ASHP Therapeutic Position Statement on the Use of Second-Generation Antipsychotic Medications in the Treatment of Adults with Psychotic Disorders

Position

The American Society of Health-System Pharmacists (ASHP) recognizes that schizophrenia, schizoaffective disorder, and other psychotic disorders are serious mental illnesses that can significantly affect an individual's perceptual, behavioral, affective, and cognitive functions. These conditions are usually chronic and recurrent, necessitating continuous treatment over the patient's lifetime. Individuals with these disorders frequently require lengthy and expensive hospitalizations, as well as a variety of ongoing rehabilitative and supportive services that can impose a significant burden on society. In addition, high rates of suicidal behavior and completed suicides have been observed in patients with psychotic disorders. The management of these disorders typically requires long-term treatment with antipsychotic medications, the use of adjunctive pharmacologic treatments, and ongoing psychosocial and supportive interventions to reduce morbidity and mortality.

ASHP encourages health professionals to consider the use of second-generation ("atypical" or "novel") antipsychotics as first-line drug treatments for individuals with psychotic disorders. Second-generation antipsychotics share the common pharmacologic action of dual serotonin–dopamine antagonism. While the acquisition costs of these agents are greater than those of older drugs, randomized controlled trials and naturalistic studies have demonstrated that second-generation antipsychotics effectively treat the symptoms of psychotic disorders while providing a tolerability profile that improves treatment adherence and reduces the severity of short- and long-term adverse motor effects. Second-generation antipsychotics have also been found to have improved profiles for cognitive impairments in schizophrenia, relative to older agents, allowing for opportunities toward psychosocial rehabilitation. There is also evidence that the use of these agents improves outcomes in patients with chronic psychotic disorders compared with older antipsychotics, specifically reducing the rates of symptom relapse and inpatient rehospitalization. However, it should be noted that second-generation antipsychotics are associated with significant treatment risks, such as adverse cardiovascular and metabolic effects, that should be carefully considered during treatment initiation and throughout the course of therapy.

Background

Schizophrenia and schizoaffective disorder are serious, chronic mental illnesses that affect perceptual, behavioral, and cognitive functioning. The *DSM-IV-TR* established criteria for five main subtypes of schizophrenia and for schizoaffective disorder.[1] Individuals with schizophrenia generally exhibit a mixture of positive, negative, and cognitive symptoms with varying intensity throughout the course of their illness (Table 1). Schizoaffective disorder differs from schizophrenia in that recurrent mood episodes (mania or depression) occur over a substantial period of time over the course of the illness in addition to chronic psychotic symptoms. These two disorders have been studied together in many clinical trials and will be considered together for the purpose of this document.

It has been estimated that the worldwide lifetime frequency of psychotic disorders is about 1%.[2,3] Onset of the first severe psychotic symptoms in a patient with schizophrenia usually occurs between the late teens and mid-30s, with onset in males peaking between ages 15 and 30 and females exhibiting a later onset, between ages 20 and 35.[4,5] Late-onset schizophrenia, occurring after 40 years of age, may have an otherwise similar course to typical adult-onset schizophrenia. Prodromal symptoms of psychosis occurring in children and adolescents (e.g., apathy, social withdrawal) may be present before the first psychotic break, but the full symptoms of these disorders are rare in this population. Because these illnesses frequently have their symptom onset in early adulthood and are characterized by a wide range of symptoms, they usually cause significant, progressive impairment in the social, occupational, and academic functioning of affected individuals.

Pharmacologic Characteristics of Antipsychotic Drugs

The effectiveness of first-generation antipsychotic agents, whose primary mechanism of action was blockade of postsynaptic dopamine type 2 (D_2) receptors in the brain, led to the initial hypothesis regarding dopamine's role in schizophrenia. While it is apparent that increased dopamine in the mesolimbic pathway is responsible for the positive symptoms of schizophrenia, it is now understood that psychotic disorders frequently involve numerous neurochemical abnormalities. Psychosis has been observed in individuals with idiopathic[6] and drug-induced[7] hypofunction of the glutamate

Table 1.
Positive, Negative, and Cognitive Symptoms of Schizophrenia

Positive Symptoms	Negative Symptoms	Cognitive Symptoms
Hostility	Emotional withdrawal	Impaired attention
Excitement	Uncooperativeness	Impaired short-term memory
Hallucinations	Blunted affect	Impaired executive functioning
Delusions	Inappropriate affect	Impaired verbal fluency
Suspiciousness	Poverty of thought	
Grandiosity	Social withdrawal	
Conceptual disorganization	Lack of spontaneity	
	Poor abstract thinking	

system. In addition, the high rate of nicotine dependence in individuals with psychotic disorders–up to 88% in one study[8]—has led to the identification and study of acetylcholine-receptor abnormalities in the pathophysiology of schizophrenia.[9]

The ideal drug for the treatment of psychotic disorders would have several important characteristics. It would provide effective relief and prevention of acute positive symptoms of schizophrenia. Other ideal characteristics would include effective relief of affective, cognitive, and negative symptoms; minimal short- and long-term adverse effects; few drug interactions; and low acquisition cost. Although no antipsychotic agent currently available completely fits all these criteria, second-generation antipsychotics offer many benefits not achieved with traditional antipsychotics.

First-generation antipsychotic agents primarily exert their therapeutic effects through the blockade of postsynaptic D_2 receptors in the mesolimbic pathway, thereby reducing positive symptoms over time. However, these drugs are not selective in their activity. Blockade of dopamine in other areas of the brain often leads to acute extrapyramidal motor effects (e.g., dystonias, parkinsonism), tardive dyskinesia, increased levels of serum prolactin, and exacerbation of negative symptoms. Although occurring infrequently at standard doses, an array of adverse neurologic, cardiovascular, and dermatologic effects are associated with these agents.

Second-generation antipsychotic drugs share the common pharmacologic action of dual serotonin–dopamine antagonism (Table 2). Aripiprazole differs slightly in that it functions as a partial agonist at dopamine receptors, reducing dopamine activity in the mesolimbic pathway.[10,11] Antagonism of serotonin type 2 ($5\text{-}HT_2$) receptors increases the release of endogenous dopamine.[12] This increase in dopamine decreases the likelihood of extrapyramidal motor symptoms and elevated prolactin levels without significantly reducing the beneficial effects against positive symptoms of psychosis. Theoretically, this property of the newer drugs may also help to improve the negative symptoms of schizophrenia.

Efficacy for Psychotic Symptoms

Second-generation antipsychotic agents have been demonstrated to be at least as effective as the traditional antipsychotic agents in the treatment of positive symptoms of schizophrenia when used in appropriate therapeutic doses. The newer antipsychotics also demonstrate benefits for affective symptoms, cognition, and psychosocial functioning not seen with the older agents.

Clozapine, the first second-generation antipsychotic introduced in the United States, has an established level of efficacy for use in individuals with psychotic disorders resistant to treatment with other antipsychotics. Kane et al.[13] conducted the landmark trial that demonstrated the superior efficacy of clozapine in individuals with treatment-resistant psychosis. This trial enrolled only patients whose psychosis was treatment resistant, defined as not responding to at least three periods of treatment in the preceding five years with antipsychotic agents from two different chemical classes at dosages equivalent to 1000 mg/day of chlorpromazine for six weeks. The previous antipsychotic trials must have failed to provide periods of good functioning or significant symptomatic relief. A six-week trial of haloperidol (mean dosage, 61 mg/day) and benztropine followed to confirm lack of drug response. Participants whose psychosis did not respond to haloperidol were randomized to receive clozapine (up to 900 mg/day) or chlorpromazine (up to 1800 mg/day) with benztropine. Using a priori criteria, response rates were 30% for patients treated with clozapine versus 4% for the chlorpromazine group. The authors found that improvements in the Brief Psychiatric Rating Scale total scores and clinical global impression (CGI) were three times greater in patients treated with clozapine.

The landmark clinical studies used in the evaluation of second-generation antipsychotics are summarized in Table 3. In general, these trials lasted four to six weeks and assessed the efficacy of these agents in the treatment of acute psychotic disorders. Because of the study designs employed, no assumptions can be made regarding the efficacy of these agents for long-term prevention of psychotic relapse, for comorbid substance abuse or mood disorders, or in other complex clinical situations. The medical literature suggests that all currently available second-generation antipsychotic agents are superior to placebo and at least as effective as the traditional antipsychotics in the reduction of positive symptoms of schizophrenia. With long-term therapy, second-generation antipsychotics may also have beneficial effects on negative symptoms; however, these benefits have not been consistently demonstrated in the four- to six-week clinical trials.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a multicenter clinical study sponsored by the National Institute of Mental Health.[25] The first phase of this study, conducted between January 2001 and December 2004, involved 1460 patients with chronic schizophrenia age 18–65 years. Patients were randomized to treatment for up to 18 months with one of four available second-generation antipsychotics (olanzapine, quetiapine, risperidone, or ziprasidone) or perphenazine, a traditional antipsychotic. The primary outcome measured was time to discontinuation of treatment for any cause, including lack of efficacy, intolerable adverse effects, or patient's decision to end treatment. Treatment with olanzapine at a mean modal dosage (MMD) of 20.1 mg/day was associated with a significantly longer median duration of treatment (9.2 months) compared with quetiapine (4.6 months; MMD, 543.4 mg/day), risperidone

Table 2.
Second-Generation Antipsychotics Currently Available in the United States

Drug (Trade Name)	Manufacturer	Year Approved
Clozapine (Clozaril)	Novartis	1989
Risperidone (Risperdal)	Janssen Pharmaceutica	1993
Olanzapine (Zyprexa)	Eli Lilly	1996
Quetiapine (Seroquel)	AstraZeneca	1997
Ziprasidone (Geodon)	Pfizer	2001
Aripiprazole (Abilify)	Bristol-Myers Squibb	2002
Paliperidone (Invega)	Janssen Pharmaceutica	2006

Table 3.
Major Efficacy Trials of Second-Generation Antipsychotics[13–24]

Ref.	Patient Population	Treatment	Duration (wk)	Results[a]
13	268 inpatients with schizophrenia refractory to treatment with adequate trials with at least three agents from two different chemical classes, after nonresponse to 6-wk trial of haloperidol	Clozapine 500–900 mg/day vs. chlorpromazine 1000–1800 mg/day + benztropine (up to 6 mg/day)	6	BPRS total, CGI: Improvement with clozapine 3 times greater than with chlorpromazine ($p < 0.001$). Patient improvement (20% reduction in BPRS and either CGI of ≤3 or BPRS total of ≤35: Clozapine, 30%; chlorpromazine, 4% ($p < 0.001$).
14	39 outpatients with schizophrenia with history of residual symptoms after at least two 6-wk trials of neuroleptics from different classes, after nonresponse to 6-wk trial of fluphenazine	Clozapine 200–600 mg/day vs. haloperidol 10–30 mg/day + benztropine (up to 4 mg/day)	10	BPRS positive symptoms: Improvement with clozapine greater than with haloperidol ($p = 0.05$). SANS: Improvement with clozapine, worsening with haloperidol ($p = 0.04$). Clinical response rate: Clozapine, 44.4%; haloperidol, 5.5% ($p = 0.017$).
15	388 inpatients with schizophrenia	Risperidone 2, 6, 10, and 16 mg/day; haloperidol 20 mg/day; placebo	8	Clinical improvement (20% reduction in PANSS): Greater improvement in patients receiving risperidone 6 and 16 mg vs. haloperidol. Clinical improvement (Kane et al. criteria): Risperidone 6, 10, and 16 mg superior to placebo ($p < 0.05$).
16	135 patients with schizophrenia	Risperidone 2, 6, 10, and 16 mg/day; haloperidol 20 mg/day; placebo	8	Clinical improvement (20% reduction in PANSS): Greater improvement in patients receiving risperidone 2, 6, 10, and 16 mg and haloperidol recipients vs. placebo. PANSS—negative subscale: Only risperidone 6 mg superior to placebo.
17	400 patients with schizophrenia	Risperidone long-acting injection 25, 50, and 75 mg every 2 wk vs. placebo	12	Improvement in PANSS and CGI (LOCF) significant for all groups vs. placebo.
18	335 patients with schizophrenia	Olanzapine-L (2.5–7.5 mg/day), olanzapine-M (7.5–12.5 mg/day), olanzapine-H (12.5–17.5 mg/day), haloperidol 10–20 mg/day, placebo	6	CGI, BPRS: Olanzapine-M, olanzapine-H, and haloperidol groups significantly improved vs. placebo. SANS: Olanzapine-H group demonstrated significant improvement vs. haloperidol.
19	152 inpatients with schizophrenia	Olanzapine 1 and 10 mg/day vs. placebo	6	BPRS total, PANSS-negative score: Olanzapine 10-mg group superior to placebo. Olanzapine 1-mg group showed no improvement over placebo for any efficacy measure.
20	361 hospitalized patients with schizophrenia	Quetiapine 75, 150, 300, 600, and 750 mg/day; haloperidol 12 mg/day; placebo	6	BPRS total: Significant improvement from baseline vs. placebo noted in all treatment groups except quetiapine 75 mg. SANS: Significant improvement vs. placebo noted in quetiapine 300 mg and haloperidol groups.

(Continued on next page)

Table 3 *(continued)*

Ref.	Patient Population	Treatment	Duration (wk)	Results[a]
21	286 hospitalized patients with schizophrenia	Quetiapine-H (up to 750 mg/day), quetiapine-L (up to 250 mg/day), placebo	6	BPRS total, CGI, SANS: Quetiapine-H demonstrated significant improvement over placebo. Quetiapine-L group did not show superiority to placebo for any efficacy measure.
22	302 patients with schizophrenia or schizoaffective disorder	Ziprasidone 80 mg/day(40 mg b.i.d.) and 160 mg/day (80 mg b.i.d.), placebo	6	BPRS, PANSS, CGI: Both active treatment groups demonstrated significant improvement over placebo. MADRS: Subset of ziprasidone 160-mg group with depressive symptomatology demonstrated improvement vs. placebo.
23	139 patients with schizophrenia or schizoaffective disorder	Ziprasidone 40 and 120 mg/day, placebo	4	BPRS total, CGI: Ziprasidone 120-mg group demonstrated significant improvement.
24	414 patients with schizophrenia or schizoaffective disorder	Aripiprazole 15 and 30 mg/day, haloperidol 10 mg/day, placebo	4	PANSS total: Significant improvement with all active treatment groups at 2 wk. CGI: Scores in LOCF analysis superior to placebo for all active treatment groups.

[a]BPRS = Brief Psychiatric Rating Scale, CGI = clinical global impression, SANS = Schedule for the Assessment of Negative Symptoms, PANSS = Positive and Negative Syndrome Scale, MADRS = Montgomery–Asberg Depression Rating Scale, LOCF = last observation carried forward.

(4.8 months; MMD, 3.9 mg/day), perphenazine (5.6 months; MMD, 20.8 mg/day), and ziprasidone (3.5 months; MMD, 112.8 mg/day). For patients remaining on the assigned treatment over the course of the study, overall psychopathology as assessed by the Positive and Negative Syndrome Scale and the CGI showed improvement over time. Notably, the traditional antipsychotic perphenazine demonstrated comparable efficacy to the second-generation comparators across all measures.

There are several concerns that need to be considered regarding CATIE. First, within the 18-month study period, 74% of the patients discontinued their initial assigned drug therapy. Second, patients with preexisting tardive dyskinesia were not assigned to perphenazine and may have been less likely to exhibit adverse motor effects during the study. Finally, 30% of the patients receiving olanzapine experienced weight gain and adverse metabolic effects, including elevated blood glucose, cholesterol, triglyceride, and glycosylated hemoglobin levels. CATIE compared a single traditional antipsychotic, perphenazine, given at a low dosage to several second-generation antipsychotics. While the data generated from this study are helpful for determining differences in effectiveness between the assigned regimens and comparing important adverse effect issues, they support the widely held notion that the selection of antipsychotic drugs should be an individualized process.

Neurocognitive Effects

Impaired cognitive functioning has long been observed as a core feature of psychotic disorders. These impairments are relatively stable over the natural course of the illness, regardless of the frequency of acute exacerbations of psychotic symptoms.[26] Furthermore, cognitive impairment may have a greater impact on psychosocial functioning than any other feature of schizophrenia.[27,28]

Many domains of cognition, including attention, short-term memory, and executive function, are affected by schizophrenia.[26] Treatment with traditional antipsychotic drugs, while relieving positive symptoms of psychosis, do little to improve cognitive functioning. The concomitant use of anticholinergic drugs intended to prevent or treat extrapyramidal symptoms that accompany antipsychotic therapy may actually worsen some cognitive functions.[29]

Second-generation antipsychotics can play an important role in facilitating the psychosocial rehabilitation of individuals with psychotic disorders by improving cognition. These agents have been shown to improve scores on assessments representing a broad range of cognitive functions. A lower degree of binding to dopamine-D_2 receptors, as well as 5-HT_2 antagonism, in the mesocortical pathway may contribute to the beneficial effects on cognition. The individualized receptor-binding properties of second-generation antipsychotics may contribute to differential improvements in various cognitive domains in individuals with psychotic disorders.

In a 14-week study of individuals with treatment-resistant schizophrenia, risperidone and olanzapine improved executive function, declarative memory, and attention.[30] Clozapine has been shown to positively affect executive function and working memory in numerous studies.[31-33] In an open-label study of 255 clinically stable patients, ar-

ipiprazole and olanzapine improved working memory from baseline after eight weeks of treatment, while aripiprazole showed a greater improvement than olanzapine in verbal learning at weeks 8 and 26.[34]

Adverse Effects

One of the primary advantages of second-generation antipsychotics in the chronic treatment of psychotic disorders is the improved tolerability profile over older antipsychotics. Adverse effects related to dopamine blockade in the central nervous system tend to occur less frequently in individuals treated with second-generation antipsychotics compared with those receiving traditional antipsychotics. However, the newer drugs have been associated with different problems that can affect drug therapy.

Motor Symptoms. Treatment with conventional antipsychotics has long been associated with both acute and chronic adverse motor effects. Acute extrapyramidal symptoms—dystonia, pseudoparkinsonism, and akathisia (a syndrome of subjective anxiety and restlessness)—are thought to be related to drug-induced blockade of dopamine receptors in the nigrostriatal pathway in the brain. Second-generation antipsychotics, possibly through a combination of 5-HT_2-receptor antagonism and rapid dissociation from D_2 receptors,[35] produce antipsychotic effects with a lower likelihood of acute extrapyramidal symptoms.[36]

Tardive dyskinesia, a potentially irreversible chronic motor disorder caused by long-term exposure to dopamine antagonists, has been another serious concern with conventional antipsychotics. Though not completely eliminating the risk, second-generation antipsychotics have been shown to have a lower risk of treatment-emergent tardive dyskinesia with maintenance treatment. Using data pooled from three controlled comparative studies, Tollefson et al.[37] reported that 50 (7.1%) of 707 olanzapine-treated patients manifested symptoms of tardive dyskinesia during the trials, compared with 32 (16.2%) of 197 individuals treated with haloperidol ($p < 0.001$). In a nine-month prospective study of outpatients age 45 years or older, the risk of developing tardive dyskinesia was over four times greater for patients treated with haloperidol than for those receiving risperidone ($p = 0.045$).[38] Similar results have been found in other controlled and noncontrolled studies of risperidone, olanzapine, and quetiapine.[39-41]

Clozapine appears to have an especially favorable profile for the prevention and management of antipsychotic-induced movement disorders. In comparative trials, clozapine exhibited little to no evidence of inducing treatment-emergent extrapyramidal symptoms.[13,42,43] The risk of tardive dyskinesia associated with clozapine treatment also appears to be minimal.[44] In fact, clozapine has been used to successfully treat preexisting tardive dyskinesia. Remission of symptoms has been reported in some, but not all, cases of preexisting tardive dyskinesia treated with clozapine.[45-47] In addition, withdrawal of clozapine in patients with tardive dyskinesia has resulted in either maintenance of reduced movements[46] or worsening of dyskinesias. The inconsistent nature of tardive dyskinesia treatment makes prevention of this syndrome a very important consideration in the pharmacotherapy of psychotic disorders.[48]

Prolactin Elevation. Dopamine antagonists may elevate serum prolactin levels by decreasing the prolactin inhibitory effects of dopamine in the hypothalamus. Prolactin elevation has been reported to cause an irregular or suppressed menstrual cycle,[49] galactorrhea,[50] gynecomastia, and sexual dysfunction[51] in the short term. With long-term elevation of plasma prolactin levels, suppression of estrogen and testosterone may occur. These effects may lead to a decrease in bone mineral density and to osteoporosis.[52]

The degree of prolactin elevation that an antipsychotic agent may exert appears to be related to its dopamine- and serotonin-binding properties. Significant prolactin elevation and its associated adverse effects can occur with moderate-to-high doses of the traditional antipsychotics and risperidone.[52] Risperidone has been consistently associated with the greatest degree of prolactin elevation among the second-generation antipsychotics.[53,54] In a prospective trial, olanzapine was found to cause a low and transient increase in prolactin levels across its dosage range, compared with the significant, persistent hyperprolactinemia associated with haloperidol.[55] The effect of quetiapine treatment across its dosage range on plasma prolactin levels was comparable to placebo, while significant elevations were associated with haloperidol.[20] Similarly, aripiprazole has been shown to be comparable to placebo for prolactin elevation.[24] Antipsychotic-associated prolactin elevation has been successfully managed by switching to an antipsychotic agent with a lower propensity toward increasing prolactin.[56,57]

Weight Gain. The metabolic effects of antipsychotic drug therapy have become a source of concern for clinicians and patients. Psychotic disorders and antipsychotic drug treatment have long been associated with comorbid obesity[58] and its related conditions: type 2 diabetes mellitus[59,60] and cardiovascular disease.[61] In addition, drug treatments[62] and lifestyle changes[63,64] aimed at weight reduction may be ineffective or difficult to implement in this population.

Varying degrees of weight gain have been reported with chronic use of traditional and second-generation antipsychotics. Among the traditional antipsychotics, loxapine[65] and molindone[66,67] are notable for weight-loss or weight-neutral profiles. Of the second-generation antipsychotics, ziprasidone and aripiprazole have been associated with the lowest likelihood for causing weight gain. A large meta-analysis by Allison et al.[68] was conducted to compare the weight gain associated with the use of various antipsychotic drugs that were approved or under investigation in the United States. Table 4 lists estimated weight gain after 10 weeks of treatment on drugs for which sufficient data are available. Clozapine and olanzapine were associated with more weight gain than all other agents included in this review. The small weight loss associated with placebo may have been due to discontinuation of antipsychotic therapy as the subjects entered the studies.

The antipsychotic agents also appear to differ in the duration and rate of weight changes. In one study, weight increases with continuous clozapine treatment occurred until about 46 months of treatment, with the greatest amount of weight being gained during the first 12 months.[69] Weight gain with olanzapine may plateau after 4-5 months.[70]

Table 4.
Estimated Body Weight Changes at 10 Weeks in Patients Receiving Antipsychotics[68]

Treatment	Weight Gain (kg)
Placebo	–0.74
Molindone	–0.39
Ziprasidone	0.04
Fluphenazine	0.43
Haloperidol	1.08
Risperidone	2.10
Chlorpromazine	2.58
Thioridazine-mesoridazine	3.19
Olanzapine	4.15
Clozapine	4.45

Diabetes Mellitus. New-onset hyperglycemia and diabetes mellitus have also been observed with antipsychotic treatment. In some instances, the initial presentation consists of life-threatening diabetic ketoacidosis or hyperosmolar coma.[71] Frequently, clinically significant weight gain does not occur before the diagnosis of diabetes.[72] Koller et al.[73] reviewed cases of hyperglycemic episodes associated with risperidone and haloperidol reported to the Food and Drug Administration's (FDA's) MedWatch surveillance program. Of the 131 cases of hyperglycemia associated with antipsychotic monotherapy with risperidone, 78 were clearly identified as newly diagnosed hyperglycemia. In the cases for which adequate data were available, 71% of cases with preexisting hyperglycemia and 48% of cases of new-onset hyperglycemia occurred within the first three months of risperidone monotherapy.

Sernyak et al.[74] conducted a large analysis of a national sample of patients treated for schizophrenia in Veterans Affairs medical centers to investigate a possible association between the use of antipsychotic medications and development of diabetes mellitus. Patients were identified as being treated with clozapine, olanzapine, quetiapine, risperidone, or traditional antipsychotics. When the patients were stratified by age, significantly higher rates of comorbid diabetes were found in patients treated with second-generation antipsychotics. Overall, clozapine, olanzapine, and quetiapine were most frequently implicated. The strongest relationships were found in individuals less than 40 years of age.

Plasma glucose regulation in individuals receiving antipsychotics and in healthy controls was assessed using oral glucose tolerance tests.[75] Olanzapine-treated patients demonstrated significantly elevated plasma glucose levels while fasting and at 15, 45, and 75 minutes postload compared with controls and patients treated with traditional antipsychotics. Clozapine-treated patients had significant elevations while fasting and at 75 minutes postload compared with controls and patients receiving traditional antipsychotics. With risperidone, the elevations in plasma glucose were seen in the fasting state and at 45 and 75 minutes postload and were significantly higher compared with healthy controls.

Dyslipidemias. Hyperlipidemia is another significant cardiac risk associated with second-generation antipsychotic treatment. Increases in serum triglycerides and low-density lipoproteins with second-generation antipsychotics have not always correlated with significant weight gain.[76]

A retrospective analysis of long-term inpatients treated with risperidone and olanzapine was conducted to determine trends of various metabolic values.[77] The investigator reported that the average increase in triglyceride concentrations was 104.8 mg/dL with olanzapine versus 31.7 mg/dL with risperidone after one year. Total cholesterol increased by 30.7 mg/dL with olanzapine and 7.2 mg/dL with risperidone. A naturalistic study of clozapine treatment revealed a significant increase in serum triglyceride level over five years of treatment.[69] In CATIE, olanzapine was associated with the greatest exposure-adjusted increases in serum cholesterol and triglycerides.[25]

In November 2003, a consensus panel that included experts from the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity was convened. Using data collected during a comprehensive literature review and presentations from representatives from the pharmaceutical industry and FDA, the consensus panel developed a statement outlining the metabolic risks of treatment with second-generation antipsychotics.[78] The panel recommended careful consideration of metabolic risks whenever second-generation antipsychotics are initiated, especially in high-risk patients. The panel also recommended considering switching antipsychotics in patients who gain 5% or more of their initial weight, experience worsening hyperglycemia, or develop worsening hyperlipidemia.

Cardiac Toxicity. Certain traditional and second-generation antipsychotics have been associated with clinically significant prolongation of the corrected Q-T (Q-Tc) interval, which may lead to torsades de pointes, a fatal ventricular arrhythmia. The risk of cardiac mortality associated with psychotropic drug treatment is particularly troublesome because of its spontaneous and unpredictable nature.

The traditional antipsychotics thioridazine, mesoridazine, pimozide, and droperidol have been implicated in numerous cases of sudden unexpected death.[79] Electrocardiographic data have revealed that patients receiving droperidol and thioridazine are more likely to have an abnormally long Q-Tc interval.[80] Numerous reports of patient fatalities and the availability of safer alternatives have prompted FDA to recommend that thioridazine, mesoridazine, pimozide, and droperidol only be used as alternative agents with extreme caution.

Although regulatory scrutiny for cardiac assessment heightened during the development of second-generation antipsychotics, these agents are generally associated with a low risk of electrocardiographic abnormalities. Ziprasidone was found to be associated with modest Q-Tc prolongation during its premarketing studies. A comparative study that sought to determine the extent of Q-Tc prolongation seen with the target therapeutic dosages of haloperidol, risperidone, olanzapine, quetiapine, and ziprasidone was later presented to FDA.[81] Thioridazine was also assessed in this study at half its maximum recommended dosage. Thioridazine was associated with an average Q-Tc-interval increase of 35.6 milliseconds. Of the second-generation agents included in this study, ziprasidone was associated with the greatest mean increase in the Q-Tc interval—20.3

milliseconds. Haloperidol-treated subjects had an average Q-Tc-interval increase of 4.7 seconds, the smallest change observed in this study. Coadministration of other interacting drugs (e.g., cytochrome P-450 isoenzyme inhibitors) did not lead to significant changes in Q-Tc measurement. Ziprasidone's labeling warned of its greater potential of Q-Tc-interval prolongation and discouraged use in patients with electrolyte abnormalities, cardiac comorbidity, or concomitant use of metabolic inhibitors.[82]

Clozapine has been associated with treatment-emergent myocarditis and cardiomyopathy. Myocarditis associated with clozapine treatment presents as an acute inflammation of the myocardium, which may lead to congestive heart failure.[83] With over 180,000 patient exposures to clozapine during the first 10 years of its clinical use in the United States, FDA received 28 reports of myocarditis, including 18 deaths.[84] The greatest risk of fatal events appears to exist during the first month of therapy. Cardiomyopathy associated with clozapine is an insidious process characterized by ventricular dilatation, impaired contraction, and symptoms of congestive heart failure.[83] A total of 41 cases of cardiomyopathy, including 10 deaths, were reported to FDA between 1989 and 1999.[84]

Cerebrovascular Events. The use of second-generation antipsychotics for the treatment of dementia-related agitation and psychosis in elderly patients is an unlabeled use that is generally supported by efficacy data in published controlled clinical trials.[85] However, post hoc analyses of the safety data for these trials revealed an elevated risk of cerebrovascular adverse events (CVAEs), including stroke and transient ischemic attacks, among patients treated with second-generation antipsychotics. These data led FDA to issue a public health advisory warning of the potential for fatal CVAEs in patients with dementia being treated with second-generation antipsychotics. The manufacturers of second-generation antipsychotic agents were also requested to place a black-box warning describing this treatment risk on the labeling of these products.

A closer look at the applicable safety data reveals that the patients in the dementia trials were often at elevated risk for CVAEs because of advanced age, poor control of chronic cardiovascular disease, and the underlying etiology of the dementia.[86] Cases of CVAEs included nonspecific events, such as hypotensive episodes, periods of unresponsiveness, and slurred speech. For example, the pooled results of six placebo-controlled randomized studies of risperidone for the treatment of behavioral disturbances in patients with dementia revealed 33 CVAEs (3.3%) in 1009 subjects receiving the drug. The frequency of CVAEs was 1.1% (8 of 712) among placebo-treated patients ($p = 0.004$). However, serious CVAEs (fatal events, life-threatening events, or CVAEs associated with hospitalization or disability) occurred in 15 (1.5%) of 1009 patients treated with risperidone and 4 (0.6%) of 712 patients treated with placebo, a difference that failed to reach statistical significance. Furthermore, most patients experiencing stroke had risk factors, including hypertension, atrial fibrillation, and previous strokes.[86]

The nature of this type of safety data makes it difficult to determine causality. It has been postulated that the adverse effects of sedation, hypotension, pseudoparkinsonism, and enhanced platelet aggregation may contribute to the observed increase in CVAEs.[86] In addition, these findings have not been widely observed among patients with psychotic disorders. It would therefore be advisable to consider stroke prophylaxis in all elderly patients receiving antipsychotic drugs, particularly high-risk patients.

Hematologic Toxicity, Respiratory Depression, and Seizures. Despite its superior efficacy for treatment-resistant psychotic disorders, the use of clozapine has remained restricted due to the potential of severe adverse effects not commonly seen with other antipsychotics. Agranulocytosis has been estimated to occur in 1–2% of patients treated with clozapine.[87] Episodes tend to occur between two and six months after initiation of treatment.[88] Fatal infectious complications may occur as a result of reduced white blood cell count. Clozapine-induced agranulocytosis can be reversed with the prompt discontinuation of treatment.

In the United States, clozapine is available only under the surveillance of one of the national manufacturer-operated registries that monitor weekly complete blood counts from individuals taking this agent. Consistent monitoring has resulted in a markedly reduced rate of agranulocytosis and mortality associated with clozapine-induced agranulocytosis.[89] Furthermore, the continual monitoring mandated by the clozapine registry programs likely allows for improved treatment adherence and outcomes.[90]

Other toxicities that are more common with clozapine than with other second-generation antipsychotics are respiratory depression and seizures. Respiratory collapse has been associated with rapid dosage adjustment and concomitant benzodiazepine use. It is therefore recommended that clozapine dosage be gradually adjusted from the starting dose if the patient is new to clozapine treatment or if two or more days have elapsed since the last dose. A dose-related reduction of the seizure threshold has been observed with clozapine.[91] Precautions should be taken for patients with seizure disorders receiving clozapine treatment.

Drug Selection and Dosing Considerations

With the notable exception of clozapine, the principal differences among the available second-generation antipsychotics lie in their adverse-effect profiles and dosage forms. Selection of an initial treatment for a patient whose psychosis is not considered to be treatment resistant should be individualized based on the patient's specific tolerability and compliance concerns.[92] Individuals with a sensitivity to extrapyramidal symptoms may benefit from quetiapine or aripiprazole. Patients with preexisting obesity or diabetes mellitus may benefit from an initial trial with ziprasidone or aripiprazole. The availability of orally disintegrating formulations of olanzapine, risperidone, and aripiprazole; liquid formulations of risperidone and aripiprazole; and a long-acting injectable formulation of risperidone provides options for patients with a history of poor treatment adherence or who have difficulty taking standard oral tablets or capsules. The traditional antipsychotics may be an initial choice for those who are at low risk for movement disorders[25] or for whom the newer drugs may be cost-prohibitive.

The importance of appropriate dosing of second-generation antipsychotics was highlighted in an analysis conducted by Love et al.[93] Results of the premarketing studies for

risperidone suggested that the dose–efficacy curve peaked at 6 mg/day, leading to the recommendation on the product labeling that risperidone be adjusted to this dosage over the first three days of treatment. After the introduction of risperidone to the mass market, numerous reports[94–96] demonstrated that the optimal dosage of risperidone for efficacy was between 4 and 6 mg/day, a dosage range not assessed in the original large efficacy studies. Aggregate computerized pharmacy records from state inpatient psychiatry facilities in Maryland revealed significantly higher discharge rates for patients receiving 2–4 mg/day than for those receiving 6 mg/day. It is now recommended that clinicians attempt to stabilize patients on risperidone 2–4 mg/day before initiating a trial at higher dosages.[93]

In general, clinical studies suggest that for most of the other second-generation antipsychotics indicated for first-line treatment, a more linear dose–response curve is applicable. Patients may require dosage adjustment to 10–20 mg/day of olanzapine, 300–800 mg/day of quetiapine, 80–160 mg/day of ziprasidone, or 10–30 mg/day of aripiprazole for control of acute psychotic symptoms.[13–24] Maintenance therapy can frequently be achieved with lower dosages, thereby reducing toxicity. Special populations, such as the elderly or individuals with hepatic impairment, may require lower doses due to increased sensitivity to adverse effects. In some individuals with a history of suboptimal response to antipsychotic treatment, additional benefit has been gained using second-generation antipsychotics with doses higher than the maximum recommended in the product labeling.[97]

In the event of nonresponse to an initial trial of antipsychotic medication, most treatment guidelines recommend sequential trials of second-generation antipsychotics with a minimum of three weeks duration at therapeutic doses.[98–100] A trial of clozapine is generally warranted for patients who demonstrate a suboptimal response to two or more trials with first-line antipsychotic agents. Traditional antipsychotics may also have a role for patients who fail treatment with second-generation antipsychotics. In addition, the adjunctive use of antidepressants, mood stabilizers, or anxiolytics may be beneficial in selected patients. The combined use of more than one antipsychotic drug is a controversial and costly practice.[101] Very little published evidence supports the use of multiple oral antipsychotics, except when attempting to transition a patient from one agent to another.[102]

Patient Monitoring

Frequent and continuous monitoring is necessary for individuals treated with antipsychotics in order to assess for therapeutic response and adverse effects. For the second-generation antipsychotics intended for first-line use, the recommended minimum trial duration is three weeks after adjustment to a recommended therapeutic dose. A longer trial is generally warranted for clozapine. Gradual reductions in the severity of psychotic symptoms (e.g., suspiciousness, hallucinations) are expected with adequate treatment.

Monitoring for metabolic adverse effects of second-generation antipsychotic therapy should consist of regular assessments of body weight, glucose levels, and lipid values (Table 5).[103] Treatment with clozapine requires weekly assessments of complete blood count and absolute neutrophil count for the first six months. If no evidence of neutropenia or granulocytopenia is found, the monitoring frequency can be reduced to every two weeks for the next six months and then every four weeks thereafter.

Despite the lower propensity for causing adverse motor effects, all patients receiving second-generation antipsychotics should be monitored for symptoms of dystonia, parkinsonism, akathisia, and tardive dyskinesia.[103] Patients should be evaluated for acute extrapyramidal symptoms weekly until two weeks after dose stabilization when antipsychotics are initiated or adjusted. Assessments for tardive dyskinesia should be conducted at least once yearly for individuals receiving continuous treatment with antipsychotics.[103]

Measurement of antipsychotic plasma levels is not clinically indicated, except to assess for treatment adherence or suspected drug interactions. However, a minimum plasma clozapine concentration of 350 ng/mL has been correlated with treatment response among patients whose psychosis has been identified as treatment resistant.[104,105] In a study of the use of therapeutic drug monitoring in long-term treatment with clozapine, relapse was more frequently associated with a decrease from a stable drug level than maintenance of a threshold minimum concentration.[106]

Treatment Outcomes

Schizophrenia and related disorders are characterized by chronic courses and periodic exacerbations. Exacerbations in the positive symptoms of schizophrenia may precipitate costly hospitalizations and may result in encounters with the legal system, while the negative and cognitive symptoms affect independent functioning, employment, and quality of life. Hospitalizations in specialty psychiatric facilities may

Table 5.
Monitoring Guidelines for Patients Treated with Second-Generation Antipsychotics

Assessment	Monitoring Frequency
Fasting blood glucose	All drugs: Baseline, then monthly for the first 3 mo and every 6 mo thereafter. More frequent assessments are indicated for individuals noted to be gaining weight.
Weight assessment	All drugs: Baseline and monthly thereafter. (Self-monitoring of weight should be encouraged.)
Electrocardiogram	Clozapine and ziprasidone: Baseline and annually thereafter. More frequent assessments may be indicated in patients over age 50 yr and in patients with a history of cardiac arrhythmias.
Complete blood count with differential	Clozapine: Weekly for the first 6 mo. Every other wk for the next 6 mo, and every 4 wk thereafter if no abnormalities are noted.
Fasting total cholesterol, low- and high-density lipoproteins, and triglycerides	All drugs: Baseline and every 2 yr thereafter if no abnormalities are noted. Every 6 mo for individuals noted to have hyperlipidemia or receiving lipid-lowering therapy.

result in lengths of stay measured in months or years. Thus, the single greatest component of the cost of schizophrenia is the cost of hospital stay. In contrast, drugs are thought to account for less than 10% of the direct costs of treating these illnesses.

Studies addressing the effect of second-generation antipsychotics on hospitalization have repeatedly found that these agents reduce the length of stay and readmission rate compared with conventional antipsychotics. Rabinowitz et al.[107] calculated a two-year rehospitalization rate of 31–33% for patients discharged from inpatient psychiatric hospitalization receiving olanzapine or risperidone, compared with a 48% rate for patients discharged on conventional antipsychotics ($p = 0.02$). In a landmark double-blind trial of risperidone versus haloperidol, Csernansky et al.[108] measured relapse by examining rehospitalization, signs of clinical decompensation, and increasing requirements for supervision. They found significantly lower relapse rates at one year and longer times to relapse with risperidone treatment. FDA accepted this trial as sufficient evidence to allow the manufacturer to indicate in the product labeling the drug's efficacy in delaying relapse.

A variety of studies have focused on the cost of second-generation antipsychotics in comparison with each other[109,110] and conventional agents.[111] In general, the generically available first-generation antipsychotics are less expensive than the newer second-generation agents. However, when overall costs of care are calculated, second-generation antipsychotics often demonstrate lower hospital utilization, improved symptomatic control, and fewer adverse effects, resulting in lower or equal total costs for the second-generation agents versus first-generation antipsychotics.[112]

While most studies examining outcomes with second-generation antipsychotics have focused on cost, hospitalization, and relapse, fewer have examined issues related to quality of life. Chouinard and Albright[113] addressed these issues by conducting a cost–utility analysis of risperidone versus haloperidol in association with a randomized clinical trial. Patients taking risperidone gained almost three quality-adjusted life years over those who received haloperidol. Franz et al.[114] conducted quality-of-life interviews with patients receiving conventional antipsychotics, clozapine, risperidone, or zotepine (not available in the United States). Patients receiving second-generation antipsychotics had a significantly higher total quality of life than those receiving conventional agents. They also demonstrated significantly superior ratings in the domains of physical well-being, social life, and everyday life.

Secondary depression is also a major problem in schizophrenia, and suicide is a leading cause of death in this population.[115] It has been estimated that about 10% of patients with psychotic disorders die by suicide.[116,117] In addition to having favorable effects on mood symptoms, there are indications that second-generation antipsychotics may also reduce suicide rates in some populations, with clozapine demonstrating a particular benefit in this regard.[118] In a study of 980 patients with schizophrenia or schizoaffective disorder at high risk for suicide, treatment with clozapine was associated with a significantly lower rate of suicide attempts and hospitalizations to prevent suicide compared with olanzapine (20.8% versus 28.8%, $p < 0.005$).[119]

Second-generation antipsychotics likely produce beneficial outcomes through a variety of effects. Compared with conventional antipsychotics and placebo, second-generation antipsychotics demonstrate improved efficacy for psychotic and cognitive symptoms. In controlled trials, these agents produce fewer disabling extrapyramidal adverse effects, such as akathisia and parkinsonism. These effects result in improved adherence to prescribed regiments, less interference with socialization and occupational function, and a feeling of improved well-being compared with the effects of conventional antipsychotics.

Summary

Psychotic disorders are chronic illnesses that impart a considerable burden on patients, families, and society. Although no known drug therapies can cure these illnesses, antipsychotic agents are a mainstay for the management of acute illness and prevention of relapse. The second-generation antipsychotics—risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone—offer numerous advantages over the older agents, including a lower risk of extrapyramidal motor symptoms and elevated serum prolactin levels, as well as improvements in cognitive symptoms. These advantages have led to improved long-term outcomes and cost-effectiveness, despite the higher acquisition costs of these drugs. Clozapine has demonstrated a unique level of efficacy for individuals with treatment-resistant psychotic disorders and for individuals at high risk for suicide and is very valuable in these subgroups, despite the additional adverse hematologic and cardiovascular effects. Metabolic adverse effects, including weight gain, glucose abnormalities, and hyperlipidemias, cause significant concern for patients receiving second-generation antipsychotics and must be managed proactively by clinicians. Health care professionals in all settings should play an active role in assisting in the selection of an appropriate antipsychotic agent, ensuring appropriate monitoring, and providing counseling to ensure that patients remain compliant with treatment. Additional readings and resources are listed in the appendix.

References

1. Schizophrenia and other psychotic disorders. In: American Psychiatric Association. DSM-IV-TR: diagnostic and statistical manual of mental disorders, 4th ed., text revision. Washington, DC: American Psychiatric Press; 2000.
2. Keith SJ, Regier DA, Rae DS. Schizophrenic disorders. In: Robins LN, Regier DA, eds. Psychiatric disorders in America: the Epidemiologic Catchment Area Study. New York: Free Press; 1991: 33–52.
3. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry.* 1994; 52:8–19.
4. Loranger AW. Sex differences in age at onset of schizophrenia. *Arch Gen Psychiatry.* 1984; 41:157–61.
5. Hafner H, Maurer K, Loeffler W, et al. The influence of age and sex on the onset and early course of schizophrenia. *Br J Psychiatry.* 1993; 162:80–6.
6. Kim JS, Kornhuber HH, Schmid-Burgk W, et al. Low cerebrospinal fluid glutamate in schizophrenia patients

and a new hypothesis on schizophrenia. *Neurosci Lett.* 1980; 20:379–82.
7. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry.* 1994; 51:199–214.
8. Hughes JR, Hatsukami DK, Mitchell JE, et al. Prevalence of smoking among psychiatric outpatients. *Am J Psychiatry.* 1986; 143:993–7.
9. Dalack GW, Healy DJ, Meador-Woodruff JH. Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. *Am J Psychiatry.* 1998; 155:1490–501.
10. Stahl SM. Dopamine system stabilizers, aripiprazole, and the next generation of antipsychotics, part I: "Goldilocks" actions at dopamine receptors. *J Clin Psychiatry.* 2001; 62:841–2.
11. Stahl SM. Dopamine system stabilizers, aripiprazole, and the next generation of antipsychotics, part II: illustrating their mechanism of action. *J Clin Psychiatry.* 2001; 62:923–4.
12. Kapur S, Remington G. Serotonin–dopamine interaction and its relevance to schizophrenia. *Am J Psychiatry.* 1996; 153:466–76.
13. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic, a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry.* 1988; 45:789–96.
14. Breier A, Buchanan RW, Kirkpatrick B, et al. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. *Am J Psychiatry.* 1994; 152:20–6.
15. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry.* 1994; 151:825–35.
16. Chouinard G, Jones B, Remington G, et al. A Canadian multi-center placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol.* 1993; 13:25–40.
17. Kane JM, Eerdekens M, Lindenmayer JP, et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry.* 2003; 160:1125–32.
18. Beasley CM, Tollfeson G, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology.* 1996; 14:111–23.
19. Beasley CM, Sanger T, Satterlee W, et al. Olanzapine vs placebo: results of a double-blind, fixed-dose olanzapine trial. *Psychopharmacology.* 1996; 124:159–67.
20. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry.* 1997; 42:233–46.
21. Small JG, Hirsch SR, Arvanitis LA, et al. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. *Arch Gen Psychiatry.* 1997; 54:549–57.
22. Daniel DG, Zimbroff DL, Potkin SG, et al. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. *Neuropsychopharmacology.* 1999; 20:491–505.
23. Keck P Jr, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. *Psychopharmacology.* 1998; 140:173–84.
24. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry.* 2002; 63:763–71.
25. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005; 353:1209–23.
26. Sharma T, Antonova L. Cognitive function in schizophrenia: deficits, functional consequences, and future treatment. *Psychiatr Clin North Am.* 2003; 26:25–40.
27. Green MF. What are the functional consequences of neurocognitive deficits of schizophrenia? *Am J Psychiatry.* 1996; 153:321–30.
28. Liddle PF. Cognitive impairment in schizophrenia: its impact on social functioning. *Acta Psychiatr Scand Suppl.* 2000; 400:11–6.
29. Spohn HE, Strauss ME. Relation of neuroleptic and anticholinergic medication to cognitive functions in schizophrenia. *J Abnorm Psychol.* 1989; 98:367–80.
30. Bilder RM, Goldman RS, Volavka J, et al. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. *Am J Psychiatry.* 2002; 159:1018–28.
31. Hagger C, Buckley P, Kenny JT, et al. Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. *Biol Psychiatry.* 1993; 34:702–12.
32. Grace J, Bellus SB, Raulin ML, et al. Long-term impact of clozapine and psychosocial treatment on psychiatric symptoms and cognitive functioning. *Psychiatr Serv.* 1996; 47:41–5.
33. Buchanan RW, Holstein C, Breier A. The comparative efficacy and long-term effect of clozapine on neuropsychological test performance. *Biol Psychiatry.* 1994; 36:717–25.
34. Cornblatt B, Kern RS, Carson WH, et al. Neurocognitive effects of aripiprazole versus olanzapine in stable psychosis. Presented at 23rd Collegium Internationale Neuropsychopharmacologicum Congress. Montreal, Canada; 2002 Jun.
35. Stahl SM. "Hit-and-run" actions at dopamine receptors, part 1: mechanism of action of second-generation antipsychotics. *J Clin Psychiatry.* 2001; 62:670–1.
36. Leucht S, Pitschel-Walz G, Abraham D, et al. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomized controlled trials. *Schizophr Res.* 1999; 35:51–68.
37. Tollefson GD, Beasley CM, Tamura RN, et al. Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. *Am J Psychiatry.* 1997; 154:1248–54.

38. Jeste DV, Lacro JP, Bailey A, et al. Lower incidence of tardive dyskinesia with risperidone compared with haloperidol in older patients. *J Am Geriatr Soc.* 1999; 47:716–9.
39. Jeste DV, Okamoto A, Napolitano J, et al. Low incidence of persistent tardive dyskinesia in elderly patients with dementia treated with risperidone. *Am J Psychiatry.* 2000; 157:1150–5.
40. Beasley CM, Dellva MA, Tamura RN, et al. Randomised double-blind comparison of the incidence of tardive dyskinesia in patients with schizophrenia during long-term treatment with olanzapine or haloperidol. *Br J Psychiatry.* 1999; 174:23–30.
41. Farah A. Reduction of tardive dyskinesia with quetiapine. *Schizophr Res.* 2001; 47:309–10. Letter.
42. Povlssen UJ, Noring U, Fog R, et al. Tolerability and therapeutic effect of clozapine: a retrospective investigation of 216 patients treated with clozapine for up to 12 years. *Acta Psychiatr Scand.* 1985; 71:176–85.
43. Kurz M, Hummer M, Oberbauer H, et al. Extrapyramidal side effects of clozapine and haloperidol. *Psychopharmacology.* 1995; 118:52–6.
44. Casey DE. Clozapine: neuroleptic-induced EPS and tardive dyskinesia. *Psychopharmacology.* 1989; 99: S47–53.
45. Lieberman JA, Saltz BL, Johns CA, et al. The effects of clozapine on tardive dyskinesia. *Br J Psychiatry.* 1991; 158:503–10.
46. Spivak B, Mester R, Abesgaus J, et al. Clozapine treatment for neuroleptic-induced tardive dyskinesia, parkinsonism, and chronic akathisia in schizophrenic patients. *J Clin Psychiatry.* 1997; 58:318–22.
47. Tamminga CA, Thaker GK, Moran M, et al. Clozapine in tardive dyskinesia: observations from human and animal model studies. *J Clin Psychiatry.* 1994; 55(suppl B):102–6.
48. Ahmed S, Chengappa KN, Naidu VR, et al. Clozapine withdrawal-emergent dystonias and dyskinesias: a case series. *J Clin Psychiatry.* 1998; 59:472–7.
49. Dickson RA, Seeman MV, Corenblum B. Hormonal side effects in women: typical versus second-generation antipsychotic treatment. *J Clin Psychiatry.* 2000; 61(suppl 3):10–5.
50. Windgassen K, Wesselman U, Schulze-Monking H. Galactorrhea and hyper-prolactinemia in schizophrenic patients on neuroleptics: frequency and etiology. *Neuropsychobiology.* 1996; 33:142–6.
51. Arana GW. An overview of side effects caused by typical antipsychotics. *J Clin Psychiatry.* 2000; 61(suppl 8):5–11.
52. Petty RG. Prolactin and antipsychotic medications: mechanisms of action. *Schizophr Res.* 1999; 35(suppl): S67–73.
53. Volavka J, Czobor P, Cooper TB, et al. Prolactin levels in schizophrenia and schizoaffective disorder patients treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychiatry.* 2004; 65:57–61.
54. Breier AF, Malhotra AK, Su T, et al. Clozapine and risperidone in chronic schizophrenia: effects on symptoms, parkinsonian side effects, and neuroendocrine response. *Am J Psychiatry.* 1999; 156:294–8.
55. Crawford AM, Beasley CM, Tollefson GD. The acute and long-term effect of olanzapine compared with placebo and haloperidol on serum prolactin concentrations. *Schizophr Res.* 1997; 26:41–54.
56. David SR, Taylor CC, Kinon BJ, et al. The effects of olanzapine, risperidone, and haloperidol on plasma prolactin levels in patients with schizophrenia. *Clin Ther.* 2000; 22:1085–96.
57. Bunker MT, Marken PA, Schneiderhan ME, et al. Attenuation of antipsychotic-induced hyperprolactinemia with clozapine. *J Child Adolesc Psychopharmacol.* 1997; 7:65–9.
58. Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. *J Clin Psychiatry.* 1999; 60:215–20.
59. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry.* 1996; 37:68–73.
60. Brambilla F, Guastalla A, Guerrini A, et al. Glucose-insulin metabolism in chronic schizophrenia. *Dis Nerv Syst.* 1976; 37:98–103.
61. Tsuang MT, Perkins K, Simpson JC. Physical diseases in schizophrenia and affective disorder. *J Clin Psychiatry.* 1983; 44:42–6.
62. Borovicka MC, Fuller MA, Konicki PE, et al. Phenylpropanolamine appears not to promote weight loss in patients with schizophrenia who have gained weight during clozapine treatment. *J Clin Psychiatry.* 2002; 63:345–8.
63. Ball MP, Coons VB, Buchanan RW. A program for treating olanzapine-related weight gain. *Psychiatr Serv.* 2001; 52:967–9.
64. Green AI, Patel JK, Goisman RM, et al. Weight gain from novel antipsychotic drugs: need for action. *Gen Hosp Psychiatry.* 2000; 22:224–35.
65. Doss FW. The effect of antipsychotic drugs on body weight: a retrospective review. *J Clin Psychiatry.* 1979; 40:528–30.
66. Parent MM, Roy S, Sramek J, et al. Effect of molindone on weight change in hospitalized schizophrenic patients. *Drug Intell Clin Pharm.* 1986; 20:873–5.
67. Gardos G, Cole JO. Weight reduction in schizophrenics by molindone. *Am J Psychiatry.* 1977; 134:302–4.
68. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry.* 1999; 156:1686–96.
69. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry.* 2000; 157:975–81.
70. Beasley CM, Tollefson GD, Tran PV. Safety of olanzapine. *J Clin Psychiatry.* 1997; 58(suppl 10):13–7,19–21.
71. Muench J, Carey M. Diabetes mellitus associated with second-generation antipsychotic medications: new case report and review of the literature. *J Am Board Fam Pract.* 2001; 14:278–82.
72. Jin H, Meyer JM, Jeste DV. Phenomenology of and risk factors for new onset diabetes mellitus associated with second-generation antipsychotics: an analysis of 45 published cases. *Ann Clin Psychiatry.* 2002; 14:59–64.

73. Koller EA, Cross JT, Doraiswamy PM, et al. Risperidone-associated diabetes mellitus: a pharmacovigilance study. *Pharmacotherapy.* 2003; 23:735–44.
74. Sernyak MJ, Leslie DL, Alarcon RD. Association of diabetes mellitus with use of second-generation neuroleptics in the treatment of schizophrenia. *Am J Psychiatry.* 2002; 159:561–6.
75. Newcomer JW, Haupt DW, Fucetola R. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry.* 2002; 59:337–45.
76. Meyer JM. Novel antipsychotics and severe hyperlipidemia. *J Clin Psychopharm.* 2001; 21:369–74.
77. Meyer JM. A retrospective comparison of weight, lipid, and glucose changes between risperidone- and olanzapine-treated inpatients: metabolic outcomes after 1 year. *J Clin Psychiatry.* 2002; 63:425–33.
78. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care.* 2004; 27:596–601.
79. Mehtonen OP, Aranko K, Malkonen L, et al. A survey of sudden death associated with the use of antipsychotic or antidepressant drugs: 49 cases in Finland. *Acta Psychiatr Scand.* 1991; 84:58–64.
80. Reilly JG, Ayis SA, Ferrier IN, et al. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet.* 2000; 355:1048–52.
81. Food and Drug Administration. Briefing document for Zeldox capsules (ziprasidone HCl). www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1a.pdf (accessed 2007 Jan 16).
82. Geodon (ziprasidone hydrochloride) prescribing information. New York: Pfizer Inc.; 2006 Nov.
83. Merrill DB, Dec GW, Goff DC. Adverse cardiac effects associated with clozapine. *J Clin Psychopharmacol.* 2005; 25:32–41.
84. La Grenade L, Graham D, Trontell A. Myocarditis and cardiomyopathy associated with clozapine use in the United States. *N Engl J Med.* 2001; 345:224–5.
85. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA.* 2005; 293:596–608.
86. Herrmann N, Lanctot KL. Do atypical antipsychotics cause stroke? *CNS Drugs.* 2005; 19:91–103.
87. Lieberman JA, Johns CA, Kane JM, et al. Clozapine-induced agranulocytosis: non-cross-reactivity with other psychotropic drugs. *J Clin Psychiatry.* 1988; 49:271–7.
88. Alvir JJ, Lieberman JA, Safferman AZ, et al. Clozapine-induced agranulocytosis—incidence and risk factors in the United States. *N Engl J Med.* 1993; 329:162–7.
89. Honigfeld G, Arellano F, Sethi J, et al. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. *J Clin Psychiatry.* 1998; 59(suppl 3):3–7.
90. Munro J, O'Sullivan D, Andrews C, et al. Active monitoring of 12,760 clozapine recipients in the UK and Ireland: beyond pharmacovigilance. *Br J Psychiatry.* 1999; 175:576–80.
91. Silvestri RC, Bromfield EB, Khoshbin S. Clozapine-induced seizures and EEG abnormalities in ambulatory psychiatric patients. *Ann Pharmacother.* 1998; 32:1147–51.
92. Sprague DA, Loewen PS, Raymond CB. Selection of atypical antipsychotics for the management of schizophrenia. *Ann Pharmacother.* 2004; 38:313–9.
93. Love RC, Conley RR, Kelly DL, et al. A dose-outcome analysis of risperidone. *J Clin Psychiatry.* 1999; 60:771–5.
94. Moller HJ, Bauml J, Ferrero F, et al. Risperidone in the treatment of schizophrenia: results of a study of patients from Germany, Austria and Switzerland. *Eur Arch Psychiatry Clin Neurosci.* 1997; 246:291–6.
95. Philipo M. Neuroleptic treatment long term: results with risperidone. Presented at 21st Collegium Internationale Neuro Psychopharmacologicum Congress. Glasgow, Scotland; 1998 Jul.
96. Sajatovic M, Ramirez LF, Belton J, et al. Health resource utilization and risperidone therapy in patients with serious mental illness. Presented at 21st Collegium Internationale Neuro-Psychopharmacologicum Congress. Glasgow, Scotland; 1998 Jul.
97. Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. *Am J Psychiatry.* 2002; 159:255–62.
98. Miller AL, Hall CS, Buchanan RW, et al. The Texas medication algorithm project—antipsychotic algorithm for schizophrenia: 2003 update. *J Clin Psychiatry.* 2004; 65:500–8.
99. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry.* 2004; 161(2 suppl):1–56.
100. Lehman AF, Steinwachs DM. Translating research into practice: the schizophrenia patient outcomes research team (PORT) treatment recommendations. *Schizophr Bull.* 1998; 24:1–10.
101. Stahl SM. Antipsychotic polypharmacy: squandering precious resources? *J Clin Psychiatry.* 2002; 63:93–4.
102. Casey DE, Saha AR, Ali MW, et al. Switching to aripiprazole monotherapy. Presented at 23rd Collegium Internationale Neuropsycholpharmacologicum Congress. Montreal, Canada. 2002 Jun.
103. Marder SR, Essock SM, Miller AL, et al. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry.* 2004; 161:1334–49.
104. Perry PJ, Miller DD, Arndt SV, et al. Clozapine and norclozapine plasma concentrations and clinical response of treatment refractory schizophrenic patients. *Am J Psychiatry.* 1991; 148:231–5.
105. Kronig MH, Munne RA, Szymanski S, et al. Plasma clozapine levels and clinical response for treatment refractory schizophrenic patients. *Am J Psychiatry.* 1995; 152:179–82.
106. Gaertner I, Gaertner HJ, Vonthein R, et al. Therapeutic drug monitoring of clozapine in relapse prevention: a five-year prospective study. *J Clin Psychopharmacol.* 2001; 21:305–10.
107. Rabinowitz J, Lichtenberg P, Kaplan Z, et al. Rehospitalization rates of chronically ill schizophrenic patients discharged on a regimen of risperi-

done, olanzapine, or conventional antipsychotics. *Am J Psychiatry.* 2001; 158:266–9.
108. Csernansky JG, Mahmoud R, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med.* 2002; 346:16–22.
109. Barbui C, Lintas C, Percudani M. Head-to-head comparison of the costs of atypical antipsychotics: a systematic review. *CNS Drugs.* 2005; 19:935–50.
110. Mladsi DM, Grogg AL, Irish WD, et al. Pharmacy cost evaluation of risperidone, olanzapine, and quetiapine for the treatment of schizophrenia in acute care inpatient settings. *Curr Med Res Opin.* 2004; 20:1883–93.
111. Coley KC, Carter CS, DaPos SV, et al. Effectiveness of antipsychotic therapy in a naturalistic setting: a comparison between risperidone, perphenazine, and haloperidol. *J Clin Psychiatry.* 1999; 60:850–6.
112. Rosenheck R, Cramer J, Allan E, et al. Cost-effectiveness of clozapine in patients with high and low levels of hospital use. *Arch Gen Psychiatry.* 1999; 56:565–72.
113. Chouinard G, Albright PS. Economic and health state utility determinations for schizophrenic patients treated with risperidone or haloperidol. *J Clin Psychopharmacol.* 1997; 17:298–307.
114. Franz M, Lis S, Pluddemann K, et al. Conventional versus second-generation neuroleptics: subjective quality of life in schizophrenic patients. *Br J Psychiatry.* 1997; 170:422–5.
115. Roy A. Depression, attempted suicide, and suicide in patients with chronic schizophrenia. *Psychiatr Clin North Am.* 1986; 9:193–206.
116. Radomsky ED, Haas GL, Mann JJ, et al. Suicidal behavior in patients with schizophrenia and other psychotic disorders. *Am J Psychiatry.* 1999; 156:1590–5.
117. Cohen LJ, Test MA, Brown RL. Suicide and schizophrenia: data from a prospective community treatment study. *Am J Psychiatry.* 1990; 147:602–7.
118. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. *Am J Psychiatry.* 1995; 152:183–90.
119. Meltzer HY, Alphs L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSEPT). *Arch Gen Psychiatry.* 2003; 60:82–91.

Appendix—Additional Readings and Resources

Andreasen NC. Scale for the assessment of negative symptoms (SANS). *Br J Psychiatry.* 1989; 155(suppl 7):53–8.

Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry.* 1989; 154:672–6.

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987; 13:261–76.

Lane RD, Glazer WM, Hansen TE, et al. Assessment of tardive dyskinesia using the Abnormal Involuntary Movements Scale. *J Nerv Ment Dis.* 1985; 173:353–7.

Lehman AF, Kreyenbuhl J, Buchanan RW, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. *Schizophr Bull.* 2004; 30:193–217.

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979; 134:382–9.

CGI: clinical global impressions. In: Guy W, Bonato RR, eds. Manual for the ECDEU assessment battery. 2nd ed. Chevy Chase, MD: National Institute of Mental Health; 1970:12-1–12-6.

Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep.* 1962; 10:799–812.

Simpson GN, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl.* 1970; 212:11–9.

Approved by the ASHP Board of Directors on June 24, 2006. Developed through the ASHP Council on Therapeutics.

Jason M. Noel, Pharm.D., BCPP, is gratefully acknowledged for authoring this therapeutic position statement. At the time of publication, Dr. Noel was Assistant Professor, University of Maryland School of Pharmacy, Baltimore, and Director of Clinical Pharmacy Services, Rosewood Center, Owings Mills, MD.

Marshall E. Cates, Pharm.D., BCPP, FASHP; Beth Dubisar, Pharm. D.; Julie A. Dopheide, Pharm.D., BCPP; W. Kennedy Klugh, Pharm. D.; Dan LeGrady, Pharm.D., FNIH; Rex S. Lott, Pharm.D.; Lisa Mican, Pharm.D.; Virginia Stauffer, Pharm.D.; and the American Academy of Nurse Practitioners are acknowledged for reviewing drafts of this document.

The bibliographic citation for this document is as follows: Noel JM. ASHP therapeutic position statement on the use of second-generation antipsychotic medications in the treatment of adults with psychotic disorders. *Am J Health-Syst Pharm.* 2007; 64:863–76.