MANU MATHEWS, MD
Department of Psychiatry and Psychology, Cleveland Clinic

DAVID J. MUZINA, MD*
Vice Chair for Research and Education, Director of the Bipolar Disorders Research Unit; and Director of Adult Inpatient Services, Department of Psychiatry and Psychology, Cleveland Clinic

Atypical antipsychotics: New drugs, new challenges

ABSTRACT

Compared with the first-generation, or "typical" antipsychotic drugs, second-generation or atypical antipsychotics cause fewer extrapyramidal (motor) problems, but they pose new challenges, as they often contribute to metabolic disturbances such as weight gain, hyperlipidemia, insulin resistance, and type 2 diabetes mellitus. Patients taking atypical antipsychotics should be monitored for glycemic and cardiovascular risk factors and should receive treatment for such problems as they arise.

KEY POINTS

The atypical antipsychotics available in the United States are clozapine (Clozaril), olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel), ziprasidone (Geodon), aripiprazole (Abilify), and paliperidone (Invega).

Although extrapyramidal effects are much less common with atypical antipsychotics, they can sometimes still occur, especially if very high doses are used.

Patients with schizophrenia are predisposed to diabetes. Use of atypical antipsychotics heightens this risk.

Of the atypical antipsychotics, clozapine and olanzapine cause the most weight gain and pose the highest risk of metabolic disturbances.

Of the atypical antipsychotics, ziprasidone and aripiprazole cause the least weight gain.

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SECOND-GENERATION ("ATYPICAL") antipsychotic drugs are much less likely than typical antipsychotics to cause movement disorders. But the newer drugs come with a new variety of side effects—ie, metabolic complications. This presents a treatment challenge, since schizophrenic patients have been found to be predisposed to diabetes.

In this article we will offer brief profiles of the atypical antipsychotics commonly used in the United States, with particular emphasis on the metabolic disturbances that have been attributed to their use.

THE FIRST VS THE SECOND GENERATION

Antipsychotics are among the most widely used drugs in psychiatric practice. They were originally intended primarily for the treatment of schizophrenia, but over the years their use has spread to other psychotic spectrum disorders, bipolar disorder, anxiety and related disorders, posttraumatic stress disorder, delirium, and personality disorders.[1]

The typical antipsychotics

First-generation antipsychotics, although effective, have been gradually falling out of favor because of their side effects, especially their extrapyramidal effects, including parkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia.

The typical antipsychotics are broadly classified into two categories:

- **Phenothiazines:** chlorpromazine (Thorazine), thioridazine (Mellaril), fluphenazine (Prolixin), pericyazine (Neuleptil), perphenazine (Trilafon), trifluoperazine (Stelazine), pipotiazine (Piportil)

TABLE 1

Side effects associated with receptor blockade

RECEPTOR BLOCKED	SIDE EFFECT
Alpha 1 adrenergic	Orthostatic hypotension, sexual side effects, nasal congestion
Muscarinic M_1	Anticholinergic: constipation, blurring of vision, urinary retention
Histamine H_1	Sedation and weight gain
Serotonin 5-HT_2	Weight gain, increased appetite
Dopamine D_2	Extrapyramidal effects (parkinsonism, dystonia, akathisia, tardive dykinesia), elevated prolactin

- **Butyrophenones:** haloperidol (Haldol), droperidol (Inapsine), bromperidol, and others.

First-generation antipsychotics are as effective as second-generation drugs in treating the "positive" symptoms of schizophrenia, such as hallucinations, delusions, and paranoia, although they vary in their propensity to cause side effects.[2]

The atypical antipsychotics

The high rates of extrapyramidal side effects with first-generation antipsychotics, their suboptimal effectiveness against schizophrenia's cognitive symptoms (eg, disorganized thoughts, poor memory, and difficulty concentrating, following instructions, and completing tasks) and its "negative" symptoms (lack of motivation and drive, lack of pleasure from activities, restricted affect), and experience with the first atypical antipsychotic, clozapine (Clozaril), all contributed to the development of newer antipsychotic drugs, broadly classified as atypical.

'Atypical' means fewer motor problems, little prolactin effect, reduction of all symptoms

Some atypicals, such as clozapine, risperidone (Risperdal), olanzapine (Zyprexa), and amisulpiride, may be superior to first-generation antipsychotics in alleviating negative symptoms[3–5] and cognitive symptoms.[6–8]

Second-generation antipsychotics are a heterogenous group. Because they act on many different receptors (eg, dopamine, serotonin [5-hydroxy-tryptamine], alpha adrenergic, histamine H_1, and muscarinic M_1), their exact mechanism of action is poorly understood. TABLE 1 lists the major side effects associated with blockade of five types of receptor.

The most commonly used atypicals in the United States are olanzapine, risperidone, quetiapine (Seroquel), ziprasidone (Geodon), aripiprazole (Abilify), and clozapine. Amisulpiride and sertindole are not sold in the United States.

What is atypical about atypical antipsychotic drugs?

The classic definition of "atypical" is a chemical that has clinical antipsychotic effect while producing minimal catalepsy in animal models.[9] The atypicals also:

- Have minimal extrapyramidal side effects or movement disorders at antipsychotic doses
- Do not or minimally elevate prolactin
- Significantly reduce positive and negative symptoms of schizophrenia.[10,11]

All antipsychotics block the subtype of dopamine receptor designated D_2, which mediates movement. However, the atypical antipsychotics have less affinity for this receptor subtype and dissociate from it faster, and these features may be the key to their "atypicality."[12,13] Animal studies have also suggested that if the number of Fos-positive cells in the core of the nucleus accumbens is greater than in the striatum, the drug may be considered atypical.[14] Other proposed molecular markers of atypicality include antipsychotic-induced depolarization-inactivation of A10 neurons, internalization of 5-HT_{2A} receptors, and neuroplasticity in the striatum.[15,16]

CLOZAPINE: NOW A SECOND-LINE DRUG

Clozapine, a dibenzodiazepine, was the first atypical antipsychotic to be marketed in the United States.[11] Clozapine is unique for its very low incidence of extrapyramidal effects,

TABLE 2

Recommended dosages for atypical antipsychotic drugs

	HALF-LIFE (HOURS, MEAN)	STARTING DOSE (TOTAL MG/DAY)	AVERAGE DOSE RANGE MG/DAY (FIRST EPISODE)	AVERAGE DOSE RANGE MG/DAY (RECURRENCE)	AVERAGE MAINTENANCE DOSE (MG/DAY)	ROUTES OF ADMINISTRATION
Clozapine (Clozaril)	10–105	25–50	150–300	400–600	400	Oral
Risperidone (Risperdal)	3–24	1–2	2–4	4–6	4–6	Oral, depot
Olanzapine (Zyprexa)	20–70	5–10	10–20	15–30	10–20	Oral, intramuscular
Quetiapine (Seroquel)	4–10	50–100	300–400	500–800	400–500	Oral
Ziprasidone (Geodon)	4–10	40–80	80–120	120–200	120–160	Oral, intramuscular
Aripiprazole (Abilify)	75–96[a]	10–15	10–30	15–30	15–30	Oral

[a]This is the half-life if we take into account its active metabolite

but it causes agranulocytosis in about 1% of patients, which has curtailed its widespread use.[9] Clozapine is also unique in its mechanism of action, having one of the most widespread neuroreceptor affinities among all antipsychotics with particular selectivity to the receptors in the mesolimbic system (A10 region).[17]

Indications

Clozapine is indicated for schizophrenia but in view of its side effects is generally used as a second-line drug, ie, when two other antipsychotics have failed. Clozapine is also the only drug other than lithium (Eskalith and other lithium preparations) that has been shown to decrease suicides.

Paralytic ileus has also been cited as a contraindication for clozapine use.

Pharmacokinetics: Interactions

Clozapine is absorbed almost completely after oral ingestion, is 90% protein-bound, and is metabolized by the liver. Its notable interaction is with cigarette smoking, which induces its metabolism by the CYP1A2 enzyme of the cytochrome P450 complex. Many patients get their symptoms under control in the hospital, where they are not allowed to smoke, but have a relapse when they get out and start smoking again.[18,19]

Another interaction is the elevation of clozapine levels when combined with citalopram (Celexa).

Clozapine is a second-line drug, used when two other antipsychotics have failed

Side effects

Clozapine-induced agranulocytosis, as described earlier, has been found to occur in 1% of users. Its affinity for alpha adrenergic receptors is responsible for sexual side effects and orthostasis, histamine H_1 receptor blockade leads to sedation and weight gain, and muscarinic M_1 receptor blockade leads to anticholinergic side effects. There have been postmarketing reports of fatal myocarditis. Its use is also related to seizures in 2% of patients taking < 300 mg/day, in 3% to 4% taking 600 mg/day, and in 5% taking 600 to 900 mg/day.

Monitor the white blood cell count

Due to the risk of agranulocytosis, a baseline white blood cell count and absolute neutrophil count and registration with the National Clozapine Monitoring Registry are mandatory. The patient should also have weekly tests for

the first 6 months and, if the results are satisfactory, can be monitored every other week thereafter for an additional 6 months, and after that once a month. The target blood counts, both before treatment and during the monitoring phase, are a white blood cell count greater than 3,500/mm^3 and an absolute neutrophil count greater than 2,000/mm.[3]

Dosages of clozapine and the other atypical antipsychotics are shown in TABLE 2.

RISPERIDONE: WIDELY USED

Risperidone, a benzisoxazole compound, was the second atypical antipsychotic to be marketed in the United States and is widely used. It has a high affinity for D_2 and 5-HT_{2A} receptors.

Indications

Risperidone is indicated for schizophrenia and to treat the manic symptoms of acute manic or mixed episodes associated with bipolar I disorder. Risperidone is the only antipsychotic indicated for schizophrenia that is available as a long-acting solution for depot injection.

Pharmacokinetics

Dose adjustment of risperidone may be needed in those with renal impairment

The drug is rapidly absorbed orally and undergoes significant first-pass metabolism. As it is eliminated in part renally, dose adjustment may be needed in patients with renal impairment.

Side effects

The rates of extrapyramidal side effects are comparable with those of some of the other second-generation antipsychotics, but patients taking doses greater than 6 mg/day may experience significant extrapyramidal side effects.[20,21] Risperidone has a low propensity to cause anticholinergic side effects. However, in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, it was the only one of the antipsychotic drugs studied that was associated with a substantial increase in levels of prolactin.[22]

OLANZAPINE: ACTION SIMILAR TO CLOZAPINE

A dibenzodiazepine in structure, olanzapine has a mechanism of action similar to that of clozapine.[23] It is antagonistic at both the D_2 and 5-HT_{2A} receptors,[2] but is more potent at the former. A dosage of 10 to 20 mg/day of olanzapine results in 71% to 80% of D_2 receptor "occupancy," whereas 30 mg/day results in a greater than 80% occupancy,[24] which may explain the higher rate of extrapyramidal symptoms at these doses. Olanzapine, like clozapine, binds to a broad range of receptors.

Indications

Olanzapine is approved for the treatment of schizophrenia and acute bipolar mania.

Pharmacokinetics

Olanzapine is well absorbed orally and has a half-life of 20 to 70 hours, which allows for once-a-day dosing. Olanzapine is also available in a short-acting intramuscular injectable form. As with clozapine, smoking induces its metabolism and clearance.

Side effects

Some of the side effects of olanzapine are weight gain, sedation, orthostatic hypotension, and constipation. It is second only to clozapine in causing weight gain.[25] A number of case reports have linked olanzapine and clozapine treatment with an increased risk of type 2 diabetes mellitus.[1,26] Patients on olanzapine report significantly lower rates of insomnia, possibly as a result of its sedating properties.[22]

QUETIAPINE

Quetiapine, a dibenzothiazepine, has a greater affinity for 5-HT_2 receptors than for D_2 receptors. It also has an affinity for H_1 and alpha 1 and alpha 2 adrenergic receptors.[9,27] The low D_2 affinity that it shares with clozapine corresponds to a low incidence of extrapyramidal side effects.

Indications

Quetiapine is indicated for mania associated with bipolar disorder and for schizophrenia.[28,29]

Pharmacokinetics

Quetiapine is one of the most rapidly absorbed oral antipsychotics. Its absorption is enhanced when given with food. It is 83% protein-bound and has an elimination half-life of 7 hours.[18]

Side effects

Prominent side effects of quetiapine include sedation, tachycardia, and agitation. Due to its low affinity for D_2 receptors, extrapyramidal effects are rare.

ZIPRASIDONE

Ziprasidone is a benzisothiazolyl piperazine derivative. The significant receptor affinities to be noted include 5-HT_{1A}, which may indicate efficacy in anxiety. It has shown benefits in affective symptoms for patients with schizophrenia,[30] possibly due to its serotonergic and norepinephrine reuptake blockade.

Indications

Ziprasidone is indicated for the treatment of schizophrenia.

Pharmakokinetics

Ziprasidone has an intermediate rate of absorption, and, as with quetiapine, absorption is enhanced by food.[19] Ziprasidone is also available in a short-acting intramuscular injectable form.

Side effects

Due to its lack of affinity for H_1 and M_1 receptors, weight gain, sedation, and anticholinergic side effects are minimal, as shown in the CATIE study.[22] There was no significant prolongation of the QTc interval in this trial, although previous studies had suggested that ziprasidone prolonged the QTc interval more than any other antipsychotic except sertindole and thioridazine.[31]

Due to the risk of QTc prolongation, ziprasidone use has been contraindicated in patients with QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure, and in those taking other QTc-prolonging drugs. Ziprasidone should be avoided or discontinued if the QTc is greater than 500 msec.

ARIPIPRAZOLE

Aripiprazole is the newest antipsychotic to be licensed. It is a partial dopamine agonist with a high affinity for D_2 and D_3 receptors.[32] It induces "functionally selective" activation of D_2 receptors coupled to diverse G proteins.[32]

Indications

Aripiprazole is indicated for the treatment of acute mania and for maintenance therapy of bipolar I disorder. In schizophrenia, it is indicated for the treatment of acute exacerbations of schizophrenia and for maintenance therapy.

Pharmacokinetics

Aripiprazole is well absorbed orally and undergoes extensive hepatic metabolism.[1]

Side effects

Aripiprazole has been associated with minimal weight gain and metabolic changes. While earlier data may have indicated a very low incidence of extrapyramidal side effects, the rates are similar to those of olanzapine and risperidone if akathisia is taken into account.

PALIPERIDONE

Paliperidone (Invega) is the newest atypical antipsychotic to be approved. It is a 9-hydroxy metabolite of risperidone. Its receptor profile is expected to be similar to that of risperidone. There are no studies comparing it with other atypical antipsychotics.

Indications

Paliperidone is currently licensed for treatment of schizophrenia, and trials are under way to study its efficacy in the treatment of bipolar disorder.

Pharmacokinetics

As with risperidone, dose reduction is recommended in moderate or severe renal impairment.[33]

Side effects

Trials so far show an increased risk of extrapyramidal side effects compared with placebo. The data at this time are insufficient for comment on metabolic risk.

ANTIPSYCHOTIC DRUGS AND MOVEMENT DISORDERS

All antipsychotics have been implicated to some extent in the development of movement disorders. These are primarily of extrapyramidal origin and include akathisia, parkinson-

Ziprasidone and aripiprazole do not appear to contribute to diabetes risk

TABLE 3

Metabolic effects of atypical antipsychotic drugs

DRUG	WEIGHT GAIN	RISK OF DIABETES	WORSENING LIPID PROFILE
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole[a]	+/–	–	–
Ziprasidone[a]	+/–	–	–

+ indicates an increase; – indicates no effect; D indicates discrepant results
[a]Newer drugs with limited long-term data

ism, and dystonia. Multiple studies have confirmed that the atypical antipsychotics carry a much lower risk than typical agents.[34]

Motor side effects to watch for: akathisia, acute dystonia, parkinsonism

Symptoms of dopamine excess and dopamine deficiency

The nigrostriatal pathway of the extrapyramidal system is critical in the regulation of motor movement.[35] Excess dopamine in this pathway is associated with hyperkinetic movement disorders such as chorea, tics, and dyskinesia. Deficiency of dopamine in this pathway is associated with extrapyramidal symptoms or with side effects, the three most common being akathisia, acute dystonia, and parkinsonism.[36]

Akathisia is a form of internal restlessness and agitation characterized by the inability to sit still, by pacing, rocking, and shifting of weight while standing, and by tapping of the feet. The onset is usually days to weeks after the start of treatment and can be incorrectly diagnosed as anxiety or worsening of anxiety.

Dystonia, an acute spasm of muscle groups, presents with fixed upper gaze, torticollis, and facial muscle spasm resulting in grimacing, clenched jaw, and difficulty with speech. This usually occurs soon after antipsychotic treatment is started.

Parkinsonism is characterized by rigidity, bradykinesia, tremors, and shuffling gait.

Dyskinesia. Long-term blockade and upregulation of D_2 receptors in the nigrostriatal pathway can cause tardive dyskinesia, a chronic and essentially irreversible movement disorder. In long-term studies, first-generation antipsychotics have been associated with an incidence of tardive dyskinesia of approximately 5% per year in adults[12,13,37] and 25% to 30% in elderly patients.[14–16,23] The symptoms include involuntary movements of the tongue and mouth, irregular involuntary movements of the extremities, and to-and-fro movement of the spine.

Neuroleptic malignant syndrome is an acute and dangerous extrapyramidal side effect of antipsychotic drugs characterized by a triad of rigidity, hyperthermia, and autonomic instability, along with elevated creatine phosphokinase levels. It is potentially life-threatening, with a death rate approaching 20% in untreated cases.

CARDIAC EFFECTS

Prolongation of the QTc interval (> 456 msec) by antipsychotic drugs has always generated significant concern. As described earlier, the risk is greatest with ziprasidone, sertindole, and thioridazine.[31] The risk of this prolongation is arrhythmia, including torsades de pointes, although to date this has not been reported, either with therapeutic doses or with overdoses of atypical antipsychotics.

METABOLIC SIDE EFFECTS OF ANTIPSYCHOTICS

Diabetes

Data from most studies suggest that the prevalence of both diabetes and obesity in people with schizophrenia and affective disorders is 1.5 to 2.0 times higher than in the general population.[1] The incidence of impaired glucose tolerance in first-episode schizophrenic patients who have not yet taken antipsychotic drugs ("drug-naive" schizophrenic patients) is 15%.[38] The prevalence of diabetes in patients with schizophrenia in the days before atypical antipsychotic drugs were widely used

ranged from 5.1% to 15%,[39] suggesting that these patients are predisposed to diabetes, independently of treatment with atypical antipsychotic drugs. Patients on atypical antipsychotics have been found to be 9% more likely to develop diabetes than those taking conventional antipsychotics.[40]

Clozapine and olanzapine have been associated with a higher risk of diabetes than other agents in many studies (**TABLE 3**).[1,26] Other studies have shown these cases to be a combination of new-onset diabetes, exacerbation of preexisting diabetes, and presentations of complications such as metabolic acidosis or ketosis.[41,42] No increase in risk was found with risperidone.

In addition to identifying effects of antipsychotic drugs on weight and adiposity, studies suggest that atypical antipsychotics may have an independent effect on insulin sensitivity. Studies by Henderson et al[43,44] comparing insulin sensitivity in patients taking clozapine, olanzapine, or risperidone showed a significant difference in insulin sensitivity between the clozapine and risperidone groups and between olanzapine and risperidone, with the clozapine and olanzapine groups showing lower insulin sensitivity numbers than the risperidone groups (higher numbers are better).[43,44] A comparison of olanzapine and aripiprazole in schizophrenic patients showed an increase in serum glucose in the olanzapine group.[45]

Ziprasidone, in spite of the limited clinical and research data, does not appear to predispose significantly to this risk. In some cases, hyperglycemia resolved promptly after the patient stopped taking the atypical antipsychotic.

Weight gain

A study by Resnick et al[46] showed that the odds of developing diabetes mellitus increases as the body mass index increases, and that insulin sensitivity decreases as the amount of abdominal tissue increases. Resnick et al concluded that abdominal fat is the best predictor of impaired glucose regulation.[46] Separate meta-analyses have shown that, of the atypical antipsychotic drugs, clozapine and olanzapine have the highest propensity to cause weight gain, and that ziprasidone, fluphenazine, and aripiprazole have the lowest risk.[26,47,48]

Recent studies show that patients on olanzapine gain more weight than patients on any other antipsychotic tested, with an average weight gain of 2 lb (0.9 kg) per month. A larger proportion of patients in the olanzapine group than in the other groups gained 7% or more of their baseline body weight (30% vs 7% to 16%, $P < .001$).[14] The onset of rapid weight gain occurs within a few months of treatment and fails to plateau 1 year after treatment.[22,26,48,49]

Hunger and satiety may be altered in people taking atypical antipsychotics because of the known binding affinities of these drugs to serotonin, norepinephrine, dopamine, and particularly histamine H_1 receptors.

Dyslipidemia

The development of dyslipidemia appears to correlate with weight gain. In a study comparing clozapine, olanzapine, haloperidol, and risperidone, mean cholesterol levels increased in patients taking clozapine and olanzapine.[50] No such association was seen in patients on ziprasidone in a separate study[51] comparing it with olanzapine, although significant increases occurred in fasting insulin levels, triglycerides, and body weight in the olanzapine arm of the study. In another population-based case-control study,[52] the chance of developing hyperlipidemia was five times higher in schizophrenic patients taking olanzapine, three times higher in those taking typical antipsychotics, and no higher in those taking risperidone.[52]

Patients on most atypical vs typical antipsychotics are 9% more likely to develop diabetes

The study comparing aripiprazole with olanzapine[45] showed no increase in serum triglyceride or glucose levels in the aripiprazole group, although a significant unfavorable change in both levels was noted in the olanzapine group.

In the CATIE study,[22] olanzapine had effects consistent with the potential development of the metabolic syndrome and was associated with greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides after randomization than were the other study drugs, even after adjustment for duration of treatment. Ziprasidone was the only study drug associated with improvement in each of these metabolic variables.

TABLE 4

Consensus monitoring recommendations for patients taking atypical antipsychotics

MONITORING	FREQUENCY[a]
Personal/family history	Baseline, then annually
Weight (body mass index)	Baseline; at 4, 8, and 12 weeks; then quarterly
Waist circumference	Baseline, then annually
Blood pressure	Baseline; at 12 weeks; then annually
Fasting plasma glucose	Baseline; at 12 weeks; then annually
Fasting lipid profile	Baseline; at 12 weeks; then every 5 years[b]

[a]More frequent assessments may be warranted based on clinical status.
[b]Recent consensus among experts tends toward annual checks.

ADAPTED FROM AMERICAN DIABETES ASSOCIATION, AMERICAN PSYCHIATRIC ASSOCIATION, AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS, NORTH AMERICAN ASSOCIATION FOR THE STUDY OF OBESITY. DIABETES CARE 2004; 27:596–601. REPRINTED WITH PERMISSION FROM THE AMERICAN DIABETES ASSOCIATION.

Based on the above discussion, a list of atypical antipsychotic drugs according to their propensity to cause dyslipidemia, from most likely to least likely, would be as follows: clozapine, olanzapine, quetiapine, ziprasidone, and aripiprazole.[53]

Patients taking atypical antipsychotics require screening for body mass index and waist circumference

MONITORING FOR GLYCEMIC AND CARDIOVASCULAR RISK FACTORS

The association of obesity, diabetes, and dyslipidemia with cardiovascular disease is well known. The relationship of second-generation antipsychotics to the development of these major cardiovascular risk factors is of great interest, and led to a joint conference in November 2003 of the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity. The result was a consensus statement regarding antipsychotic drugs and diabetes,[1] which concluded that:

- Given the serious health risks, patients taking second-generation antipsychotics should receive appropriate baseline screening and ongoing monitoring.
- The initial physical screening should include the patient's height and weight (body mass index) and waist circumference.
- It is particularly important to monitor any change in weight after a change in medication.
- The patient's psychiatric illness should not discourage clinicians from addressing the metabolic complications for which these patients are at increased risk.[1]

Monitoring should be performed as shown in TABLE 4. It should be determined whether the patient is:

- Overweight (body mass index 25.0–29.9 kg/m^2) or obese (body mass index ≥ 30)
- Prediabetic (fasting plasma glucose 100–125 mg/dL) or diabetic (fasting plasma glucose > 126 mg/dL)
- Hypertensive (blood pressure > 140/90 mm Hg)
- Dyslipidemic.

If any of these conditions is identified, the patient should receive appropriate treatment and referral.[1] A significant weight gain (> 5%), dyslipidemia, and worsening glycemia should trigger reduction of the dosing of the current antipsychotic drug and "cross-tapering" with a safer antipsychotic (ie, starting a safer drug at a low dose and gradually increasing the dose while decreasing the dose of the first drug).

The consensus document also includes recommendations for nutritional and physical activity counseling for all patients who are overweight or obese, particularly if they are starting treatment with a second-generation antipsychotic that is associated with signifi-

cant weight gain. Referral to a weight management program may be appropriate.[1]

Patients, family members, and all health care professionals should be aware of the signs and symptoms of potentially life-threatening complications, such as diabetic ketoacidosis and nonketotic diabetic acidosis. For patients who are at high risk of metabolic complications and who are taking other drugs associated with weight gain (eg, valproate [Depakote], lithium, medroxyprogesterone [Depo-Provera]), it may be preferable to start treatment with an atypical antipsychotic drug with a lower propensity to cause weight gain and glucose intolerance.[3]

In summary, the panel recommends the following:

- Consideration of metabolic risks when starting second-generation antipsychotics
- Patient, family, and caregiver education
- Baseline screening
- Regular monitoring
- Referral to specialized services when appropriate.[1]

WARNING ABOUT USE OF ATYPICALS IN DEMENTIA

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at higher risk of death than those who take a placebo. Although the causes of death are varied, most deaths appear to be either from cardiovascular disease (heart failure, sudden death) or from infections (mostly pneumonia).

The US Food and Drug Administration has recommended a "black box" label warning of this risk for all atypical antipsychotic drugs. This concern emerged from a clinical trial evaluating risperidone in the management of behavioral and psychological symptoms of dementia, and a subsequent meta-analysis of the risperidone trials for this indication also showed more cerebrovascular adverse events in participants receiving risperidone (4%) than among participants receiving placebo (2%).[54]

Pooled data from clinical trials evaluating olanzapine for the treatment of behavioral and psychological symptoms of dementia have shown that it may also be associated with an increased risk of adverse cerebrovascular events.[55] These data suggest around a threefold increase in the relative risk of cerebrovascular events among people taking risperidone or olanzapine. Some evidence suggests no difference in the risk of stroke between atypical and typical antipsychotics in patients with dementia.[56]

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ADDRESS: *David J. Muzina, MD, Department of Psychiatry and Psychology, P57, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail muzinad@ccf.org.*