of second-generation antipsychotics on negative symptoms compared with that of first-generation drugs has received much attention. Second-generation agents such as clozapine, olanzapine and risperidone demonstrate significantly greater efficacy than conventional agents in reducing negative symptoms.

However, there is a continuing debate as to whether these effects are related to a reduction in EPS or to a direct effect on primary negative symptoms. Moreover, the effect sizes of improvement on negative symptoms for second-generation agents are usually moderate to small in comparison with

placebo or conventional agents. Path analyses have suggested that both risperidone and olanzapine exert direct effects on (primary) negative symptoms independent of differences in psychotic, depressive, or extrapyramidal symptoms. A collaborative working group concluded that second-generation drugs are superior in terms of the "totality" of negative symptoms, but their impact on specific components is still under investigation. This and other clinical questions will become clear as the new agents are tested in clinical trials.

Cognitive Symptoms   Cognitive impairment appears to be an integral characteristic of schizophrenia and may be evident in up to 60% of patients. Measurable deficits are prominent in tasks involving attention, verbal fluency, memory, and executive function. A wide range of cognitive deficits are usually present at the time of the first psychotic episode and remain relatively stable or only slowly progressive during the course of the illness, independent of psychotic symptoms. Cognitive deficits are particularly prominent in patients meeting criteria for the deficit syndrome and in patients with TD. They are more strongly related to social and vocational functioning than psychotic symptoms and may influence the quality of life of patients. Thus, targeting cognitive impairments appears to be a major focus of the treatment of schizophrenia.

Conventional neuroleptics produce small and inconsistent effects on cognitive functioning. In general, clozapine, risperidone, and olanzapine have demonstrated superior efficacy compared to first-generation antipsychotics on tests of verbal fluency, digit–symbol substitution, fine motor function, and executive function. Measures of learning and memory were least affected by second-generation agents. Because these tests all measure performance during a timed trial, enhanced performance with second-generation drugs could result, in part, from reduced parkinsonian side effects. Preliminary evidence suggests that risperidone may be more effective for visual and working memory than clozapine.

Mood Symptoms and Suicidal Behavior   Depressive symptoms frequently occur in the context of psychotic symptoms or intercurrently between psychotic episodes. Antidepressant

medication used adjunctively to antipsychotic drugs is generally indicated and effective. Atypical antipsychotics have been reported to have selective benefits against mood symptoms in schizophrenia, both manic and depressive.

Suicidal behavior presents a particular problem in patients with schizophrenia. Clozapine is approved for use in suicidal patients with schizophrenia on the basis of results in the InterSePT study. This study found that clozapine treatment produced a lower rate of suicidal behavior than the comparison treatment of olanzapine in patients with active or histories of suicidal behavior.

Drug Selection for the Treatment of Bipolar Disorder

Antipsychotic agents are effective in treating acute manic episodes; these agents are believed to possess antimanic qualities in addition to their antipsychotic properties. One benefit is their rapid onset compared to mood stabilizers; as a result, these agents are often used preferentially or combined until the mood stabilizer has reached its therapeutic effectiveness. All the second-generation antipsychotics (except clozapine) are now approved for the treatment of acute manic episode in the United States, as well as the acute treatment of mixed episodes (except clozapine and quetiapine). Olanzapine and aripiprazole are also approved for maintenance treatment.

A concern with the use of antipsychotics in this population is the potential for TD. As a result, it is recommended that atypical antipsychotics be used with this population when clinically indicated but that attempts be made to treat this population with mood-stabilizing agents by themselves if possible.

Drug Selection for the Treatment of Major Depression With Psychotic Features

Clear psychotic symptoms, such as delusions or hallucinations, are observed in approximately 25% of patients with major depressive disorder. These symptoms often respond poorly to antidepressants when they are administered alone, and usually require the use of adjunctive antipsychotic agents.

Treatment can be initiated simultaneously, though many clinicians prefer to start the antipsychotic dose first and then add the antidepressant to the regimen. Though there are limited data on the adequate dose of antipsychotic for this group, most clinicians would recommend 5 to 10 haloperidol equivalents. This group of unipolar depressed patients may be at the highest risk of TD; thus the antipsychotic dosage should be tapered and then discontinued when the patient's psychotic symptoms remit.

Drug Selection for the Treatment of Delusional Disorder

Delusional disorder differs from other psychotic disorders in terms of family history and age distribution. In addition, it has displayed a difference in treatment response; as a general rule, patients with delusional disorder do not respond well to antipsychotic agents. Some uncontrolled clinical data have suggested that these patients may do better with drugs from the diphenylbutylpiperidine class (e.g., pimozide). However, the majority of this group of patients are untreated and do not seek psychiatric help. There is only very limited experience with atypical drugs in this population.

Drug Selection for the Treatment of Delirium

Antipsychotics are effective in treating the psychotic symptoms and agitation associated with deliria of various etiologies. In treating a delirium, high-potency agents are preferable to low-potency agents because low-potency agents usually have more anticholinergic properties and cardiovascular side effects, which can adversely affect a delirious patient. Antipsychotic drugs are commonly given parenterally when used for this indication, including by intravenous routes.

Risperidone is also relatively free from anticholinergic side effects and has a favorable side-effect profile in relation to the production of EPS. The newer agents olanzapine and quetiapine are now being utilized for these conditions. The parenteral forms of the atypical drugs should be particularly useful for this indication.

Drug Selection for the Treatment of Psychosis and Agitation Associated with Dementia

Antipsychotics are effective in treating the psychotic symptoms that are often associated with dementias. Additionally, they have been demonstrated to have anti-aggressive and calming effects against dysregulated behavior and affect. Although many patients with dementia have agitation and behavioral disturbances that clearly require the use of antipsychotic drugs, these drugs should be used judiciously.

The atypical drugs offer several potential advantages over typical drugs in treating dementia. They produce fewer EPS and less TD, side effects to which elderly patients are highly susceptible. They also may have broader efficacy against the constellation of pathologic symptoms and behaviors (e.g., mood symptoms, hostility) that occur in dementia. To date, extensive placebo-controlled trials have been conducted with risperidone, olanzapine and aripiprazole. Other atypical drugs must be systematically evaluated to determine their efficacy for this disorder and to determine how well their antiadrenergic and anticholinergic properties are tolerated.

Elderly patients with dementia who are treated with an antipsychotic agent are at increased risk of death. Analyses of clinical trials with a modal duration of 10 weeks suggest that the excess risk is 1.6–1.7 compared with placebo. Most of the deaths appear to be due to cardiovascular events (including heart failure and sudden death) or infection. Because these events have been associated with antipsychotics regardless of their chemical structure, this is probably a class effect associated with their pharmacological activity and the risk applies also to both atypical and older antipsychotics and to drugs that were not included in these trials. The FDA has reminded prescribers that these agents are not approved for the treatment of dementia in older people.

Drug Selection for the Treatment of Mental Retardation and Developmental Disorders

Patients with mental retardation are another patient population with psychotic symptoms and behavioral disturbances

about whom there has been controversy. As with patients with dementia, a number of these patients have documented psychosis, and for these patients the use of antipsychotics is clearly indicated. There are other patients, however, whose primary symptoms are those of behavioral dyscontrol. In this group it is possible that the risks of antipsychotics may outweigh their benefits, especially in long-term treatment. Again, atypical drugs may be advantageous because of their lower EPS and TD liabilities, to which these patients are highly susceptible.

Drug Selection for Huntington's Disease and Tourette's Disorder

Antipsychotics have been shown to be effective in the management of Huntington's disease and Tourette's disorder. In Huntington's, various antipsychotics have been used to help control the agitation and chorea as well as the psychotic symptoms associated with the disorder. In Tourette's disorder, the antipsychotics used most extensively to manage patients' vocalizations and tics include haloperidol and pimozide. Most recently, risperidone has shown promise in this patient population. Beyond risperidone, there is little experience with atypical drugs in these disorders. The exception to this is clozapine, which was found to have little therapeutic benefit in either condition.

On the basis of this evidence, the typical drugs might be the preferred therapeutic option in these disorders; nonstriatal weak D_2 agents would be less likely to be effective.

Substance-induced Psychoses

PSYCHOSTIMULANT- AND PHENCYCLIDINE-INDUCED PSYCOSES
Substance intoxication resulting in psychotic symptoms may be treated effectively with antipsychotic drugs. This is particularly the case with intoxication from psychostimulants such as amphetamine, methamphetamine, and cocaine and from phencyclidine. Previously the clinical approach was not to use typical neuroleptics for fear of exacerbating the patient's condition with side effects but, rather, to employ benzodiazepines

and a calm low-stimulus environment, unless the condition persisted for days or well beyond the period of the toxin's elimination. With the availability of the atypical drugs and their ability to alter the effects of NMDA receptor antagonists as well as psychostimulants, the use of these agents should be evaluated. At present, however, only limited data on their efficacy in these conditions are available.

LEVODOPA-INDUCED AND STEROID-INDUCED PSYCHOSIS

Antipsychotics are an integral part of the treatment of medication-induced psychotic syndromes. The psychosis induced by levodopa in the treatment of Parkinson's disease presents unique clinical dilemmas. Treatment of the symptoms with first-generation antipsychotic agents will by definition worsen the Parkinson's symptoms. The clinician is often caught between attempts to reduce the patient's severe paranoid state and attempts to keep the patient from becoming more immobile from worsening rigidity and akinesia. Recently, case reports utilizing clozapine and risperidone in this population have shown encouraging results.

Steroid-induced psychotic symptoms have proved to be somewhat more complicated: psychotic symptoms may be prolonged, requiring the use of antipsychotics, and at the same time, despite the emergence of psychosis, some patients may still require steroid treatment for their medical condition. There have been a few case reports in which patients known to become psychotic during a steroid course were pretreated with antipsychotics or with a mood stabilizer, with good results.

ADVERSE EFFECTS OF ANTIPSYCHOTICS

Antipsychotics as a group have a wide range of potential side effects corresponding to their pharmacologic properties. Atypical and typical drugs vary markedly in their side-effect profiles; clozapine has the most complicated and potentially serious side effects. The side effects for representative high-, mid-, and low-potency typical drugs and individual atypical drugs are shown in Table 1-4.

■ TABLE 1-4. Side-Effect Profile of Second-Generation Antipsychotic Drugs

DRUG	CONVENTIONAL AGENTS	CLOZAPINE	RISPERIDONE	OLANZAPINE	QUETIAPINE	ZIPRASIDONE	SERTINDOLE	AMISULPRIDE	ARIPIPRAZOLE	ILOPERIDONE
Side effect										
EPS[a]	+++	0	++	+	0	+	0	++	+	+
TD	+++	0	++	+	0	+	0 to +	+	+	+
NMS	++	+	+	+	?	+	+	+	?	?
Prolactin elevation	+++	0	+++	0 to +	0	0 to +	0 to +	++	0	0 to +
Weight gain	+ to ++	+++	+	+++	+	0	+	0	0	?
Prolonged QT[a]	+ to +++	0	0	0	+	++	+++	+	0	0
Hypotension[a]	+ to ++	+++	++	++	++	+	+	+	+	+
Sinus tachycardia[a]	+ to +++	+++	+	++	++	+	+	0	0	+
Anticholinergic effects[a]	+ to ++++	+++	0	++	+	0	0	0	0	0
Hepatic transaminitis	+ to ++	++	+	++	+	+	+	+	0	+
Agranulo-cytosis	0 to +	++	0	0	0	0	0	0	0	0
Sedation	+ to +++	+++	+	++	+++	+	+	+	+	+
Seizures[a]	0 to +	+++	0	0 to +	0 to +	0 to +	0 to +	0 to +	0 to +	0 to +

EPS, extrapyramidal side effects; TD, tardive dyskinesia; NMS, neuroleptic malignant syndrome.

+ to +++, active to strongly active; 0, minimal to none; ?, questionable to unknown activity.

[a] Dose dependent.

Adapted and modified with permission from Dawkins K, Lieberman JA, Lebowitz BD, et al. (1999) Antipsychotics: Past and future. National Institute of Mental Health Division of Services and Intervention Research Workshop (July 14, 1998). *Schizophr Bull* 25, 395–404; Burns MJ (2001) The pharmacology and toxicology of atypical antipsychotic agents. *J Clin Toxicol* 39, 1–14.

Acute Extrapyramidal Side Effects (Dystonia, Parkinsonism, Akathisia)

Antipsychotic-induced EPS occur both acutely and after chronic treatment. All antipsychotic medications are capable of producing EPS. In general, first-generation antipsychotics are more likely to cause EPS than second-generation antipsychotics when the drugs are used at usual therapeutic doses. Among second-generation drugs, clozapine and quetiapine have been shown to carry minimal to no risk for EPS within the therapeutic dosage range. Risperidone can produce dose-related EPS (≥ 6 mg/day). With the exception of akathisia, the incidence of EPS with olanzapine, aripiprazole, and ziprasidone is not appreciably different from that with placebo. The relative liability of the individual second-generation agents to produce EPS will become apparent only when they have been directly compared with each other in prospective clinical trials.

Commonly occurring acute EPS include akathisia, dystonia, and parkinsonism, with each having a characteristic time of onset. This group of acute EPS develops relatively soon after the initiation of antipsychotic medications and remits soon after the drugs are discontinued. These movement disorders are dose-dependent and reversible.

Dystonias tend to be sudden in onset, the most dramatic form of acute EPS, and extremely distressing to patients. They present as sustained muscle contraction with contorting, twisting, or abnormal postures affecting mainly the musculature of the head and neck but sometimes the trunk and lower extremities. Dystonic reactions usually occur within the first few days of therapy. Laryngeal dystonias are the most serious, and are potentially fatal. Risk factors for acute dystonias include a history of prior dystonias, young age, male gender, use of high-potency neuroleptic agents such as haloperidol or fluphenazine, high dose of medication, and parenteral administration.

Medication-induced parkinsonism is characterized by the symptoms of idiopathic parkinsonism, including rigidity, tremor, akinesia, and bradykinesia. Risk factors include older age, higher dose, a history of parkinsonism, and underlying damage in the basal ganglia.

Patients with akinesia or bradykinesia suffer from slow movement, apathy, and with difficulty with spontaneity of speech and initiating movement. These symptoms need to be distinguished from negative symptoms of schizophrenia, depressive symptoms, and catatonia.

Akathisia, the most common EPS of conventional antipsychotics agents, is characterized by both the subjective and objective somatic restlessness. Patients with akathisia may usually experience an inner tension, discomfort, irritation, anxiety, or irresistible urge to move various parts of their bodies. Akathisia appears objectively as psychomotor agitation, such as continuous pacing, rocking from foot to foot, or the inability to sit still. Akathisia is typically witnessed in a few hours to days after medication administration. This side effect can be seen in up to 20 to 25% of patients treated with conventional agents. Akathisia is frequently cited as a reason for poor drug compliance, since it is often extremely distressing to patients. It can also result in dysphoria and aggressive or suicidal behavior.

The treatment of acute EPS depends on the specific side effect. Dystonia can be quickly and successfully treated with an intramuscular injection of an anticholinergic (i.e., benztropine, diphenhydramine). The initial treatment of parkinsonian side effects is lowering the dose of antipsychotic. If an adequate response is not achieved, adding an anticholinergic, or amantadine (a weak dopamine agonist), may be efficacious. If symptoms persist, switching to an second-generation antipsychotic or a low-potency conventional antipsychotic should be considered. Akathisia is less responsive to treatment than are other acute EPS. The first step of the treatment of akathisia is lowering the antipsychotic dose. The next step is individual trials of beta-adrenergic blockers (i.e., propranolol), and benzodiazepines (i.e., lorazepam and clonazepam).

Tardive Dyskinesia and Other Tardive Syndromes

TD is a repetitive, involuntary, hyperkinetic movement disorder caused by sustained exposure to antipsychotic medication. TD is characterized by choreiform movements,

tics and grimaces of the oro-facial muscles, and dyskinesia of distal limbs, often the paraspinal muscles, and occasionally the diaphragm. Younger patients with TD tend to exhibit slower athetoid movements of the trunk, extremities, and neck. In addition to the more frequently observed oro-facial and choreoathetoid signs of TD, tardive dystonias (sustained abnormal postures or positions) and tardive akathisia (persistent subjective and/or objective signs of restlessness) have been described. The abnormal movements of TD are usually increased with emotional arousal and are absent when the individual is asleep. According to the diagnostic criteria proposed by Schooler and Kane, the movements should be present for at least four weeks, and exposure to antipsychotic drugs should have totaled at least three months. The onset of the abnormal movements should occur either while the patient is receiving an antipsychotic agent or within a few weeks of discontinuing the offending agent.

Prevalence surveys indicate that mild forms of TD occur in approximately 20% of patients who receive chronic treatment with conventional antipsychotic medication. A major prospective research demonstrates that the cumulative incidence of TD is 5% in the first year, 10% the second year, 15% the third year, and 19% the fourth year in a patient who receives a typical neuroleptic. Prevalence rates of TD may exceed 50% in high-risk groups, such as the elderly. The reported prevalence of tardive dystonia is around 1.5 to 4%. Among the most significant predictors of TD are older age, female gender, presence of EPS, diabetes mellitus, affective disorders, and certain parameters of neuroleptic exposure such as dose and duration of therapy.

All first-generation antipsychotic agents are associated with a risk of TD. Studies of newer antipsychotics suggest that TD liability is much lower with the second-generation agents, and clozapine is associated with a substantially lower risk for development of TD than other antipsychotic medications. A double-blind, random assignment study of 1,714 patients found a 0.52% long-term risk of TD with olanzapine treatment, as compared to a 7.45% risk with haloperidol. Another published double-blind randomized study showed a

significantly lower risk of TD in olanzapine-treated patients (1%) than haloperidol-treated schizophrenic patients (4.6%). In a double-blind, randomized 1-year study comparing risperidone to haloperidol, the rate of TD was 0.6% in the risperidone group and 2.7% in the haloperidol group. Among a sample of geriatric patients, a lower incidence of TD in patients treated with risperidone than in those treated with haloperidol, at least over a 9-month period, has been reported. The rate of TD with risperidone has been reported to be low (0.6%) for doses currently used (2–8 mg/day). The incidence of TD with quetiapine is preliminarily reportedly low or virtually non-existent, although this remains to be demonstrated prospectively. The risk of TD with ziprasidone and aripiprazole is not known but is expected to be similarly low.

For most patients, TD does not appear to be progressive or irreversible. The onset of TD often tends to be insidious with a fluctuating course. With time, TD will either stabilize or improve even if the antipsychotic medication is continued, although there are reports of TD worsening during continued drug therapy. After discontinuation of antipsychotic medication, a significant proportion of patients with TD will have remission of symptoms, especially if the TD is of recent onset or the patient is young. Unfortunately, withdrawal of antipsychotic agents is seldom an option for patients with serious psychosis.

The American Psychiatric Association Task Force on TD has issued a report in which a number of recommendations were made for preventing and managing TD. These include (1) establishing objective evidence that antipsychotic medications are effective for an individual; (2) using the lowest effective dose of antipsychotic drugs; (3) prescribing cautiously for children, elderly patients, and patients with mood disorders; (4) examining patients on a regular basis for evidence of TD; (5) considering alternatives to antipsychotic drugs, obtaining informed consent, and also considering a reduction in dosage when TD is diagnosed; and (6) considering a number of options if the TD worsens, including discontinuing the antipsychotic medication, switching to a different drug, or considering a trial of clozapine.

Although a large number of agents have been studied for their therapeutic effects on TD, there is no definitive drug treatment for it. Second-generation antipsychotics, in particular clozapine, have been used in clinical practice to treat TD, but there have been no adequately controlled trials to date to support this practice. It has been suggested that second-generation antipsychotics should be used as first-line treatment for patients who have TD or are at risk for TD. Guidelines for treating TD recommend using second-generation agents for mild TD symptoms, and clozapine or a newer agent for more severe symptoms.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is characterized by the triad of rigidity, hyperthermia, and autonomic instability in association with the use of an antipsychotic medication. NMS is often associated with elevation of creatine kinase (greater than 300 U/mL), leukocytosis (greater than 15,000 mm^3), and change in level of consciousness. NMS can be of sudden and unpredictable onset, usually occurring early in the course of antipsychotic treatment, and can be fatal in 5 to 20% of untreated cases.

The incidence of NMS varies from 0.02 to 3.23%, reflecting differences in criteria. Prevalence rates are unknown, but are estimated to vary from 1 to 2% of patients treated with antipsychotic medication. The relative risk of second-generation antipsychotics for NMS is likely to be lower, but conclusive data are not yet available. NMS has been reported with clozapine, risperidone, olanzapine, and quetiapine. Proposed risk factors include prior episode of NMS, younger age, male gender, physical illness, dehydration, use of high-potency antipsychotics, rapid dose titration, use of parenteral (IM) preparations, and pre-existing neurological disability.

If NMS is suspected, the offending antipsychotic agent should be discontinued and supportive and symptomatic treatment started. Both dantrolene and dopamine agonists such as bromocriptine have also been used in the treatment of NMS. These agents, however, have not shown greater efficacy compared to supportive treatment.

The usual course of treatment is between 5 and 10 days. Long acting depot preparations will prolong recovery time. After several weeks of recovery, treatment may be cautiously resumed with a different antipsychotic medication with gradually increased doses.

Endocrine and Sexual Effects

All standard antipsychotic drugs elevate serum prolactin levels by blocking the tonic inhibitory actions of dopamine on lactotrophic cells in the pituitary. Among second-generation antipsychotics, risperidone and amisulpride can produce dose-dependent hyperprolactinemia to a greater extent than first-generation antipsychotics, whereas clozapine, olanzapine, ziprasidone, and quetiapine do not cause a sustained elevation of prolactin above normal levels. Aripiprazole, being a partial DA agonist, produces no elevation of prolactin and even suppresses prolactin levels slightly. Hyperprolactinemia in women can lead to menstrual disturbances, including anovulatory cycles and infertility, menses with abnormal luteal phases, or frank amenorrhea and hypoestrogenemia. Women have also reported decreased libido and anorgasmia, and there are reports of increased long-term risk of osteoporosis although this is controversial. Antipsychotic-induced gynecomastia has been reported in 3% of women and 6% of men. Galactorrhea occurs in 2.7% of men and 10 to 50% of women. The major effects of hyperprolactinemia in men are loss of libido, impotence, hypospermatogenesis, and erectile or ejaculatory disturbances. Although amisulpride and risperidone cause significant elevations of prolactin levels, a number of studies have found only a small incidence of sexual dysfunctions in patients treated with these drugs. This may be due to the fact that these reports have relied on spontaneous reporting of sexual side effects. In a drug monitoring study, in which side effects profiles of haloperidol and clozapine were investigated, a significantly higher frequency of sexual disturbances have been found. Using a side effect rating scale, it was shown that the prevalence of these adverse events was high during the first weeks of the study. However, side effects usually remitted spontaneously despite continuous treatment in the majority of patients.

Metabolic Effects

Various degrees of weight gain have been recognized as a common problem with conventional antipsychotic medications. Weight gain is an important issue in the management of patients, because this adverse effect may be associated with non-compliance and certain medical illnesses, such as diabetes mellitus, cardiovascular disease, certain cancers, and osteoarthritis.

Differences have been discovered among second-generation antipsychotics with respect to their ability to induce weight gain (Table 1-4). A recent meta-analysis, which estimates the weight change after 10 weeks of treatment at a standard dose, demonstrated that mean increases were 4.45 kg for clozapine, 4.15 kg for olanzapine, 2.10 kg for risperidone, and 0.04 kg for ziprasidone. The long-term risk of weight gain with quetiapine appears to be less than that with olanzapine and clozapine. Short-term weight gain (2.16 kg over 10 weeks) with quetiapine appears comparable to risperidone. Ziprasidone has been associated with minimal weight gain, which could distinguish it among other second-generation antipsychotics. Similarly, aripiprazole appears to cause little or no weight gain. During long-term treatment, clozapine and olanzapine have the largest effects on weight gain; risperidone produces intermediate weight gain; quetiapine and ziprasidone produce the least weight gain. Weight gain does not appear to be dose-dependent, tends to plateau between 6 and 12 months after initiation of treatment, and is mainly due to an increase in body fat. The mechanism by which weight gain occurs during treatment with antipsychotics is poorly understood, but the broader receptor affinities of the agents and their antagonism of histamine H_1 and serotonin 5-HT_{2C} receptors have been implicated. There is currently no standard approach to the management of weight gain induced by antipsychotic medication. Patient education prior to initiating treatment should be provided, and regular exercise should be encouraged in all patients receiving antipsychotic medication. Switching to other second-generation antipsychotics with fewer propensities for producing weight gain may be the most efficient way to deal with antipsychotic-induced weight gain.

Abnormalities in peripheral glucose regulation and diabetes mellitus (DM) occur more commonly in schizophrenic patients compared with the general population. There is growing concern with metabolic disturbances associated with antipsychotic use, including hyperglycemia, hyperlipidemia, exacerbation of existing type 1 and 2 DM, new-onset type 2 DM, and diabetic ketoacidosis. A number of case reports have implicated both clozapine and olanzapine in the emergence of non-insulin-dependent (type 2) DM and diabetic ketoacidosis. There are fewer reports describing an association between DM and quetiapine or risperidone, but these drugs do appear to have this side effect potential albeit to a lesser degree. In contrast there are many fewer reports for ziprasidone and aripiprazole which suggests they may have less or no metabolic side effect liability. The limited reporting for ziprasidone may be related to the relatively limited use of the agent at the present time. Although no clear mechanism of action of the second-generation agents has been established, significant weight gain or antagonism of specific serotonin receptor subtypes may contribute to the development of these abnormalities. Physicians employing second-generation agents should routinely monitor weight, fasting blood glucose, and lipid profiles.

Cardiovascular Effects

Orthostatic hypotension is usually seen with low-potency conventional antipsychotic agents (e.g., chlorpromazine or thioridazine) and clozapine through alpha-l-adrenergic antagonism. Among the first-line second-generation antipsychotics, quetiapine has the greatest potential for inducing orthostasis although all agents have this potential. Orthostasis is most likely to occur during the first few days after initiation of treatment, or when increasing the dose of medications; most patients develop tolerance to it in the following four to six weeks. Elderly patients are particularly vulnerable to this side effect and it may predispose them to falls and increase the incidence of serious injuries or fractures. A gradual upward titration of dosage may help to reduce the risk of hypotension, and patients should be advised to change posture slowly.

Tachycardia may occur as a result of the anticholinergic effects of antipsychotic medications on vagal inhibition, or secondary to orthostatic hypotension. Clozapine produces the most pronounced tachycardia; approximately 25% of patients will have a sinus tachycardia with an increase of about 10 to 15 beats per minute. Although quetiapine has virtually no cholinergic activity, tachycardia is a possible side effect, perhaps secondary to its adrenergic effects on blood pressure. Most patients will develop tolerance to this side effect over time. If tachycardia is sustained or becomes symptomatic, an electrocardiogram (ECG) should be obtained. Low doses of a peripherally acting beta-blocker such as atenolol can be useful to treat medication-induced tachycardia without hypotension.

ECG changes are observed with many antipsychotic agents. Chlorpromazine may cause prolongation of the QT and PR intervals, ST depression, and T-wave flattening or inversion, and thioridazine may cause QT and T-wave changes. These effects rarely cause clinically relevant symptoms within therapeutic dose ranges.

Ziprasidone has very specific recommendations in the package insert as to the types of patients it should not be used in. Needless to say, antipsychotics that lead to QTc-prolongation must not be combined with other drugs that have similar effects. The effect of many but not all antipsychotic drugs on the QT interval appears to be dose-related. Several antipsychotic drugs have infrequently been associated with malignant arrhythmias such as *torsade de pointes*. To date, *torsade de pointes* has not been reported following therapeutic doses or overdose with ziprasidone or other second-generation antipsychotics.

Sudden unexplained deaths have been rarely reported with therapeutic doses of antipsychotic drugs, and such deaths could result from cardiac arrhythmias in the absence of another explanation. There is, however, currently no evidence that antipsychotic drugs are associated with an increased prevalence of sudden deaths due to cardiac events, although a number of case reports and case series concerning death following cardiomyopathy, potentially induced by clozapine are a matter of concern.

Gastrointestinal Effects

The anticholinergic effects of antipsychotic medications can induce dry mouth and constipation as well as tachycardia, urinary retention, and blurring of vision. These adverse effects are relatively commonly encountered with low-potency first-generation antipsychotics and may be dose related. In cases of more serious gastrointestinal adverse events, such as paralytic ileus, which has been reported following treatment with clozapine, medication must be discontinued immediately and relevant medical or surgical interventions may become necessary. Anticholinergic manifestations are common with poisoning from clozapine and olanzapine.

Hepatic Effects

Asymptomatic mild, transient, and reversible elevations of liver enzyme levels occur infrequently with both first- and second-generation antipsychotic drugs. These abnormalities usually occur during the first three months of treatment, are idiosyncratic, and seldom a serious concern. Rarely, symptomatic hepatotoxicity (cholestatic or hepatitic) may be associated with second-generation antipsychotics; in these cases, the offending medication should be discontinued. Recovery occurs in up to 75% of patients within two months; 90% recover within one year. Patients taking antipsychotics who have nausea, fever, abdominal pain, and rash should have their liver function evaluated to exclude hepatotoxicity. Since antipsychotic-induced jaundice is infrequent, other etiologies should be ruled out before the cause is judged to be antipsychotic treatment.

Hematological Effects

Antipsychotic medications may cause blood dyscrasias, including neutropenia, leukopenia, leukocytosis, thrombopenia, and agranulocytosis. Leukopenia, usually transient, commonly occurs early in treatment, and resolves spontaneously. Chlorpromazine has been associated with benign leukopenia, which occurs in up to 10% of patients. This

phenomenon is even more common following clozapine administration.

Agranulocytosis (granulocyte count less than 500/mm^3) is a fatal side effect of antipsychotic drugs. The risk of agranulocytosis with clozapine is 1% and is greatest early in treatment, usually within the first 8 to 12 weeks of treatment. It tends to occur slightly more often in women, the elderly, and young patients (less than 21 years old). Agranulocytosis from clozapine is usually reversible if the drug is withdrawn immediately. Olanzapine is not associated with severe agranulocytosis. Despite these encouraging studies, there are a number of case studies reporting agranulocytosis during treatment with olanzapine (and quetiapine) in patients who had suffered this adverse event during previous clozapine exposure.

Before initiating treatment with clozapine, patients in the USA must be registered in a program that ensures that they receive weekly monitoring of their white blood cell (WBC) count during the first six months of treatment. Current guidelines require weekly monitoring for one month after the termination of clozapine treatment. Guidelines on the use of clozapine vary between different countries.

Other Side Effects

Sedation is the single most common side effect among low-potency conventional antipsychotics, as well as clozapine, zotepine, and quetiapine. Although sedation is often beneficial at the beginning of treatment to calm down an anxious or aggressive patient, it usually impairs functioning during long-term treatment. Most patients usually develop tolerance over time, or it may be possible to minimize sedation by dose reduction or by shifting most of the medication to night to reduce daytime sleepiness.

Antipsychotic medications can lower the seizure threshold to some degree. Seizure is more common with low-potency first-generation antipsychotics and clozapine. Clozapine is associated with dose-related increase in seizures. For example, doses of clozapine below 300 mg/day have been found to have a seizure rate of about 1%, doses between 300 and 600 mg/day

have a seizure rate of 2.7%, and doses above 600 mg/day have a rate of 4.4%. Strategies to reduce the risk for seizures include slower dose titration, a lower dose, and the addition of an anticonvulsant agent (i.e., valproic acid).

DRUG INTERACTIONS AND ANTIPSYCHOTIC AGENTS

Most antipsychotics are metabolized by hepatic microsomal oxidases (cytochrome P450 system); the major isoenzyme systems involved are CYP1A2, CYP2C19, CYP2D6, and CYP3A4. Induction or inhibition of these enzymes by other drugs may occasionally produce clinically important drug interactions. Table 1-5 summarizes clinically significant pharmacokinetic drug interactions involving second-generation antipsychotic drugs. SSRI's, particularly fluoxetine and paroxetine, can increase plasma concentrations of antipsychotic medications by inhibiting CYP2D6 and decreasing the clearance of antipsychotics, possibly leading to toxicity. Conventional antipsychotic drug clearance can be decreased by 50% with concurrent administration of certain heterocyclic antidepressants, beta-blockers, some antibiotic/antifungal agents, and cimetidine. Clozapine toxicity has occurred following co-administration with the CYP1A2 inhibitors cimetidine, erythromycin, and fluvoxamine.

Quetiapine, ziprasidone, and aripiprazole toxicity can be caused by inhibitors of CYP3A4 such as erythromycin, fluoxetine, nefazadone, and protease inhibitors.

In contrast, drugs such as carbamazepine, phenobarbital, and phenytoin can reduce plasma concentrations of antipsychotic drugs by increasing the metabolism of the antipsychotic agent. For example, carbamazepine, commonly combined with antipsychotic medications, can reduce the plasma concentration of haloperidol by 50%. Anticonvulsants, however, may not have a significant effect on the metabolic clearance of olanzapine or risperidone as they are not substantially metabolized through CYP3A4. Cigarette smoking increases drug clearance for many antipsychotic drugs, including clozapine and olanzapine. The clearance rate of clozapine and olanzapine are increased by 20 to 50%.

■ **TABLE 1-5.** Pharmacokinetic Drug Interactions Involving Second-Generation Antipsychotic Agents

DRUG AND CYTOCHROME P-450 ISOENZYME(S)	INHIBITORS	INDUCERS
Clozapine		
1A2	Fluoroquinolones, fluvoxamine	Smoking, PAHs[a]
3A4	Erythromycin, ketoconazole, ritonavir, sertraline,[b] cimetidine	Rifampin, carbamazepine, phenytoin, barbiturates
2D6	Ritonavir, quinidine, risperidone,[b] fluoxetine,[b] sertraline[b]	None
Risperidone		
2D6	Paroxetine, fluoxetine	Rifampin, carbamazepine, phenytoin, barbiturates
Olanzapine		
1A2	Fluvoxamine	Smoking, PAHs, carbamazepine
2D6	None	Phenytoin
Quetiapine		
3A4	Ketoconazole, erythromycin	Rifampin, carbamazepine, phenytoin, barbiturates
Ziprasidone		
3A4	Ketoconazole, erythromycin	Rifampin, carbamazepine, phenytoin, barbiturates
	None	None
Aripiprazole		
3A4	Ketoconazole, erythromycin	Rifampin, carbamazepine, phenytoin, barbiturates
2D6	Paroxetine, fluoxetine	None

[a] PAHs, polycyclic aromatic hydrocarbons.
[b] Case reports of mild to moderate elevations in serum concentration.

Adapted from Worrel JA, Marken PA, Beckman SE, et al. (2000) Atypical antipsychotic agents: A critical review. *Am J Health Syst Pharm* 57, 238–255.

Other common interactions are:

- Antacids: can decrease the absorption of the antipsychotic agent from the gut.
- Antipsychotics: can antagonize the effects of dopamine agonists or levodopa when these drugs are used to treat parkinsonism
- Antipsychotic agents: may also enhance the effects of CNS depressants such as analgesics, anxiolytics, and hypnotics.
- Doses of pre-anesthetic medication or general anesthetics may need to be reduced.

Antipsychotic Medications and Pregnancy

Most antipsychotic agents readily cross the placenta and are secreted in breast milk to some degree. There is little data to demonstrate whether prenatal exposure to antipsychotic agents is linked to spontaneous abortion, congenital malformations, carcinogenesis, intrauterine growth retardation, or behavioral teratogenicity.

Fetal exposure over the course of pregnancy may affect development of the dopamine system; the benefits of controlling psychotic symptoms during pregnancy versus the possible risks to the mother and the fetus of withdrawing treatment and the risks to the fetus of continuing treatment must be considered.

There is no evidence that second-generation antipsychotics are teratogenic in humans. However, if possible, use of antipsychotic medication should be avoided during the first trimester, especially between weeks six and ten, unless the patient's psychosis places the mother and/or her fetus at significant risk. Antipsychotic medications may be relatively safe during the second and third trimesters of pregnancy.

If a first-generation antipsychotic is used, high-potency agents appear to be preferable for first-line management, due to a lower propensity to cause orthostasis. Low doses should be given, administration of antipsychotic medication should be as brief as possible, and the medication should be discontinued five to ten days before delivery to minimize the chances of the newborn experiencing EPS. This notion, however, has been re-evaluated, since discontinuation of medication before

delivery may put the mother at risk for decompensation. Anticholinergic agents should also be avoided during pregnancy, especially for the first trimester. Since antipsychotics are also secreted into breast milk, the infants should not be breast-fed if the mother resumes antipsychotic medication postpartum.

ADDITIONAL READING

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