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-generation antipsychotic (FGA) or a second-generation antipsychotic (SGA) based upon the adverse effect profile of the drug and the 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 state that at least 2 out of 5 symptoms must be present for at least 1 month, and at least one of those symptoms must be 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 2 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 in schizophrenia, social and occupational dysfunction need not occur for diagnosis of schizoaffective disorder, according to DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*) criteria (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 (eg, anxiety, sleep disturbances, social withdrawal, 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 5 years of the illness, deemed the critical period.[10] A recent study assessed 12-month mortality for patients with FEP as being 24 times higher than for the general US population.[11]

Childhood-onset schizophrenia resembles the essential features seen in adult-onset schizophrenia. Prodromal symptoms of psychosis occurring in children and

adolescents (eg, 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 and 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/hyperactivity disorder, post-traumatic stress 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 neurological 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 adverse effect profile. Low potency agents, dosed in the 100s of milligrams, (eg, 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,(eg, haloperidol, fluphenazine, loxapine, perphenazine, thiothixene, trifluoperazine) are more likely to cause extrapyramidal adverse effects (eg, dystonias, parkinsonism, akathisia) and tardive dyskinesia (Table 2).[20] FGAs are also associated with hematologic (eg, agranulocytosis), endocrine (eg, prolactin elevation, menstrual irregularities, sexual dysfunction), dermatologic (eg, blue-gray skin coloration, photosensitivity, allergic reactions) and ophthalmologic (eg, 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 1 month (untreated), but often last for 3 to 6 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 to 4 months, and 83% achieving stable remission by the end of 1 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, adverse 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 12 months after remission.[31,58] As many as 83% of patients with FEP will experience a relapse in symptoms within 5 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 1 year of maintenance antipsychotic therapy, while the rate of relapse for patients on placebo is between 60% and 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 2 or more antipsychotics (at least 1 of those should be a SGA) from differing chemical classes given at therapeutic doses for a minimum of 2 to 8 weeks per agent.[1,58,64-66]

A trial of clozapine is generally warranted for patients who demonstrate a suboptimal response to 2 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 1 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 3 periods of treatment in the preceding 5 years with antipsychotics from 2 different chemical classes at dosages equivalent to 1,000 mg/day of chlorpromazine for 6 weeks. The previous antipsychotic trials must have failed to provide periods of good functioning or significant symptomatic relief.

A 6-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 3 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% to 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% to 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 (vesicular monoamine transporter 2) inhibitor, 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 1 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 to 3 kg in the first 10 to 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 10- to 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 ratio of total cholesterol to high-density lipoprotein at 12 weeks, 6 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 QT (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 (eg, 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 CYP-450 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 6 placebo-controlled randomized studies of risperidone for the treatment of behavioral disturbances in patients with dementia revealed 33 CVAEs (3.3%) in 1,009 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 1,009 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 8 weeks of therapy. The greatest incidence of agranulocytosis in the FGAs occurs with thioridazine and chlorpromazine. Among the SGAs 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 2 and 6 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% to 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 1,000 to 1,500 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 2 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 >1,000mg/day and clozapine at doses >300 mg/day.[152] There is an intermediate risk of seizures for chlorpromazine doses <1,000mg/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 anti-seizure medications, 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 adverse 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 (eg, 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 6 months. If no evidence of neutropenia or granulocytopenia is

found, the monitoring frequency can be reduced to every two weeks for the next 6 months and then every 4 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 1 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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Additional information

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References

1. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guidelines for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry.* 2010:161(2)(suppl):1-56.
2. Meltzer HY, Alphs L, Green AI. Clozapine treatment for suicidality in schizophrenia. International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry.* 2003;60(1):82-91.
3. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: cost utility of the latest antipsychotic drugs in schizophrenia (CUtLASS 1). *Arch Gen Psychiatry*. 2006;63(10):1079-1087.
4. Schizophrenia spectrum and other psychotic disorders. In: American Psychiatric Association. *DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*. Washington, DC: American Psychiatric Press; 2013.
5. Ross CA. Problems with the psychosis section of DSM-5. *Psychosis.* 2014;6:3,235-241.

6. Peraia J. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry.* 2007;64(1):19-28.

7. Heinssen RK, Goldstein AB, Azrin ST; for National Institute of Mental Health. Evidence-based treatments for first episode psychosis: components of coordinated specialty care. RA1SE website. https://www.nimh.nih.gov/health/topics/schizophrenia/raise/nimh-white-paper-csc-for-fep_147096.pdf. Published April 14, 2014. Accessed August 7, 2018.

8. Addington J, Heinssen RK, Robinson DG, et al. Duration of untreated psychosis in community treatment settings in the United States. *Psychiatric Serv*. 2015;66(7):753-756. doi:10.1176/appi.ps.201400124.

9. Nicholl D, Akhras KS, Diels J, Schadrack J. Burden of schizophrenia in recently diagnosed patients: healthcare utilization and cost perspective. *Curr Med Res Opin*. 2010;26(4):943-955.

10. Byrne P. Managing the acute psychotic episode. *BMJ*. 2007;334:686-692.

11. Schoenbaum M, Sutherland JM, Chappel A, et al. Twelve-month health care use and mortality in commercially insured young people with incident psychosis in the United States. *Schizophrenia Bull*. 2017;43(6):1262-1272.

12. Driver DI, Gogtay N, Rapoport JL. Childhood onset schizophrenia and early onset schizophrenia spectrum disorders. *Child Adolesc Psychiatr Clin N Am*. 2013;22(4):539-555.

13. Folsom DP, Lebowitz BD, Lindamer LA, et al. Schizophrenia in late life: emerging issues. *Dialogues Clin Neurosci*. 2016; 8(1):45-52.

14. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophrenia Bull.* 2009;35(3)549-562.

15. Brisch R, Saniotis A, Wolk R, et al. The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: old fashioned, but still in vogue. *Front Psychiatry.* 2014:5:110.

16. Javitt DC. Glutamatergic theories of schizophrenia. *J Psych Relat Sci*. 2010;47(1):4-16.

17. Javitt DC, Zukin SR, Heresco-Levy U, Umbricht D. Has an angel shown the way? Etiological and therapist implications of the PCP/NMDA model of schizophrenia. *Schizophrenia Bull*. 2012;38(5):958-966.

18. Hughes JR, Hatsukami DK, Mitchell JE, et al. Prevalence of smoking among psychiatric outpatients. *Am J Psychiatry*. 1986;143:993-997.

19. Brunzell D, McIntosh JM. Alpha 7 nicotinic acetylcholine receptors modulate motivation to self-administer nicotine: implications for smoking and schizophrenia. *Neuropsychopharmacology.* 2012;37:1134-1143.

20. Jibson MD, Marder S, Hermann R. First-generation antipsychotic medications: pharmacology, administration, and comparative side effects. In: UpToDate [database online]. Waltham, MA: Wolters Kluwer Health. Accessed March 6, 2017.

21. Stahl SM. Dopamine system stabilizers, aripiprazole, and the next generation of antipsychotics, part I: “Goldilocks” actions at dopamine receptors. *J Clin Psychiatry*. 2001;62:841-842.

22. Stahl SM. Dopamine system stabilizers, aripiprazole, and the next generation of antipsychotics, part II: illustrating their mechanism of action. *J Clin Psychiatry*. 2001;62:923-924.

23. Möller H. The relevance of negative symptoms in schizophrenia and how to treat them with psychopharmaceuticals? *Psychiatria Danubina.* 2016:28(4):435-440.

24. Dollfus S, Lyne J. Negative symptoms: history of the concept and their position in diagnosis of schizophrenia. *Schizophr Res*. 2017;186:3-7.

25. Mitra S, Mahintamani T, Kavoor AR, Nizamie SH. Negative symptoms in schizophrenia. *Ind Psychiatry J*. 2016;25(2):135-144.

26. Kantrowicz JT. Managing negative symptoms of schizophrenia: how far have we come? *CNS Drugs*. 2017;31:373-388.

27. Aleman A, Lincoln TM, Bruggeman R, et al. Treatment of negative symptoms: where do we stand and where do we go. *Schizophr Res*. 2017;186:55-62.

28. Kirschner M, Aleman A, Kaiser S. Secondary negative symptoms—a review of mechanisms, assessment and treatment. *Schizophr Res.* 2017;186:29-38.

29. Remington G, Foussias G, Fervaha G, et al. Treating negative symptoms in schizophrenia: an update. *Curr Treat Options Psychiatry.* 2016;3:133-150.

30. Leucht S, Cipriani A, Spineli L. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet.* 2013;382:951-962.

31. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull.* 2010;36:71-93.

32. Andreasen NC, Liu D, Ziebell S, et al. Relapse furation, treatment intensity, and brain tissue loss in schizophrenia: a prospective longitudinal MRI study. *Am J Psychiatry.* 2013;170:609-615.

33. Green MF. What are the functional consequences of neurocognitive deficits of schizophrenia? *Am J Psychiatry*. 1996;153:321-330.

34. Liddle PF. Cognitive impairment in schizophrenia: its impact on social functioning. *Acta Psychiatr Scand Suppl*. 2000;400:11-16.

35. Sharma T, Antonova L. Cognitive function in schizophrenia: deficits, functional consequences, and future treatment. *Psychiatr Clin North Am*. 2003;26:25-40.

36. Spohn HE, Strauss ME. Relation of neuroleptic and anticholinergic medication to cognitive functions in schizophrenia. *J Abnorm Psychol*. 1989;98:367-380.

37. 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;159:11018-11028.

38. 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;34:702-712.

39. 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;47:41-45.

40. Buchanan RW, Holstein C, Breier A. The comparative efficacy and long-term effect of clozapine on neuropsychological test performance. *Biol Psychiatry*. 1994;36:717-725.

41. Cornblatt B, Kern RS, Carson WH, et al. Neurocognitive effects of aripiprazole versus olanzapine in stable psychosis. Presented at 23rd Collegium Internationale Neuropsychopharmacologicum Congress; June 2002; Montreal, Canada.

42. Davidson M, Galderisi S, Weiser M, et al. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). *Am J Psychiatry*. 2009;166(6):675-82.

43. Keefe RS, Bilder RM, Davis SM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. *Arch Gen Psychiatry.* 2007;64:633-647.

44. Goldberg TE, Goldman RS, Burdick KE, et al. Cognitive improvements after treatment with SGAs in first episode schizophrenia: is it a practice effect? *Arch Gen Psychiatry.* 2007;64:1115-1122.

45. Albus M, Hubmann W, Mohr F, et al. Neurocognitive functioning in patients with first-episode schizophrenia. *Eur Arch Psychiatry Clin Neurol.* 2006;256:442-451.

46. Hill SK, Shuepback D, Herbener ES, Keshavan MS, Sweeney JA. Pretreatment and longitudinal studies of neuropsychological deficits in antipsychotic-naïve patients with schizophrenia. *Schizophr Res.* 2004;68:49-63.

47. Hoff AL, Sakuma M, Wieneke M, Horon R, Kushner M, DeLisi LE. Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. *Am J Psychiatry.* 1999;156:1336-1341.

48. Keefe RS, Perkins DO, Gu H, Zipursky RB, Christensen BK, Lieberman JA. A longitudinal study of neurocognitive function in individuals at-risk for psychosis. *Schizophr Res.* 88:26-35.

49. Crespo-Facorro B, Rodriguez-Sanchez JM, Perez-Inglesias R, et al. Neurocognitive effectiveness of haloperidol, risperidone, and olanzapine in first episode psychosis: a randomized, controlled 1-year follow-up comparison. *J Clin Psychiatry.* 70:717-729.

50. Keefe RS, Malhotra AK, Meltzer H, et al. Efficacy and safety of donepezil in patients with schizophrenia or schizoaffective disorder: significant placebo/practice effects in a 12 week, randomized, double-blind, placebo-controlled trial. *Neuropsychopharmacology.* 2008;33:1217-1228.

51. Hill SK, Bishop JR, Palumbo D, Sweeney JA. Effect of second-generation antipsychotics on cognition: current issues and future challenges. *Expert Rev Neurother.* 2010;10(1):43-57.

52. Andersen R, Fagerlund B, Rasmussen H, et al. Cognitive effects of six months of treatment with quetiapine in antipsychotic-naïve first-episode schizophrenia. *Psychiatry Res.* 2011;187(1-2):49-54.

53. Suzuki H, Gen K, Inoue Y. An unblended comparison of the clinical and cognitive effects of switching from first-generation antipsychotics to aripiprazole, perospirone or olanzapine in patients with chronic schizophrenia. *Prog Neuropsychopharmacology Biological Psychiatry.* 2011;35(1):161-168.

54. Cuesta MJ, Jalon EG, Campos MS, Peralta V. Cognitive effectiveness of olanzapine and risperidone in first-episode psychosis. *Br J Psychiatry.* 2009;194:439-445.

55. Guo X, Zhai J, Wei Q, et al. Neurocognitive effects of first- and second-generation antipsychotic drugs in early-stage schizophrenia: a naturalistic 12-month follow-up study. *Neurosci Lett.* 2011;503(2):141-146.

56. Robles O, Zabala A, Bombin I, et al. Cognitive efficacy of quetiapine and olanzapine in early-onset first-episode psychosis. *Schizophrenia Bull.* 2011;37(2):405-415.

57. Frazier JA, Giuiano AJ, Johnson JL, et al. Neurocognitive outcomes in the treatment of early-onset schizophrenia spectrum disorders study. *J Am Acad Child Adolesc Psychiatry.* 2012;51(5):496-505.

58. Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World J Biol Psychiatry.* 2012;13:318-378.

59. Gardner KN, Nasrallah HA. Managing first-episode psychosis: an early state of schizophrenia with distinct treatment needs. *Curr Psychiatr.* 2015;14(5):32-42.

60. Rosenheck R, Leslie D, Sint K, et al. Cost effectiveness of comprehensive, integrated care for first episode psychosis in the NIMH RAISE early treatment program. *Schizophrenia Bull*. 2016;42(4):896-906.

61. Zipursky RB, Menezes NM, Streiner DL. Risk of symptom recurrence with medication discontinuation in first-episode psychosis: a systematic review. *Schizophrenia Res*. 2014;152:408-414.

62. Kishimoto T, Agarwal V, Kishi T, Leucht S, Kane JM, Correll CY. Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first generation antipsychotics. *Mol Psychiatry.* 2013;18:53-66.

63. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet.* 2012;379:2063-2071.

64. National Collaborating Centre for Mental Health. The NICE guideline on core interventions in the treatment and management of schizophrenia in adults in primary and secondary care (updated edition). London, UK: British Psychological Society; 2010.

65. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic, a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1994;152:20-26.

66. McIlwain ME, Harrison J, Wheeler AJ, Russell BR. Pharmacotherapy for treatment-resistant schizophrenia. *Neuropsychiatr Dis Treat.* 2011;7:135-149.

67. Stahl SM. Antipsychotic polypharmacy: squandering precious resources? *J Clin Psychiatry.* 2002;63:93-94.

68. Newcomer JW, Weiden PJ, Buchanan RW. Switching antipsychotic medications to reduce adverse event burden in schizophrenia: establishing eveidence-based practice. *J Clin Psychiatry.* 2013;74(11):1108-1120.

69. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1209-1223.

70. Siskind D, McCartney L, Goldschlager R, Kisely S. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *Br J Psychiatry.* 2016;209(5):382.392. doi:10.1192/bjp.bp.115.177261.

71. Siskind D, McCartney L, Goldschlager R, Kisely S. Systematic review and meta-analysis of clozapine for treatment refractory schizophrenia. *Aust N Z J Psychiatry.* 2015:49:73-74.

72. Heres S, Davis J, Maino K, et al. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. *Am J Psychiatry.* 2006;163:185-194.

73. Lewis S, Lieberman J. CATIE and CUtLASS: can we handle the truth? *Br J Psychiatry.* 2008;192:161-163.

74. Farah A. Atypicality of atypical antipsychotics revisited. *Curr Psychiatry Rev.* 2013;9(4):316-324.

75. Weiden PJ. EPS profiles: the atypical antipsychotics are not all the same. *J Psychiatry Pract.* 2007;(13(1):13-24.

76. Casey DE. Implications of the CATIE trial on treatment: extrapyramidal symptoms. *CNS Spectr.* 2006;11(7):25-31.

77. Tandon R. Antipsychotics in the treatment of schizophrenia: an overview. *J Clin Psychiatry.* 2011;72(1):4-8.

78. Fischer-Barnicol D, Lanquillon S, Haen E, et al. Typical and atypical antipsychotics-the misleading dichotomy: results from the working group "Drugs in Psychiatry (AGATE)," *Neuropsychobiology.* 2008;57:80-87.

79. Shirzadi AA, Ghaemi SN. Side effects of atypical antipsychotics: extrapyramidal symptoms and the metabolic syndrome. *Harv Rev Psychiatry.* 2006;14(3):152-164.

80. Jesic MP, Jesic A, Filipovic JB, et al. Extrapyramidal syndromes caused by antipsychotics. *Medicinski Pregled.* 2012;65:521-526.

81. Kumar R, Sachdev PS. Akathisia and second-generation antipsychotic drugs. *Curr Opin Psychiatry.* 2009;22(3):293-299.

82. Miller DD, Caroff SN, Davis SM, et al. Extrapyramidal side-effects of antipsychotics in a randomized trial. *Br J Psychiatry.* 2008;193(4):279-288.

83. Kane JM, Fleischhacker WW, Hansen L, Perlis R, Pikalov A, Talbott SA. Akathisia: an updated review focusing on second-generation antipsychotics. *J Clin Psychiatry.* 2009;70(5):629-643.

84. Thomas JE, Cabellero J, Arrington CA. The incidence of akathisia in the treatment of schizophrenia with aripiprazole, asenapine, and lurasidone: a meta analysis. *Curr Neuropharmacology.* 2015,13:681-691.

85. Casey DE. Tardive dyskinesia and atypical antipsychotic drugs. *Schizophr Res.* 1999;35:S61-S66.

86. Llorca P, Chereau I, Bayle F, Lancon C. Tardive dyskinesia and antipsychotics: a review. *Eur Psychiatry*. 2002;17(3):129-138.

87. Carbon M, Hsied CH, Kane JM, Correll CU. Tardive dyskinesia prevalence in the period of second-generation antipsychotic use: a meta-analysis. *J Clin Psychiatry.* 2017;78(3):e278. doi;10.4888/JCP.16r10832.

88. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second- generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry.* 2004;161:414-425.

89. Vijayakumar D, Jankovic J. Drug-induced dyskinesia, part 2: treatment of tardive dyskinesia. *Drugs.* 2016;76:779-787.

90. 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;71:176-185.

91. Kurz M, Hummer M, Oberbauer H, et al. Extrapyramidal side effects of clozapine and haloperidol. *Psychopharmacology.* 1995;118:52-56.

92. Casey DE. Clozapine: neuroleptic-induced EPS and tardive dyskinesia. *Psychopharmacology.* 1989;99:S47-S53.

93. Lerner PP, Miodownik C, Lerner V. Tardive dyskinesia (syndrome): current concept and modern approaches to its management. *Psychiatry Clin Neurosci*. 2015;69(6):321-334.

94. Hazari N, Kate N, Grover S. Clozapine and tardive movement disorders: a review. *Asian J Psychiatr*. 2013;6(6):439-451.

95. Ahmed S, Chengappa KN, Naidu VR, et al. Clozapine withdrawal-emergent dystonias and dyskinesias: a case series. *J Clin Psychiatry.* 1998;59:472-477.

96. O'Brien CD, Jimenez R, Hauser RA, et al. NBI-98854, a selective monoamine transport inhibitor for the treatment of tardive dyskinesia: a randomize, double-blind, placebo–controlled study. *Mov Disord*. 2015;30:1681-1687.

97. Hauser RA, Factor SA, Marder SR, et al. KINECT 3: a phase 3 randomized, double-blind, placebo-controlled trial of valbenzapine for tardive dyskinesia. *Am J Psychiatry*. 2017;174:476-484.

98. Kaur N, Kumar P, Jamwal S, et al. Tetrabenazine: spotlight on drug review. *Ann Neurosci*. 2016;23:176-185.

99. Fernandez HH, Factor SA, Hauser RA, et al. Randomized controlled trial of deutetrabenzaine for tardive dyskinesia: the ARM-TD study. *Neurology*. 2017;88:2003-2010.

100. Brooks M. FDA OKs deutetrabenazine (Austedo) for tardive dyskinesia. Medscape Medical News. www.medscape.com/viewarticle/885051. Published August 30, 2017. Accessed August 7, 2018.

101. Barak Y, Swartz M, Shamir E, et al. Vitamin E (alpha-tocopheol) in the treatment of tardive dyskinesia: a statistical meta-analysis. *Ann Clin Psychiatry*. 1998;10:101-105.

102. Soares-Weiser K, Maayan N, McGrath J. Vitamin E for neuropetic-induced tardive dyskinesia. *Cochrane Database Syst Rev*. 2011;2:CD000209.

103. Thaker GK, Nguyen JA, Strauss ME, Jacobson R, Kaup BA, Tamminga CA. Clonazepam treatment of tardive dyskinesia: a practical GABAmimetic strategy. *Am J Psychiatry.* 1990;147:445-451.

104. Pappa S, Tsouli S, Apostolou G, Mavreas V, Konitsiotis S. Effects of amantadine on tardive dyskinesia: a randomized, double-blind, placebo-controlled study. *Clin Neuropharmacol.* 2010;33:271-275.

105. Zheng W, Xiang YQ, Ng CH, et al. Extract of Gingko biloba for tardive dyskinesia: meta- analysis of randomized controlled trials. *Pharmacopsychiatry*. 2016;49:107-111.

106. Adelufosi AO, Abayomi O, Ojo TM. Pyridoxal 5 phosphate for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev*. 2015;4:CDO01501.

107. Richardson MA, Bevans ML, Read LL, et al. Efficacy of the branched-chain amino acids in the treatment of tardive dyskinesia in men. *Am J Psychiatry*. 2003;160;1117-1124.

108. Dickson RA, Seeman MV, Corenblum B. Hormonal side effects in women: typical versus geneation antipsychotic treatment. *J Clin Psychiatry*. 2000;61(suppl 3):10-15.

109. Windgassen K, Wesselman W, Schulze-Monking H. Galactorreha and hyperprolactineia in schizophrenic patients on neuroleptics: frequency and etiology. *Neuropsychobiology*. 1996;33:142-146.

110. Arana GW. An overview of side effects caused by typical antipsychotics. *J Clin Psychiatry*. 2000; 61(suppl 8):5-11.

111. Petty RG. Prolactin and antipsychotic medications: mechanisms of action. *Schizophr Res*. 1999; 35(suppl):S67-S73.

112. 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;22:1085-1096.

113. Bunker MT, Marken PA, Schneiderhan ME, et al. Attenuation of antipsychotic-induced hyperprolactinemia with clozapine. *J Child Adolesc Psychopharmacol*. 1997;7:65-69.

114. Inder WJ, Castle D. Antipsychotic-induced hyperprolactinemia. *Aust N Z J Psychiatry.* 2011;45:830-837.

115. Melkersson K. Differences in prolactin elevation and related symptoms of atypical antipsychotics in schizophrenic patients. *J Clin Psychiatry.* 2005;66:761-767.

116. Bruijnzeel D, Tandon R. Spotlight on brexpiprazole and its potential in the treatment of schizophrenia and as adjunctive therapy for the treatment of major depression. *Drug Des Devel Ther.* 2016:10;1641-1647.

117. Mattingly G, Anderson R. Cariprazine for schizophrenia and bipolar I disorder. *Curr Psychiatry.* 2016;15(1):e1-e6.

118. Sogawa R, Shimomura Y, Minami C. Aripiprazole-associated hypoprolactinemia in the clinical setting. *J Clin Psychiatry.* 2016;36(4)385-387.

119. Chen JX, Su YA, Bian QT, Wei LH, Zhang RZ. Adjunctive aripiprazole in the treatment of risperidone-induced hyperprolactinemia: a randomized, double-blind, placebo-controlled, dose response study. *Psychoneuroendocrinology.* 2015;58:130-140.

120. Qiao Y, Yang F, Guo Q, Wen H, Zhu S, et al. Add-on effects of a low-dose aripiprazole in resolving hyperprolactinemia induced by risperidone or paliperidone. *J Child Adolesc Psychopharmacol.* 2016;26(5):490-491.

121. Cordes J, Bechdolk A, Engelke C, et al. Prevalence of metabolic syndrome in female and male patients at risk of psychosis. *Schizophr Res.* 2017;179:57-63.

122. Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. *J Clin Psychiatry*. 1999;60:215-220.

123. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry*. 1996;37:68-73.

124. Brambilla F, Guastalla A, Guerrini A, et al. Glucose-insulin metabolism in chronic schizophrenia. *Dis Nerv Syst*. 1976;37:98-103.

125. Tsuang MT, Perkins K, Simpson JC. Physical diseases in schizophrenia and affective disorder. *J Clin Psychiatry*. 1983;44:42-46.

126. 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;63:345-348.

127. Ball MP, Coons VB, Buchanan RW. A program for treating olanzapine-related weight gain. *Psychiatr Serv.* 2001;52:967-969.

128. Green AI, Patel JK, Goisman RM, et al. Weight gain from novel antipsychotic drugs: need for action. *Gen Hosp Psychiatry.* 2000;22:224-235.

129. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999;156:1686-1696.

130. Leucht S, Cipriani A, Spineli L. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet.* 2013;382:951-962.

131. Bak M, Fransen A, Jansen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. *PloS One*. 2014;9(4):e94112.

132. Lu ML, Wang TN, Lin TY, et al. Differential effects of olanzapine and clozapine on plasma levels of adipocytokines and total ghrelin. Prog Neuropsychopharmacol Biol Psychiatry. 2015;58(3)47-50.

133. De Hert M, Yu W, Detraux J, et al. Body weight and metabolic adverse effects of asenapine, iloperidone, lurasidone and paliperidone in the treatment of

schizophrenia and bipolar disorder: a systematic review and exploratory meta-analysis. *CNS Drugs*. 2012;26(9):733-759.

134. Greenhalgh AM, Gonzalez-Blanco L, Garcia-Rizo C, et al. Meta-analysis of glucose tolerance, insulin, and insulin resistance in antipsychotic-naïve patients with non-affective psychosis. *Schizophr Res.* 2017;179:57-63.

135. 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;14:278-282.

136. Jin H, Meyer JM, Jeste DV. Phenomenology of and risk factors for new onset diabetes mellitus associated with second-generation antipsychiotcis: an analysis of 45 published cases. *Ann Clin Psychiatry*. 2002;14:59-64.

137. Hirsch L, Yang J, Bresee L, et al. Second-generation antipsychotics and metabolic side effects: a systematic review of population-based studies. *Drug Saf*. 2017. doi: 10.1007/s40264-017-0543-0. Accessed August 7, 2018.

138. Falissar B, Mauro M, Shaw K, et al. The METEOR study: frequency of metabolic disorders in patients with schizophrenia. Focus on first and second generation and level of risk of antipsychotic drugs . *Int Clin Psychopharmacol.* 2011;26(6):291-302.

139. Mitchell AJ, Vancamptfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders—a systematic review and meta-analysis. *Schizophr Bull.* 2013;39(2):304-318.

140. Misiak B, Stanczykiewicz B, Lacmanski L, Frydecka D. Lipid profile disturbances in antipsychotic naïve patietns with first-episode non-affective psychosis: a systematic

review and meta-analysis. *Schizophr Res.* 2017. http://dx.doi.org/10.1016/j.schres.2017.03.031. Accessed August 7, 2018.

141. Meyer JM. Novel antipsychotics and sever hyperlipidemia. *J Clin Psychopharmacol.* 2001;21:369-374.

142. Gonclaves P, Araujo JR, Martel F. Antipsychotic-induced metabolic alterations: focus on adipose tissue and molecular mechanisms. Eur Neuropsychopharmacol. 2015;25:1-16.

143. Olfson M, Marcus SC, Corey-LisleP, Tuomari AV, Hines P, L'Italien GJ. Hyperlipidemia following treatment with antipsychotic medications. *Am J Psychiatry.* 2006;163(10):1821-1825.

144. Clark M, Dubowski K, Colmore J. The effect of chlorpromazine on serum cholesterol in chronic schizophrenic patients. *Clin Pharmacol Ther* .1970;11(6):883-889.

145. Meyer JM, Koro CE. The effects of antipsychotic therapy on serum lipids: a comprehensive review. *Schizophrenia Res.* 2004;70(1):1-17.

146. Koro CE, Meyer JM. Atypical antipsychotic treatment and hyperlipidemia: a review. *Essn Psychopharm.* 2005;6(3):148-157.

147. 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.

148. American Diabetes Association. Standards of medical care in diabetes—2017. *Diabetes Care.* 2017;4(suppl 1):S1-S134.

149. Cooper SJ, Reynolds GP. The BAP guidelines on the management of weight gain, metabolic disturbances, and cardiovascular risk associated with psychosis and antipsychotic drug treatment. *J Psychopharmacol.* 2016;30(8):717-748.

150. Khasawneh FT, Shankar GS. Minimizing cardiovascular adverse effects of atypical antipsychotic drugs in patients with schizophrenia. *Cardiol Res Pract.* 2014. http://dx.doi.org/10.1155/2014/273060. Accessed August 7, 2018.

151. 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.

152. Reilly JG, Ayis SA, Ferrier IN, et al. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet.* 2000;355:1048-1052.

153. Food and Drug Administration. Psychopharmacological Drugs Advisory Committee. Briefing document for Zeldox capsules (ziprasidone HCl). https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm535446.htm. Accessed August 7, 2018.

154. Laughren T, Gordon M. FDA background on Zeldox (ziprasidone hydrochloride capsules) Pfizer, Inc. Psychopharmacological Drugs Advisory Committee. July 19, 2000.

155. Geodon [prescribing information]. New York, NY: Pfizer Inc.; November 2006.

156. Fanapt [package insert]. Washington, DC: Vanda Pharmaceuticals; May 2016.

157. Hasnain M, Vieweg WV. QTc interval prolongation and torsade de pointes associated with second-generation antipsychotics and antidepressants: a comprehensive review. *CNS Drugs*. 2014;28(10):887-920.

158. Merrill DB, Dec GW, Goff DC. Adverse cardiac effects associated with clozapine. *J Clin Psychopharmacol.* 2005;25:32-41.

159. Ronaldson KJ, Fitzgerald PB, McNeil JJ. Clozapine-induced myocarditis, a widely overlooked adverse reaction. *Acta Psychiatr Scand*. 2015;132(4):231-240.

160. Karjalainen J, Heikkila J. Incidence of three presentations of acute myocarditis in young men in military service. A 20-year experience. *Eur Heart J.* 1999;20:1120-1125.

161. Haas SJ, Hill R, Krum H, et al. Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993-2003. *Drug Saf.* 2007;30:47-57.

162. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA.* 2005;293:596-608.

163. Hsu WT, Esmaily-Fard A, Lai CC, et al. Antipsychotics and the risk of cerebrovascular accident: a systematic review and meta-analysis of observational studies. *J Am Med Dir Assoc*. 2017;18(8):692-699.

164. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med*. 2005;353:2335-2341.

165. Chen WY, Chen LY, Liu HC, et al. Antipsychotic medications and stroke in schizophrenia: a case-crossover study. *PLoS One*. 2017;12(6):e0179424.

166. Hsieh PH, Hsiao FY, Gau CS. Use of antipsychotics and risk of cerebrovascular events in schizophrenic patients: a nested case-control study. *J Clin Psychopharmacol.* 2013;33:299-305.

167. Food and Drug Administration. FDA public health advisory: deaths with antipsychotics in elderly patients with behavioral disturbances. http://psychrights.org/Drugs/FDAatypicalswarning4elderly.pdf. Accessed August 7, 2018.

168. Herrmann N, Lanctot KL. Do atypical antipsychotics cause stroke? *CNS Drugs.* 2005;19:91-103.

169. Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic induced side effects. *World J Biol Psychiatry.* 2013;14:2-44.

170. Bogers JPAM, Schulte PFJ, Van Dijk D. Clozapine underutilization in the treatment of schizophrenia: how can clozapine prescription rates be improved? *J Clin Psychopharmacology.* 2016;36(2):109-111.

171. Sanders K, McLean AJ, Adair DK, Hepburn B, Sims B. Clozapine underutilization: addressing the barriers 2016. https://www.nasmhpd.org/sites/default/files/Assessment%201_Clozapine%20Underutilization.pdf. Accessed August 7, 2018.

172. Stanton RJ, Paxos C, Geldenhuys WJ, Boss JL. Clozapine underutilization in treatment-resistant schizophrenia. *Ment Health Clin*. 2015;5(2):63-67.

173. Hill M, Freudenreich O. Clozapine: key discussion points for prescribers. *Clin Schizophr Relat Psychoses*. 2013;6(4):177-185.

174. Alvir JJ, Lieberman JA, Safferman AZ, et al. Clozapine-induced agranulocytosis-incidence and risk factors in the United States. *N Engl J Med.* 1993;329:162-167.

175. Lally J, Flanagan RJ. Severe neutropenia and agranulocytosis. In: *Life-Threatening Effects of Antipsychotic Drugs*. Cambridge, MA: Academic Press; 2016:105.

176. Raja M, Raja S. Clozapine safety, 40 years later. *Curr Drug Saf.* 2014;9:163-195.

177. Food and Drug Administration. FDA drug safety communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine;

approves new shared REMS program for all clozapine medicines. http://www.fda.gov/Drugs/DrugSafety/ucm461853.htm. Accessed August 7, 2018.

178. Haddy TB, Rana SR, Castro O. Benign ethnic neutropenia: what is a normal absolute neutrophil count? *J Lab Clin Med*. 1999;133:15-22.

179. Thobakgale CF, Ndung'u T. Neutrophil counts in persons of African origin. *Curr Opin Hematol.* 2014;21:50-57.

180. Manu P, Sarvaiya N, Rogozea LM, Kane JM, Correll CU. Benign ethnic neutropenia and clozapine use: a systematic review of the evidence and treatment recommendations. *J Clin Psychiatry.* 2016;77:e909-e916.

181. Wilson MP, Chen N, Vilke GM, Castillo EM, MacDonald KS, Minassian A. Olanzapine in ED patients: differential effects on oxygenation in patients with alcohol intoxication. *Am J Emerg Med.* 2012;30:1196-1202.

182. Bitter R, Bemler TL, Opler L. Safety evaluation of the concomitant use of clozapine and benzodiazepines: a retrospective, cross-sectional chart review. *J Psych Pract.* 2008;14:265-270.

183. Wilson MP, MacDonald K, Vilke GM, Feifel D. Potential complications of combining intramuscular olanzapine with benzodiazepines in emergency department patients. *J Emerg Med.* 2012;43:889-896.

184. Williams AM, Park SH. Seizure associated with clozapine: incidence, etiology, and management. *CNS Drugs.* 2015;62:345-354.

185. Alper K, Schwartz KA, Kolts RL, Khan A. Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. *Biol Psychiatry.* 2007;62:345-354.

186. Marks RC, Luchins DJ. Antipsychotic medications and seizures. *Psychol Med.* 1991;9(1):37-52.

187. Pisani F, Oteri G, Costa C, DiRaimondo G, DiPerri R. Effects of psychotropic drugs on the seizure threshold. *Drug Saf.* 2002;25(2):91-110.

188. Citrome L, McEvoy JP, Saklad SR. A guide to the management of clozapine-related tolerability and safety concerns. *Clin Schizophr Relat Psychoses.* 2016;10:163-177.

189. Sprague DA, Loewen PS, Raymond CB. Selection of atypical antipsychotics for the management of schizophrenia. *Ann Pharmacother.* 2004;38:313-319.

190. Correll CU, Canas F, Larmo I, et al. Individualizing antipsychotic treatment selection in schizophrenia: characteristics of empirically derived patient subgroups. *Eur Psychiatry.* 2011;26:3-16.

191. Heres SI, Schmitz FS, Leucht S. The attitude of patients towards antipsychotic depot treatment. *Int Clin Psychopharmacol*. 2007;22(5):275-282.

192. Patel MX, De Zoysa N, Bernadt M, David A. Depot and oral antipsychotics: patient preferences and attitudes are not the same thing. *J Psychopharmacol.* 2009;23:789-796.

193. San L, Casillas M, Ciudad A, Gilaberte I. Olanzapine orally disintegrating tablet: a review of efficacy and compliance. *CNS Neurosci Ther.* 2008;14:203-214.

194. Love RC, Conley RR, Kelly DL, et al. A dose-outcome analysis of risperidone. *J Clin Psychiatry.* 1999;60:771-775.

195. Citrome L, Jaffe A, Levine J, Lindenmayer JP. Dosing of quetiapine in schizophrenia: how clinical practice differs from registration studies. *J Clin Psychiatry.* 2005;66:1512-1516.

196. Citrome L, Jaffe A, Levine J. How dosing of ziprasidone in a state hospital system differs from product labeling. *J Clin Psychiatry.* 2009;70:975-982.

197. Marcus SC, Zummo J, Pettit AR, et al. Antipsychotic adherence and rehospitalization in schizophrenia patients receiving oral versus long-acting injectable antipsychotics following hospital discharge. *J Manag Care Spec Pharm*. 2015;21:754-768.

198. Beresford R, Ward A. Haloperidol decanoate: a preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in psychosis. *Drugs.* 1987:33;31-49.

199. Correll CU, Citrome L, Haddad PM, et al. The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. *J Clin Psychiatry.* 2016;77(suppl 3):1-24.

200. Samara MT, Leucht C, Leeflang MM, et al. Early improvement as a predictor of later response to antipsychotics in schizophrenia: a diagnostic test review. *Am J Psychiatry*. 2015;172:617-629.

201. Marder SR, Essock SM, Miller AL, et al. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry.* 2004;161:1334-1349.

202. Spina E, Avenoso A, Facciola G, et al. Relationship between plasma concentrations of clozapine and norclozapine and therapeutic response in patients with schizophrenia resistant to conventional neuroleptics. *Psychopharmacol (Berl)*. 2000;148:83-89.

203. Kronig MH, Munne RA, Szymanski S, et al. Plasma clozapine levels and clinical response for treatment refractory schizophrenic patients. *Am J Psychiatry.* 1995;152:179-182.

204. Gaertner I. Gaertner HJ, Vonthein R, et al. Therapeutic drug monitoring of clozapine in relapse prevention: a five-year prospective study. *J Clin Psychophamrcol.* 2001;21:305-310.

205. Xiang YQ, Zhang, ZJ, Weng YZ, et al. Serum concentrations of clozapine and norclozapine in the prediction of relapse of patients with schizophrenia. *Schizophr Res*. 2006;83:201-210.

206. Gejman PV, Sanders AR, Duan J. The role of genetics in the etiology of schizophrenia. *Psychiatr Clin North Am.* 2016;33:35-66.

207. Miller BJ, Culpepper N, Rapaport MH, Buckley P. Prenatal inflammation and neurodevelopment in schizophrenia: a review of human studies. *Prog Neuropsychopharmacol Biol Psychiatry.* 2013;42:92-100.

208. Lee KW, Woon PS, Teo YY, Sim K. Genome wide studies (GWAS) and copy number variation (CNV) studies of the major psychoses: what have we learnt? *Neurosci Biobehav Rev.* 2012:36:556-571.

209. Xu Q, Wu X, Xiong Y, Xing Q, He L, Qin S. Pharmacogenomics can improve antipsychotic treatment in schizophrenia. *Front Med.* 2013;7(2):180-190.

210. Meltzer HY. Treatment resistant schizophrenia-the role of clozapine. *Curr Med Res Opin*. 1999;14(1)1-20.

211. Kirchheiner J, Nickchen K, Bauer M, et al. Pharmacogenetics of antidepressants and antipsychotcis: the contribution of allelic variations to the phenotype of drug response. *Mol Psychiatry.* 2004;9(5):442-473.

212. Eum S, Lee Am, Bishop JR. Pharmacogenetic tests for antipsychotic medications: clinical implications and considerations. *Dialogues Clin Neurosci*. 2016;18:323-337.

213. Drozda K, Muller DJ, Bishop JR. Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options. *Pharmacotherapy.* 2014;34(2):166-184.

214. Carbon M, Correll CU. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. *CNS Spectr.* 2004;19(suppl S1):38-52.

215. Kitchen H, Rofail D, Heron L, Sacco P. Cognitive impairment associated with schizophrenia: a review of the humanistic burden. *Adv Ther.* 2012;29:148-162.

216. Foussias G, Agid O, Fervaha G, Remington G. Negative symptoms of schizophrenia: clinical features, relevance to real world functioning and specificity versus other CNS disorders. *Eur Neuropsychopharmacol.* 2014;24:693-709.

217. Mueser KT, Deavers F, Penn DL, Cassisi JE. Psychosocial treatments for schizophrenia. *Ann Rev Clin Psychol.* 2013;9:465-497.

218. Rabinowirz J, Lichtenberg P, Kaplan Z, et al. Rehospitalization rates of chronically ill schizophrenic patients discharged on a regimen of risperidone, olanzapine, or conventional antipsychotics. *Am J Psychiatry.* 2001;158: 266-269.

219. 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.

220. Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry.* 2005;62:247-253.

221. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic- resistant schizophrenia: impact on risk-benefit assessment. *Am J Psychiatry.* 1995;152:183-190.

222. Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products [database online]. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 7, 2018.

223. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin Pharmacol Ther.* 2011;89:464-471.

224. Bank PCD. Caudle KE, Swen JJ, et al. Comparison of the guidelines of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenomics Working Group. *Clin Pharmacol Ther*.2018;103:595-618.

225. Abilify [prescribing information]. Princeton, NJ: Otsuka Pharmaceutical Co; 2014.

226. Abilify Maintena [prescribing information]. Princeton, NJ: Otsuka Pharmaceutical Co; 2013.

227. Clozaril [prescribing information]. Rosemount, PA; HLS Therapeutics; 2017.

228. Fanapt [prescribing information]. Rockville, MD; Vanda Pharmaceuticals; 2009.

229. Risperidal [prescribing information]. Titusville, NJ; Janssen Pharmaceuticals; 2003.

230. Dutch Pharmacogenomics Working Group. PharmGKB search engine. https://www.pharmgkb.org/. Accessed August 7, 2018.

Table 1. DSM-5 Criteria for Schizophrenia and Schizoaffective Disorder[4]

Schizophrenia Criteria	Schizoaffective Disorder Criteria
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 (eg, frequent derailment or incoherence) 4. Grossly disorganized or catatonic behavior 5. Negative symptoms (ie, diminished emotional expression or avolition)	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. Level of function in a major area (personal or occupational functioning) must be less than prior to the onset of symptoms.	B. Delusions or hallucinations for 2 or more weeks in the absence of a major mood episode (depressive or manic) during the lifetime duration of the illness.
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 1 month of symptoms from A above, and may include prodromal, residual or negative symptoms.	C. Symptoms that meet criteria for a major mood episode are present for the majority of
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.	

Abbreviation: DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.

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

Drug (Trade Name)	Usual Therapeutic Doses	Year Approved
Chlorpromazine (Thorazine)	300-1,000 mg (maximum, 1,000 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 or 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)	1.5-6 mg/day	2015
Clozapine (Clozaril)	100-800 mg/day (maximum 900 mg)	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]

Treatment	Weight Change (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 Supple-mentation	Maintenance Dose	Dosing Interval	Notes
Fluphenazine decanoate	12.5-25 mg	None	12.5-100 mg	2-3 weeks	
Haloperidol	100 mg	None	100-300	4 weeks	
Risperidone microspheres (Risperdal	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 the Zyprexa Relprevv Patient Care
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	273-819 mg	None	273-819 mg	Every 3 months	To be initiated only in patients stabilized on
Aripiprazole monohydrate (Abilify	400 mg	2 weeks	300-400 mg	Monthly	
Aripiprazole lauroxil (Aristada)	441-882 mg	3 weeks	441-882 mg	4-6 weeks	
	1,064			8 weeks	

Table 6. Monitoring Guidelines for Patients Treated With Second-Generation Antipsychotics

Assessment	Monitoring Frequency
Fasting blood glucose	All drugs: at baseline, then monthly for the first 3 months and every 6 months thereafter; more frequent assessments are indicated for individuals noted to be gaining weight
Weight assessment	All drugs: at baseline and monthly thereafter (self-monitoring of weight should be encouraged)
Electrocardiogram	Clozapine and ziprasidone: at 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: at baseline and every 2 years thereafter if no abnormalities are noted; every 6 months for individuals noted to have hyperlipidemia or receiving lipid-lowering therapy

Table 7. Pharmacogenomics Considerations With Use of 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 CYP3A4 inhibitor, decrease dose of aripiprazole by half (50%) In individuals taking a strong CYP2D6 or CYP3A4 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	In CYP2D6 PMs, adjust 300-mg dose to 200 mg In individuals taking 400 mg receiving a strong CYP2D6 and CYP3A4 inhibitor, decrease dose to 300 mg In individuals taking 300 mg, decrease dose to 200 mg in strong CYP2D6 and CYP3A4 inhibitors and decrease the dose to 160 mg in those taking a combination of CYP2D6 and CYP3A4 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 CYP3A4 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 interval and may lead to cardiac arrhythmias (torsades de pointes)

Abbreviations: CYP, cytochrome P-450; PM, poor metabolizer; NM, normal metabolizer (previously called extensive metabolizer).
[a]Clinical Pharmacogenetics Implementation Consortium make no recommendations for dose

changes in patients receiving antipsychotic agents.

[b]Dutch Pharmacogenomics Working Group recommends using no more than 10 mg of aripiprazole in CYP2D6 PMs.[230]