ASHP Therapeutic Position Statement on the Use of Antipsychotic Medications in the Treatment of Adults with Schizophrenia and Schizoaffective Disorder

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Position

The American Society of Health-System Pharmacists (ASHP) recognizes that schizophrenia and schizoaffective disorder 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.[1] In addition, high rates of suicidal behavior and completed suicides have been observed in patients with schizophrenia or schizoaffective disorder.[2] The management of the psychotic symptoms associated with 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.

For the pharmacologic management of psychosis associated with schizophrenia and schizoaffective disorder, ASHP encourages health professionals to select either a first or second generation antipsychotic agent based upon the adverse effect profile of the drug and the

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individual characteristics of the patient. Antipsychotics, both first and second generation agents, have similar efficacy and are the treatment of choice in individuals with schizophrenia or schizoaffective disorder with psychosis.

All antipsychotics have limitations and, in the usual dosage range doses, FGAs are generally equivalent in tolerability to SGAs.[3] Patients have different reasons for not tolerating a particular agent, and antipsychotic selection should be individualized to the patient. Upon selection of an effective treatment, clinicians must monitor therapy on an ongoing basis to ensure tolerability and adherence in order to optimize treatment outcomes.

The goal of this therapeutic position statement (TPS) is to provide a summary of FGAs and SGAs and provide recommendations for the clinician to consider when selecting an appropriate agent to treat psychosis in the adult patient with schizophrenia and schizoaffective disorder.

Background

Schizophrenia and schizoaffective disorder are serious, chronic mental illnesses that affect perceptual, behavioral, affective, and cognitive functioning. Individuals with schizophrenia generally exhibit a mixture of positive, negative, and cognitive symptoms with varying intensity throughout the course of the illness The DSM-5 diagnostic criteria for schizophrenia states that at least two out of five symptoms must be present for at least one month, and at least one of those one of those symptoms must include delusions, hallucinations or disorganized speech (Table 1).[4] The symptoms of schizophrenia must be continuous for at least 6 months. Schizoaffective disorder differs from schizophrenia in that delusions or hallucinations only have to occur for a minimum of two weeks without signs of a mood disturbance sometime during the course of the

illness. Symptoms of mania or depression are present during the majority of the longitudinal course of the illness.[4] Unlike schizophrenia, DSM-5 criterion states that social and occupational dysfunction does not have to occur in schizoaffective disorder (Table 1).[4] The worldwide lifetime prevalence of schizophrenia and schizoaffective disorder is about 1.2%.[5,6] Schizophrenia and schizoaffective disorders have been studied together in many clinical trials and will be considered together for the purpose of this document.

First episode psychosis (FEP) refers to the first acute episode of psychosis following a prodromal period. The prodromal period is defined as a period of time in which an individual begins to experience behavioral changes (e.g. anxiety, sleep disturbances, social withdrawal, and irritability, a reduction in concentration and motivation and/or suspiciousness) prior to the onset of the first episode of psychosis. As many as 100,000 teens and young adults in the United States experience FEP each year, with the peak onset occurring between 15 and 25 years of age.[7] It is important to recognize and treat FEP because the duration of untreated psychosis, defined as the time between the first psychotic symptoms and initiation of antipsychotic treatment, plays a major role in clinical patient outcomes.[8] The longer an individual goes untreated the worse their long-term behavioral and cognitive symptoms, morbidity and mortality, quality of life, and functional capacity.[8] Patients with FEP tend to present late for medical attention, on average the duration between the first symptoms and adequate treatment is 7 to 10 years.[8] In addition, as many as 80% of individuals with FEP will experience a relapse of symptoms requiring inpatient care and adding to the total cost of care.[9] The highest risk of suicide in individuals with psychosis occurs during the first five years of the illness, deemed the critical period.[10] A recent study assessed the twelve month mortality for patients with FEP at 24 times higher than the general US

population.[11]

Childhood-onset of schizophrenia resembles the essential features seen in 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. In children, delusions, auditory and visual hallucinations are common, but may be less sophisticated than those symptoms seen in adults. It is important to differentiate between childhood onset schizophrenia and other diagnoses seen in children such as autism spectrum disorder, and attention deficit activity disorder, as well as normal fantasy play. Childhood onset schizophrenia includes significant negative symptoms, and typically has a poor outcome, including significant, progressive impairment in the social, occupational, and academic functioning of affected individuals.[12]

Late-onset schizophrenia, occurring after 40 years of age, may have an otherwise similar course to typical adult onset schizophrenia. Often individuals with late-onset illness will maintain affect and social functioning often they will be or have been married during their life. Often the symptoms of psychosis, such as hallucinations and delusions may not be as severe as they appear in those with an earlier onset of the illness.[13] Very late onset of schizophrenia is diagnosed if the first appearance of the illness occurs after the age of 65. This occurs more frequently in women and in those with general medical conditions like dementia.[13]

Pathophysiology of schizophrenia

The effectiveness of FGAs whose primary mechanism of action, blockade of dopamine in the brain, led to the initial hypothesis regarding dopamine's role in schizophrenia.[14] While it is apparent that

increased dopamine in the mesolimbic pathway is responsible for the positive symptoms of schizophrenia, it is now understood that psychosis frequently involves numerous neurochemical abnormalities.[14,15] Psychosis has been observed in individuals with idiopathic and drug-induced hypofunction of the glutamate system.[16,17] In addition, the high rate of nicotine dependence in individuals with schizophrenia-up to 88% in one study - led to the identification of alpha 7 nicotinic acetylcholine-receptor abnormalities in the pathophysiology of schizophrenia.[18,19]

Pharmacologic characteristics of antipsychotic drugs

The FGAs primarily exert their therapeutic effects by antagonizing postsynaptic dopamine2 receptors in the cortical and nigrostriatal pathway. However, these drugs are not selective in their activity. Each of the FGAs has effects on other receptors to varying degrees, including serotonin 2A, alpha 1, muscarinic and histaminic receptors. The level of receptor binding correlated to the specific antipsychotic side effect profile. Low potency agents, dosed in the 100s of milligrams, (e.g. chlorpromazine, thioridazine) have a greater propensity to causing orthostatic hypotension, QT interval prolongation, anticholinergic effects, and sedation. High potency agents, dosed in the 10's of milligrams,(e.g. haloperidol, fluphenazine, loxapine, perphenazine, thiothixene, trifluoperazine) are more likely to cause extrapyramidal side effects (e.g. dystonias, parkinsonism, akathisia), and tardive dyskinesia (Table 2).[20] FGAs are also associated with hematologic (e.g. agranulocytosis), endocrine (e.g. prolactin elevation, menstrual irregularities, sexual dysfunction), dermatologic (e.g. blue-gray skin coloration, photosensitivity, allergic reactions) and ophthalmologic (e.g. pigmentary retinopathy, corneal and lenticular deposits leading to cataracts, and rare cases of photophobia, and difficulty with visual accommodation.)

Other adverse effects include seizures, difficulty regulating body temperature and increased incidence of falls.[20]

The SGAs share the common pharmacologic action of dual serotonin-dopamine antagonism (Table 3.). Aripiprazole, brexpiprazole and cariprazine differ slightly in that they function as partial agonists at dopamine receptors, reducing dopamine activity in the mesolimbic pathway.[21,22] In addition to antagonism at serotonin 2A and D2 receptors, SGAs interact with a multitude of other receptors including muscarinic, histaminic and alpha adrenergic receptors. Like FGAs some of the SGAs block D2 in the hypothalamic pituitary region causing hyperprolactinemia. Other SGAs block dopamine in the nigrostriatal area causing extrapyramidal motor effects. Some of the SGAs may alter insulin resistance and increase fasting cholesterol levels secondary to actions at receptors that are not currently well understood. None of the SGAs have identical neurotransmitter binding profiles, which gives each of them a unique clinical profile.

Efficacy for negative symptoms

Negative symptoms are considered to be the core deficit in schizophrenia.[23] Primary negative symptoms include flattened or blunted affect, avolition, asociality, amotivation, alogia and apathy.[24] Individuals diagnosed with schizophrenia typically experience a prodromal period, characterized by negative symptoms, in their late teens to mid-twenties. The prodromal period precedes the onset of psychotic or positive symptoms. Based upon DSM-5 criteria, positive symptoms such as delusions and hallucinations have to last for at least one month (untreated), but often last for three to six months prior to resolution.[4,24] After the resolution of positive symptoms the period of chronicity is called residual schizophrenia. This period is marked by

continued negative symptoms which is a source of poor outcomes for many individuals.[24,25] Because of the difficulty in treating a deficit syndrome, greater effort has been given to treating positive symptoms of schizophrenia with antipsychotics, but it has been suggested that antipsychotics aggravate negative symptoms.[26,27] Some references divide negative symptoms into primary negative symptoms (disease related) and secondary negative symptoms (due to side effects of medications, substance abuse, and environmental issues).[28] For the purposes of this TPS, we will focus on primary negative symptoms.

Negative symptoms have been difficult to treat. Antidepressants, stimulants and antipsychotics are among the treatment strategies that have been studied for negative symptoms.[29] There was initial excitement with the use of SGAs because many of them appeared to demonstrate efficacy for both positive and negative symptoms in initial registration studies.[30] Clozapine, olanzapine, quetiapine, risperidone, asenapine, paliperidone and lurasidone all demonstrated effectiveness for negative symptoms in these studies.[25] Unfortunately, these studies suffered from small sample sizes, inconsistent diagnoses or stage of illness, and length of trial (typically 6-12 weeks).[25] Improvement of negative symptoms was measured during the active phase of the illness, and it is difficult to differentiate what improvements are from changes in the positive symptoms versus the negative symptoms.[25] Larger studies, such as the CUtLASS trial did not show a significant difference between FGAs and SGAs in the treatment of negative symptoms.[3] In 2009, the Patient Outcomes Research Team (PORT) guidelines state that "the level of evidence is currently insufficient to support a treatment recommendation for any pharmacological treatment of negative symptoms in schizophrenia."[31]

Efficacy for positive symptoms

Positive symptoms are typically seen during exacerbations of schizophrenia. Positive symptoms include hallucinations, delusions, thought disorders, and disorganized speech. Finding medications to treat these symptoms has led positive symptoms to be the primary focus in the treatment of schizophrenia.[10] First and second-generation antipsychotic agents have been demonstrated to be equally effective in the treatment of positive symptoms of schizophrenia when used in therapeutic doses.[3]

Neurocognitive effects

Impaired cognitive functioning has long been observed as a core feature of schizophrenia. Longitudinal studies have shown that patients with schizophrenia have progressive brain tissue loss after onset of illness. These impairments are relatively stable over the natural course of the illness, regardless of the frequency of acute exacerbations of psychotic symptoms.[32] Furthermore, cognitive impairment may have a greater impact on psychosocial functioning than any other feature of schizophrenia.[33,34]

Many domains of cognition, including attention, short-term memory, and executive function, are affected by schizophrenia.[35] Treatment with 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 EPS that accompany antipsychotic therapy may actually worsen some cognitive functions.[36]

Early studies of SGAs suggested that they might have a role in the treatment of cognition and psychosocial function in schizophrenia.[37-41] More recent studies have not established a

significant effect of SGAs over FGAs on cognition, and there is a suggestion on review of previous studies that differences in results may be due to practice or placebo effect.[42-57]

First-episode psychosis

Patients with FEP are more responsive to treatment than patients with multiple psychotic episodes, but can also be more sensitive to the side effects of antipsychotics.[58] The majority of patients with FEP are responsive to treatment with more than 70% achieving full remission of signs and symptoms of psychosis within 3-4 months, and 83% achieving stable remission by the end of one year.[1,59]

Studies have shown that patients with FEP often respond well to low-dose antipsychotic medication.[58-60] Selection of an antipsychotic should be based upon patient preference, side effect profile, route of administration, presence of co-morbid medical conditions, and potential interactions with other prescribed medications, and cost. Patients with FEP initiated on an antipsychotic should be monitored closely to evaluate treatment response.[60] Adherence to treatment is crucial and can minimize the emotional distress and disruption of the patient's life.[60] Patients with a first episode of psychosis should continue treatment for at least twelve months after remission.[31,58] As many as 83% of patients with FEP will experience a relapse in symptoms within five years.[61]

Multi-episode schizophrenia

Multi-episode schizophrenia or relapse is part of the natural continuum of psychotic illness. The most common causes of relapse include stress, nonadherence, and substance use.[58] It is important

to recognize that it is not uncommon to have a relapse in psychotic symptoms even while maintaining adherence.[58] The average rate of relapse is between 15 and 37% after one year of maintenance antipsychotic therapy, while the rate of relapse for patients on placebo is between 60-80%.[31,58,62-63]

When relapse occurs it is important to determine the reasons behind it, and to re-establish treatment as quickly as possible with the same or another medication.[58] The antipsychotic chosen should be based on the patient's previous response, side effects, route of administration, co-morbid medical conditions, potential drug interactions and the patient's preference.[58] Once an antipsychotic agent has been chosen, the dose should be initiated at an appropriate starting dose and titrated to a therapeutic dose. Titrating the dose too rapidly or using a dose above the therapeutic range may be associated with nonadherence and intolerance. Improvement in symptoms may take between 6 to 12 weeks.[58] If no symptom improvement is seen in 2 weeks at therapeutic doses, consider switching medications.[58] If a partial response is seen within 12 weeks, consider increasing the dose to the highest therapeutic dose as long as the patient is not experiencing side effects.[58] If the patient continues to experience only a partial response to this dose, consider augmentation with a different agent or switching to another antipsychotic agent. While evidence supporting augmentation is based upon limited and sometimes mixed results, it may benefit individuals who have a partial response versus initiating a new antipsychotic. Lifetime treatment with the lowest effective dose of an antipsychotic is recommended in individuals who have experienced multiple relapses.[58]

Treatment-resistant schizophrenia

Treatment-resistant schizophrenia is defined as inadequate improvement in target symptoms despite treatment with two or more antipsychotics (at least one of those should be a SGA) from differing chemical classes given at therapeutic doses for a minimum of two to eight weeks per agent.[1, 58,64-66]

A trial of clozapine is generally warranted for patients who demonstrate a suboptimal response to two or more trials with first- and second-line antipsychotic agents, and it is considered to be the third line agent for all guidelines.[58] In addition, the adjunctive use of antidepressants, mood stabilizers, or anxiolytics may be beneficial in select patients.[58] The combined use of more than one antipsychotic drug is a controversial and costly practice.[67] Very little published evidence supports the use of multiple oral antipsychotics, except when attempting to transition a patient from one agent to another.[68] In the case of non-response or inability to tolerate clozapine other treatment strategies include treatment with other SGAs, augmentation, antipsychotic combinations, and electroconvulsive therapy, although there is limited evidence for these strategies.[69]

Clozapine, the first SGA introduced in the United States, has an established level of efficacy for use in individuals with psychosis resistant to treatment with other antipsychotics. Kane et al conducted the landmark trial that demonstrated the superior efficacy of clozapine in individuals with treatment resistant psychosis.[65] 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 antipsychotics 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 (BPRS) total scores and Clinical Global Impression (CGI) scale were three times greater in the patients treated with clozapine. These results were confirmed in large pragmatic trials and meta-analyses in which clozapine was compared to SGAs in treatment resistant patients resulting in symptom improvement and median time to discontinuation.[70,71]

Adverse effects

Since the efficacy between FGAs and SGAs in treating psychosis is equivalent, the decision for choosing a particular agent often rests on the individual person with psychosis and the adverse effect profile of a specific antipsychotic. SGAs were originally marketed as having fewer adverse effects, especially fewer neurologic and motor symptoms and increased tolerability compared to FGAs. Much of this information came from short term, industry sponsored trials with carefully selected patient populations, and non-inferiority comparisons of symptom ratings.[72,73] Non-industry sponsored studies with rigorous randomized studies designed to match real world treatment scenarios have provided information that demonstrates first and second generation agents have nearly equal limitations; this supports the widely held notion that selection of an antipsychotic drug should be an individualized process.[3,69]

Motor symptoms. Treatment with FGAs has long been associated with both acute and chronic motor adverse effects. Acute extrapyramidal symptoms (EPS)-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.

Improved tolerability with SGAs has given this class of medications some advantage over the first generation agents; however experience has shown that all of the SGAs excluding clozapine, quetiapine and iloperidone, have the propensity to cause some degree of EPS.[74] Recent trials have shown that there is no advantage to SGA agents in improving tolerability and effectiveness over FGAs. Akathisia is estimated to occur in 25% of patients taking a FGA while it is estimated to occur with SGAs at an incidence of 7-30% depending on the SGA used.[3,75-84]

Tardive dyskinesia, a potentially irreversible chronic motor disorder caused by long-term exposure to dopamine antagonists, has been another serious concern with FGAs. The average rate of tardive dyskinesia with the FGAs is between 24-30%.[85,86] SGAs were initially thought to have a lower risk of treatment emergent tardive dyskinesia with maintenance treatment. Studies suggest that the risk of tardive dyskinesia with SGAs (excluding clozapine) is more than half of that with FGAs, or more than two-thirds of the risk with clozapine.[87] A meta-analysis of 203 studies from 2017 reported that the prevalence of tardive dyskinesia with SGAs (20.7%) is slightly lower than with treatment using FGAs (30%).[87] The data suggest that the risk of tardive dyskinesia may be slightly lower with SGAs, but not eliminated.[88]

The first step in treating tardive dyskinesia is to discontinue the antipsychotic that is thought to have caused the adverse effect.[89] If discontinued too quickly the patient may experience withdrawal dyskinesia, so a slow taper is recommended.[89] A risk benefit analysis

regarding discontinuing the offending agent may find that the individual will continue to need an antipsychotic agent.[89] In this case, switching to an agent with a lower risk of tardive dyskinesia, such as clozapine is recommended.

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 EPS.[65,90,91] The risk of tardive dyskinesia associated with clozapine treatment also appears to be minimal.[92,93] 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.[58,65,66] In addition, withdrawal of clozapine in patients with tardive dyskinesia has resulted in either maintenance of reduced movements or worsening of dyskinesias.[94] The inconsistent nature of tardive dyskinesia treatment makes prevention of this syndrome a very important consideration in the pharmacotherapy of schizophrenia and schizoaffective disorder.[95]

Valbenazine, a VMAT2 inhibitor (vesicular monoamine transporter 2), has been FDA approved for the treatment of tardive dyskinesia.[96,97] There is some evidence for two other VMAT2 inhibitors as well, tetrabenazine and deutetrabenazine, both FDA approved for the treatment of Huntington's chorea. Tetrabenazine is currently in phase III trials for schizophrenia and schizoaffective disorders.[98,99] Deutetrabenazine was approved for tardive dyskinesia in August, 2017.[100]

Studies have noted modest benefit for the use of adjunctive vitamin E in low doses to protect against worsening symptoms of tardive dyskinesia.[101,102] There is limited evidence for the efficacy of clonazepam, amantadine, zonisamide, levetiracetam, essential fatty acids, melatonin,

piracetam, propranolol, reservatol, ginkgo biloba and vitamin B6 for use in treatment.[93,103-106] Branched chain amino acids (BCAAs) have been FDA approved for use in treating tardive dyskinesia in men only..[107]

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, galactorrhea, gynecomastia, and sexual dysfunction in the short-term.[108-110] 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.[111]

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 FGAs, paliperidone, and risperidone.[111] Risperidone has been consistently associated with the greatest degree of prolactin elevation among both the SGAs and the FGAs.[112,113] Clozapine causes the least prolactin elevation (<5%), while olanzapine, quetiapine, ziprasidone, asenapine, lurasidone, and brexpiprazole cause low to moderate hyperprolactinemia (10-40%).[114-116] Cariprazine does not appear to affect prolactin levels.[117] Aripiprazole causes hypoprolactinemia and may be used adjunctively to decrease prolactin level elevations occurring with other antipsychotics.[118-120]

Weight gain. The metabolic effects of antipsychotic drug therapy have become a source of concern for clinicians and patients. Schizophrenia and antipsychotic drug treatments have long

been associated with comorbid obesity and its related conditions: type 2 diabetes mellitus and cardiovascular disease.[121-125] In addition, drug treatments and lifestyle changes aimed at weight reduction may be ineffective or difficult to implement in this population.[126-128]

In multiple published analyses, clozapine and olanzapine have been associated with the greatest degree of weight gain among the antipsychotics (Table 4.).[129,130] For example, in an analysis of data from registration trials, Allison et al found that at 10 weeks of treatment, olanzapine- treated patients gained an average of 4.15 kg, while clozapine-treated patients gained 4.45 kg.[129] Weight changes with clozapine and olanzapine are known to continue for up to one year or more.[131,132]

Drugs associated with a moderate degree of treatment-emergent weight gain include SGAs iloperidone, quetiapine, and risperidone and the FGA chlorpromazine. These agents typically produce weight gain of about 2 to3 kg in the first 10-12 weeks of treatment.[129,133] A lower degree of weight gain is seen with higher potency FGAs, such as haloperidol and fluphenazine, and SGAs aripiprazole, asenapine, lurasidone, and ziprasidone. Mean observed weight gain with these agents in 10to 12 week clinical studies have been 2 kg or less.[118,122]

Diabetes mellitus. Individuals with a prodromal and first episode schizophrenia have an increased incidence of developing diabetes regardless of treatment with antipsychotics.[121,134] In addition, new-onset hyperglycemia and diabetes mellitus have been observed with antipsychotic treatment. In some instances, the initial presentation consists of life-threatening diabetic ketoacidosis or hyperosmolar coma.[135] Frequently, clinically significant weight gain does not occur before the diagnosis of diabetes.[136]

In an analysis of public health registries and commercial databases carried out by Hirsch et al., the most consistent associations of type 2 diabetes mellitus diagnosis were found with olanzapine and clozapine treatment.[137] Other antipsychotics, including aripiprazole, quetiapine, risperidone, and ziprasidone, demonstrated statistically significant associations with type 2 diabetes.[138]

Dyslipidemia. Hyperlipidemia is another significant cardiac risk associated with 40% of antipsychotic naïve individuals diagnosed with schizophrenia as well as some antipsychotic treatments.[139,140] While risk factors for hyperlipidemia typically include glucose intolerance, dietary changes and weight gain, increases in serum triglycerides and low-density lipoproteins with SGAs have not always correlated with significant weight gain.[141,142] Antipsychotic medications may have an effect on adipose tissue leading to increased lipogenesis, insulin resistance, and decreased lipolysis.[142]

Of the antipsychotics, haloperidol and aripiprazole are considered to be lipid neutral, with ziprasidone, risperidone, and other high potency antipsychotics potentially causing mild to no risk of dyslipidemia. Low potency phenothiazines (chlorpromazine and thioridazine), clozapine, olanzapine, and quetiapine cause a significant increase in serum cholesterol and triglycerides.[143-146]

A 2004 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 SGAs.[147] The panel recommended careful consideration of metabolic risks whenever SGAs are initiated, especially in high-risk patients. The panel also recommended considering switching antipsychotics in patients who gain more than 7% of their initial weight, experience worsening hyperglycemia, or develop worsening hyperlipidemia. The most recent American Diabetes Association Standards of Care Guideline recommends that individuals taking atypical antipsychotics should be screened annually for prediabetes or diabetes.[148] Adolescents and adults with changes in their weight glycemic control and lipid levels should be monitored.[148] The British Association of Psychopharmacology recently published guidelines similar to the ADA guidelines with the exception of adding a review of the total cholesterol/ high density lipoprotein ratio at 12 weeks, six months, and annually.[149]

Cardiovascular risk. Antipsychotic medications can cause cardiovascular effects such as arrhythmia, elevations in blood pressure, orthostatic hypotension, and more rarely, congestive heart failure, myocarditis and sudden death.[150] Antipsychotic naïve individuals with schizophrenia are at a higher risk of mortality due to cardiovascular factors than the general population, so the use of antipsychotics in these individuals increases patient risk factors.[150] Certain antipsychotic medications have been associated with clinically significant prolongation of the corrected Q-T (QTc) 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 FGAs thioridazine, pimozide, and droperidol have been implicated in numerous cases

of sudden unexpected death.[151] Electrocardiographic data have revealed that patients receiving droperidol and thioridazine are more likely to have an abnormally long QTc interval.[152] Numerous reports of patient fatalities and the availability of safer alternatives have prompted the FDA to recommend that thioridazine, pimozide, and droperidol only be used as alternative agents with extreme caution.[153]

Although regulatory scrutiny for cardiac assessment heightened during the development of SGAs, these agents are generally associated with a low risk of electrocardiologic abnormalities. Ziprasidone was found to be associated with modest QTc prolongation during its premarketing studies. A comparative study that sought to determine the extent of QTc prolongation seen with the target therapeutic dosages of haloperidol, risperidone, olanzapine, quetiapine, and ziprasidone was later presented to the FDA.[153] Thioridazine was associated with an average QTc interval increase of 35.8 milliseconds. Of the second-generation agents included in the study, ziprasidone was associated with the greatest mean increase in the QTc interval-20.6 milliseconds. Haloperidol-treated subjects had an average QTc interval increase of 4.7 milliseconds, the smallest change observed in this study.[154] Coadministration of other interacting drugs (e.g. cytochrome P-450 isoenzyme inhibitors) did not lead to significant changes in QTc measurement. Ziprasidone's labeling warned of its greater potential of QTc interval prolongation and discouraged use in patients with electrolyte abnormalities, cardiac comorbidity, or concomitant use of metabolic inhibitors.[155] Since this study was completed several new antipsychotics have come to market and several of those have QTc ranges that have been measured in clinical trials. Of those agents, iloperidone appears to have a QTc of 9 milliseconds, but when combined with CYP450 inhibitors its QTc can increase to 19 milliseconds.[156] It is important to recognize that most of the SGA's do

cause QTc prolongation, but currently there is not enough data to stratify agents by potential to cause QT prolongation, so drug choice should be made keeping the cardiovascular risk factors and the QTc of the patient in mind.[157]

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.[158] The incidence has been estimated between 0.7 and 3%.[159-161] 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.[158]

Cerebrovascular events. The use of antipsychotics for the treatment for dementia-related agitation and psychosis in elderly patients is an unlabeled use that is generally supported by efficacy data in published controlled clinical trials.[162] 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 antipsychotics.[163-166] In 2003, the FDA requested that manufacturers of antipsychotic agents place a black box warning describing this treatment risk on the labeling of these products.[167] 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.[168] 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.[168]

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.[168] In addition; these findings have not been widely observed among patients with schizophrenia and schizoaffective disorder. It would therefore be advisable to monitor high risk elderly patients on antipsychotics for symptoms of stroke.

Hematologic toxicity. Transient cases of agranulocytosis can occur in 0.01% of patients receiving FGAs during the first eight weeks of therapy. The greatest incidence of agranulocytosis in the FGAs occurs with thioridazine and chlorpromazine. Among the SGA's the greatest incidence of neutropenia occurs with clozapine and olanzapine.[169]

Despite its superior efficacy for treatment-resistant schizophrenia, clozapine has remained underutilized due to concerns about its minor risk of agranulocytosis.[170-172] Agranulocytosis has been estimated to occur in 0.38% of patients treated with clozapine.[173] Episodes tend to occur between two and six months after initiation of treatment.[174] 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 2015, the FDA established a new Risk Evaluation and Mitigation Strategy (REMS) program that transitioned the oversight of hematologic monitoring from the use of multiple manufacturer-based registries to a centralized program.[177] As with prior manufacturer-based registries, the Clozapine REMS Program requires coordination between prescribers and pharmacies to ensure regular blood monitoring of patients in order to initiate or continue treatment with clozapine. The new REMS program differs from the guidelines used in the previous registry programs in that the primary basis for treatment recommendations is now the patient's absolute neutrophil count (ANC), regardless of total white blood cell (WBC) counts.

The REMS program also provides separate guidelines for patients with Benign Ethnic Neutropenia (BEN), a hereditary condition seen in 10-30% of individuals of African and Middle Eastern descent who have no history of repeated infections despite maintaining lower baseline WBC and ANC levels.[178,179] Individuals with BEN do not have a greater risk of clozapine-induced agranulocytosis, and are therefore not considered neutropenic within the ANC range of 1000-1500 cells/µL.[180]

Respiratory depression. Respiratory depression is more common with clozapine and olanzapine than with other antipsychotics. Respiratory collapse has been associated with rapid dosage adjustment, alcohol, and concomitant benzodiazepine use.[181] 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. It is recommended to avoid the combination of clozapine and olanzapine with benzodiazepines if possible, and if used together,

monitor the patient for respiratory depression.[182,183]

Seizure threshold changes. Most FGAs and SGAs lower the seizure threshold, with the greatest risk in patients with risk factors for seizures including epilepsy, traumatic brain injury, hyponatremia, rapid titration of antipsychotic agent, and higher drug serum levels. Risk of seizures is highest (>1%) for chlorpromazine at doses >1000mg/day and clozapine at doses >300 mg/day.[152] There is an intermediate risk of seizures for chlorpromazine doses <1000mg/day, clozapine 300 mg/day, olanzapine, quetiapine and thioridazine.[184] A low risk of seizures (<0.5%) is associated with the high potency antipsychotics, aripiprazole, ziprasidone, risperidone and paliperidone.[185-187] Precautions should be taken for patients with seizure disorders receiving antipsychotic treatment, potentially including the concurrent use of an anticonvulsant, such as lamotrigine or levetiracetam.[188]

Drug selection and dosing considerations

With the notable exception of clozapine, the principal differences among the available 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 concerns.[189,190] For example, individuals with a known sensitivity to EPS may benefit from quetiapine. Patients with preexisting metabolic disorders or those at risk for developing metabolic disorder may benefit from high potency FGAs or SGAs, such as aripiprazole, lurasidone, and ziprasidone that have a lower propensity for causing metabolic side effects.

The availability of orally disintegrating tablets, sublingual tablets, oral liquid formulations, and long acting injectable formulations of several antipsychotics provide options for patients who have difficulty taking standard oral tablets or capsules, those with a history of poor treatment adherence, or those with an expressed interest for these dosage forms.[191-193] Loxapine is also available as a powder for oral inhalation that has been FDA approved for treatment of acute agitation associated with Schizophrenia or Bipolar Disorder. Its use is restricted by an FDA-approved REMS program which requires that it be given in a healthcare facility due to the risk of bronchospasm, pulmonary distress, and pulmonary arrest.

Dosing. The dosage ranges of antipsychotic drugs used for symptom remission in acute schizophrenia have been established in registration trials and in some post-marketing analyses.[194-196] The target doses of FGAs and SGAs for acute treatment are listed in Tables 2. and 3.

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 SGAs with doses higher than the maximum recommended in the product labeling.[206]

Long-acting injectable formulations. The development and use of long-acting injectable (LAI) antipsychotic formulations have sought to reduce some barriers to treatment adherence and provide more convenient options for patients.[191,192,197] LAI agents are administered in intervals ranging from 2- to 12-weeks between doses, reducing the need to administer oral drug on a daily

basis.

The available LAI antipsychotics are described on Table 5. The first generation agents, fluphenazine decanoate and haloperidol decanoate are oil-based formulations that are released gradually from muscle tissue after injection and hydrolyzed to the active drug.[198] The newer second generation LAIs are water-based products that use a variety of delivery technologies to release the active drug over time.

While LAI antipsychotics have consistently demonstrated symptomatic efficacy and reduced relapse frequency compared to placebo, it has been more difficult to establish these outcomes in head-to-head studies with oral antipsychotics due to methodologic limitations.[199] Adverse effect profiles of LAI antipsychotics are generally comparable to those of the corresponding oral drug. However, due to their extended duration of action, any untoward effects from LAI treatment are not easily reversible.

The LAI formulations should be considered in patients with a stated preference for their use or in individuals with a previous history of poor adherence. They may be initiated after patients have achieved a degree of clinical stability with the corresponding oral medication.

Patient monitoring

Frequent and continuous monitoring is necessary for individuals treated with antipsychotics in order to assess for therapeutic response and adverse effects. An evaluation of efficacy is warranted after week 2 of treatment, as it has been shown that nonresponse at this point predicts a low likelihood of response.[200] 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 antipsychotic therapy should consist of regular assessments of body weight, glucose levels, and lipid values (Table 6).[149,201] Treatment with clozapine requires weekly assessment 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 SGAs, in addition to patients receiving FGAs, should be monitored for symptoms of dystonia, parkinsonism, akathisia, and tardive dyskinesia.[201] Patients should be evaluated for acute EPS weekly until two weeks after dose stabilization, from when antipsychotics are initiated or adjusted. Assessments for tardive dyskinesia should be conducted at least once yearly for individuals receiving continuous treatment with antipsychotics.[201]

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.[202-204] In maintenance treatment, a clozapine serum level of at least 200 ng/mL optimally correlated with low risk of relapse.[205]

Pharmacogenomics

Schizophrenia is a complex illness with an etiology involving environmental factors and approximately 80% heritability.[206] Studies have shown that there is a higher incidence of synaptic

pruning in the brains of those individuals diagnosed with schizophrenia versus those in the general population.[207] Genome wide association studies have shown multiple susceptibility loci for schizophrenia, yet these studies have been difficult to replicate.[208]

Treatment of schizophrenia can be difficult due to lack of an empirical approach to choosing appropriate medications. Individuals with schizophrenia are typically treated based on a "trial and error" basis which can lead to non-adherence and adverse effects.[209] As many as 30-40% of individuals taking an antipsychotic will not respond to an individual agent, even though other individuals taking the same medication at the same dose for the same amount of time will exhibit response and even remission.[210] Variability in treatment response is also complex. Environmental factors – such as cigarette smoking, alcohol consumption, and dietary choices – can impact drug response. Comorbid psychiatric diagnoses, concurrent medications, and demographic factors, including gender, age, and ethnicity play a role in medication response as well. Pharmacogenomic factors help account for the wide variability of treatment responses seen across the population.

The Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group provide valuable analyses and guidance related to pharmacogenomic considerations for select medications, including medications used in schizophrenia and schizoaffective disorder. Pharmacogenomic research on antipsychotics has focused on metabolic enzymes (cytochrome P450), neurotransmitters (dopamine, serotonin), and drug transporters (p-glycoprotein). A very large number of potential genes involved in efficacy and adverse effects of antipsychotics have been identified. For example, over 90 variants of the CYP2D6 gene have been recognized.[211] However, many of these pharmacogenomic studies have been difficult to replicate or are limited to *in vitro* studies.

Pharmacogenomic testing has become commercially available for clinical use, but standardized guidelines for their use predicting antipsychotic treatment response have not yet been established.[212] Analysis of polymorphisms across the neurotransmitters, metabolic enzymes, and drug transporters need to be systematically analyzed in large enough sample sizes to develop enough sensitivity and specificity to provide clinicians with adequate guidance to predict individual response to antipsychotics.

Despite the current limitations in utility of pharmacogenomic application in schizophrenia treatment, some antipsychotics carry FDA labelling indicating that they have potentially applicable biomarkers.[213] This pharmacogenomic information is primarily useful for initiating and targeting doses that might result in drug interactions (Table 7). Guidance to clinicians on who should receive this testing is still unclear. Improvements in testing options continue to grow. Not all companies that test genetic variants test for the same medications, so it is important to ascertain whether the test used for an individual will give the results that the clinician is seeking.[213]

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. However, negative and cognitive symptoms may have the greatest impact on patients' functional status.[214] Among the domains of functioning affected include activities of daily living, employment, treatment adherence, socialization, and quality of life.[215,216] A variety of evidence-based psychosocial treatments have been demonstrated to have a positive impact on functional outcomes.[217]

Studies addressing the effect of antipsychotics on hospitalization have repeatedly found that these agents reduce the length of stay and readmission rate compared with placebo.[62] Rabinowitz, et al. 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).[218] In a landmark double-blind trial of risperidone versus haloperidol, Csernansky et al. measured relapse by examining rehospitalization, signs of clinical decompensation, and increasing requirements for supervision.[219] 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. Kishimoto and colleagues in a meta-analysis showed no difference between FGAs and SGAs in regards to relapse unless you pool all of the SGAs.[62] If all SGA agents studied are pooled, results do show some superiority for relapse, treatment failure, hospitalization and tolerability over FGAs.

Suicide is a leading cause of death in this patient population, with a lifetime suicide mortality rate estimated at 4-6%.[220] Risk factors of suicidality in schizophrenia include depressed mood, history of previous suicide attempts, male gender, number of psychiatric hospitalizations and young age. In addition to having favorable effects on mood symptoms, there are indications that SGAs may also reduce suicide rates in some populations, with clozapine demonstrating a particular benefit in this regard.[221] 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%, $p<0.005$).[2]

Summary

Schizophrenia and schizoaffective disorder are chronic illnesses that can present with a broad range of symptoms and can affect many domains of functioning. The currently available antipsychotic drugs, while not curative, can have a dramatic effect on the acute symptoms of psychosis and the overall trajectory of schizophrenia and schizoaffective disorder. Clozapine has demonstrated a unique level of efficacy for individuals with treatment-resistant schizophrenia 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 SGAs and must be managed proactively by clinicians. Extrapyramidal effects, including dystonic reactions, parkinsonism, and akathisia affect the tolerability of antipsychotics and should be monitored throughout the treatment course. Pharmacists and 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 help achieve optimal outcomes with treatment.

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Table 1. DSM-5 criteria for schizophrenia and schizoaffective disorder[4]

Schizophrenia Criterion	Schizoaffective Disorder Criterion
A. Two (or more) of the following symptoms, each present for the greater part of a one-month period (or less if treated successfully). At least one of these must be 1, 2, or 3 below. 1. Delusions 2. Hallucinations 3. Disorganized speech (e.g. frequent derailment or incoherence). 4. Grossly disorganized or catatonic behavior 5. Negative symptoms (i.e. diminished emotional expression or avolition) B. Level of function in a major area (personal or occupational functioning) must be less than prior to the onset of symptoms. C. There must be continuous signs of the illness for at least 6 months. During this 6 month time frame there must be a least one month of symptoms from A. above, and may include prodromal, residual or negative symptoms. D. Schizoaffective, depressive or bipolar disorder has been ruled out. E. The disturbance is not due to the effects of a substance (medication or drug of abuse) or a medical condition. F. If there is a history of autism spectrum or a communication disorder or childhood, a diagnosis of schizophrenia is only made if hallucinations or delusions are prominent.	A. An uninterrupted period of illness during which there is a major mood episode (major depressive or manic) concurrent with Criterion A of schizophrenia. (Note: The major depressive episode must include Criterion A1: Depressed mood.) B. Delusions or hallucinations for two or more weeks in the absence of a major mood episode (depressive or manic) during the lifetime duration of the illness. C. Symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active as well as residual portions of the illness. D. The disturbance is not the result of the effects of a substance (e.g., a drug of misuse or a medication) or another underlying medical condition.

Table 2. First-generation antipsychotics currently available in the United States

Drug Trade Name	Usual Therapeutic Doses	Year Approved
Chlorpromazine (Thorazine)	300-1000 mg (maximum dose of 1000 mg/day)	1953
Fluphenazine (Prolixin)	5-20 mg (maximum 40 mg/day)	1959
Haloperidol (Haldol)	2-20 mg (maximum 100 mg/day)	1967
Loxapine (Loxitane/Adasuve)	50-150 mg (maximum 250 mg/day)/ 10 mg/day (inhalation)	1975
Perphenazine (Trilafon)	16-64 mg (maximum 64 mg/day)	1957
Pimozide (Orap)	2-10 mg (maximum 10 mg/day)	1985
Thioridazine (Mellaril)	100-800 mg (maximum 800 mg/day);	1958
Thiothixene (Navane)	4-50 mg (maximum 60 mg);	1967
Trifluoperazine (Stelazine)	5-40 mg (maximum 40 mg/day).[	1959

Table 3. Second-generation antipsychotics currently available in the United States

Drug (Trade Name)	Usual Therapeutic Doses	Year Approved
Aripiprazole (Abilify)	15-30 mg/day	2002
Asenapine (Saphris)	10-20 mg/day	2009
Brexpiprazole (Rexulti)	2-4 mg/day	2015
Cariprazine (Vraylar)	1.5-6mg/day	2015
Clozapine (Clozaril)	100-800 mg/day (900 mg maximum dose)	1989
Iloperidone (Fanapt)	6-24 mg/day	2009
Lurasidone (Latuda)	40-120 mg/day	2010
Olanzapine (Zyprexa)	10-20 mg/day	1996
Paliperidone (Invega)	3-12 mg/day	2006
Quetiapine (Seroquel)	300-800 mg/day	1997
Risperidone (Risperdal)	2-8 mg/day	1993
Ziprasidone (Geodon)	80-160 mg/day	2001

Table 4. Mean body weight changes at 10-12 weeks in patients receiving antipsychotics[129,131,133]

Treatments	Weight Gain (kg)
Placebo	-0.75
Molindone	-0.39
Ziprasidone	0.04
Fluphenazine	0.43
Lurasidone	0.59
Paliperidone	1.03
Haloperidol	1.08
Asenapine	1.24
Risperidone	2.10
Iloperidone	2.16
Chlorpromazine	2.58
Thioridazine	3.19
Mesoridazine	3.19
Olanzapine	4.15
Clozapine	4.45

Table 5. Long-acting injectable antipsychotics available in the United States

Drug	Starting Dose	Oral Supplementation	Maintenance Dose	Dosing Interval	Notes
Fluphenazine decanoate	12.5 – 25 mg	None	12.5 – 100 mg	2-3 weeks	
Haloperidol decanoate	100 mg	None	100-300 mg	4 weeks	
Risperidone microspheres (Risperdal Consta)	25 mg	3 weeks	25-50 mg	2 weeks	
Olanzapine pamoate (Zyprexa Relprevv)	210 – 405 mg	None	150-405 mg	2-4 weeks	Requires postinjection observation for 3 hours after each dose due to risk of post-injection delirium sedation syndrome. Because of this risk, it is available only through a restricted distribution program called ZYPREXA RELPREVV Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment.
Paliperidone palmitate (Invega Sustenna)	234 mg, then 156 mg	None	78 – 234 mg	Monthly	Loading doses given as two doses 3-11 days apart
Paliperidone palmitate (Invega Trinza)	273 – 819 mg	None	273 – 819 mg	Every 3 months	To be initiated only in patients stabilized on Invega Sustenna
Aripiprazole monohydrate (Abilify Maintena)	400 mg	2 weeks	300 – 400 mg	Monthly	
Aripiprazole lauroxil (Aristada)	441 – 882 mg	3 weeks	441 – 882 mg	4-6 weeks	
	1064 mg			8 weeks	

Table 6. Monitoring guidelines for patients treated with second-generation antipsychotics

Assessment	Monitoring Frequency
Fasting blood glucose	All drugs: Baseline, then monthly for the first three months and every 6 months 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 years and in patients with a history of cardiac arrhythmias.
Complete blood count with differential	Clozapine: Weekly for the first 6 months. Every other week for the next 6 months, and every 4 weeks thereafter if no abnormalities are noted.
Fasting total cholesterol, low-and high-density lipoproteins,	All drugs: Baseline and every two years thereafter if no abnormalities are noted. Every 6 months for individuals noted to have hyperlipidemia or receiving lipid-lowering therapy

Table 7. Pharmacogenomic considerations for antipsychotic medications[211-213,223-229]

Antipsychotic[a]	FDA Labeling Information
Aripiprazole[b]	In CYP2D6 PM and individuals receiving aripiprazole in addition to a strong CYP2D6 or 3A4 inhibitor, decrease dose of aripiprazole in half (50%) In individuals taking a strong CYP2D6 or 3A4 inhibitor in addition to aripiprazole, decreased the dose of aripiprazole to a quarter of the dose (25%) The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole in NMs and PMs respectively
Aripiprazole, extended-release injectable suspension	CYP2D6 PMs adjust 300 mg dose to 200 mg In individuals taking 400 mg receiving a strong CYP2D6 and 3A4 inhibitor decrease dose to 300 mg In those individuals taking 300 mg decrease dose to 200 mg in strong CYP2D6 and 3A4 inhibitors and decrease the dose to 160 mg in those taking a combination of CYP2D6 and 3A4 inhibitors Do not use in CYP3A4 inducers concomitantly with aripiprazole, extended-release
Clozapine	May have higher plasma levels in CYP1A2/3A4/2C19 PMs Use 33% of clozapine dose if given with CYP1A2 inhibitors Do not use clozapine with strong CYP3A4 inducers
Iloperidone	Reduce dose 50% in CYP2D6 and 3A4 PM.
Perphenazine	CYP2D6 PMs will have higher concentrations than NMs
Risperidone	CYP2D6 NMs convert risperidone rapidly into 9-hydroxyrisperidone; CYP2D6 PMs convert it more slowly. CYP2D6 NMs have lower risperidone and higher 9-hydroxyrisperidone concentration than PMs. Given that 9-hydroxyrisperidone is an active metabolite, no changes in dose need to be made.
Thioridazine	Thioridazine is contraindicated in CYP2D6 PMs. Reduced CYP2D6 activity in individuals taking thioridazine may cause prolongation of QTc inverval of thioridazine and may lead to cardiac arrhythmias (Torsades de pointes)

PM-poor metabolizers; NM-normal metabolizer (previously was called EM, extensive metabolizer); [a]Clinical Pharmacogenetics Implementation Consortium make no recommendations for dose changes in antipsychotic agents; [b]Dutch Pharmacogenomics Working Group recommends using no more than 10 mg of aripiprazole in CYP2D6 PMs[230]