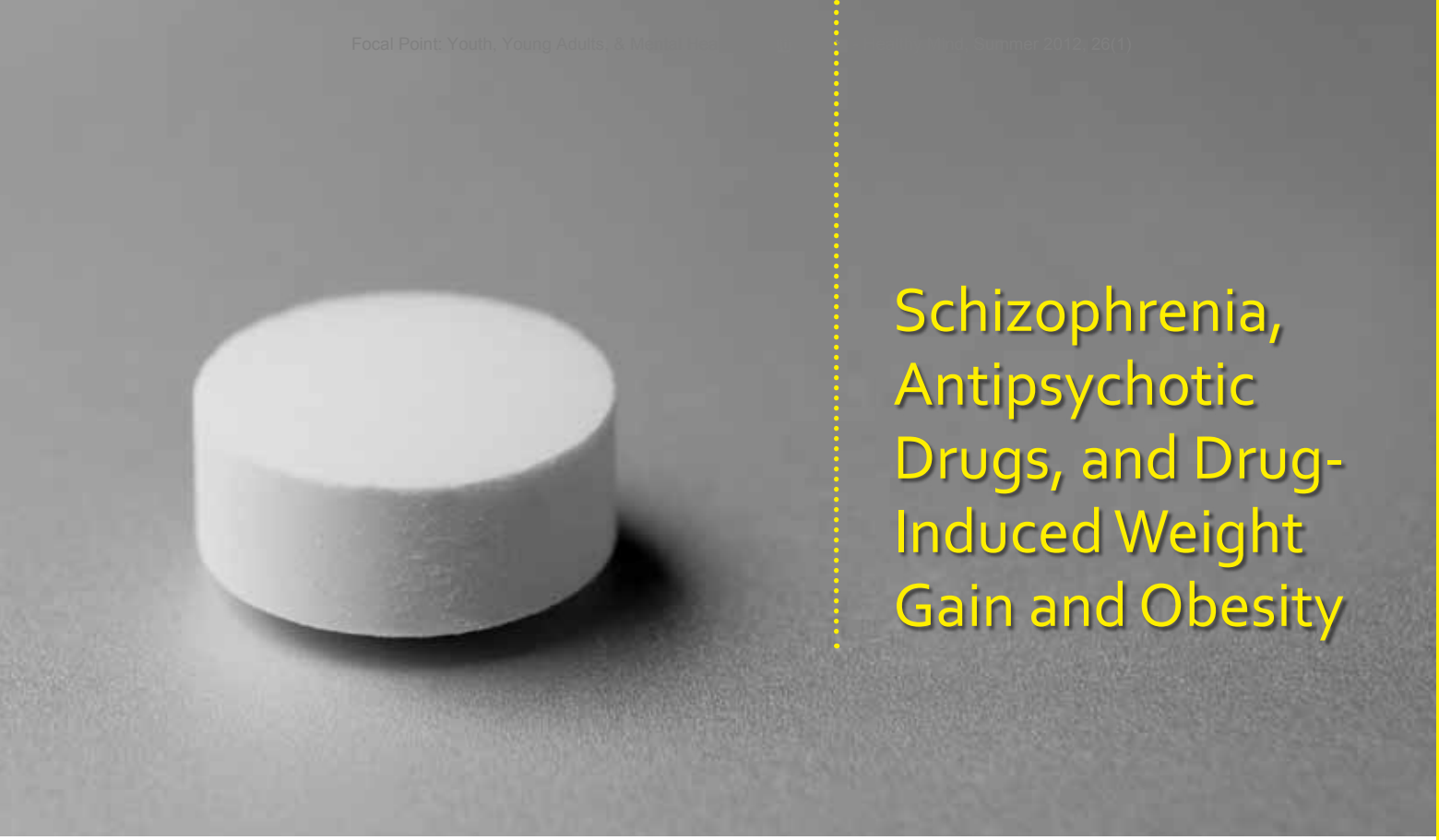

Schizophrenia, Antipsychotic Drugs, and Drug-Induced Weight Gain and Obesity

This article addresses weight gain and related side effects that may occur while taking medications to manage schizophrenia, as well as the trade-offs of taking some medications as opposed to others. As we state below, not all medications are the same. It's important to talk with your health care provider to find the medication that's right for you and also find ways to manage your health to live a fulfilling life.

Unfortunately, people suffering from schizophrenia, on average, die about 25 years earlier than individuals from the general population. Some of this reduced life expectancy is due to coronary heart disease (CHD), [1] although other factors also contribute. Current findings suggest that this mortality gap increased recently.[2] The underlying cause of CHD is coronary artery disease (CAD—the narrowing of the coronary arteries). Well-established risk factors for CAD include smoking, diabetes, high cholesterol, high blood pressure, and obesity. Many of these risk factors converge to form the metabolic syndrome, the group of risk factors that occur together and increase the risk for coronary artery disease, stroke, and type 2 diabetes. Many of the individual risk factors and the metabolic syndrome itself are more prevalent in subjects with schizophrenia than the general population.[3] Unhealthy lifestyle, adverse metabolic effects of medications used to treat schizophrenia (usually antipsychotic drugs) and possible genetic susceptibility best explain this increased prevalence. In this article, we focus on the potential adverse metabolic effects of antipsychotic drug treatment and how to best manage them.

SCHIZOPHRENIA AND ANTIPSYCHOTIC DRUGS

Schizophrenia is a mental condition characterized by problems in perception, thinking, cognition, mood, and volition. Symptoms typically include hallucinations and delusions, or psychosis. In most cases, schizophrenia starts in late adolescence or early adulthood with progressive academic, functional, and social challenges following the onset of psychosis. Schizophrenia is a chronic condition and people living with the condition often require long-term treatment with antipsychotic drugs.

Antipsychotic drugs are the medications most commonly used to treat schizophrenia. The older antipsychotic drugs were associated with motor side effects like tremor and other involuntary movements. The newer antipsychotic drugs are relatively safe in this regard. The older antipsychotic drugs are called "typical" or "first-generation" antipsychotic drugs and the newer ones are called "atypical" or "second-generation" antipsychotic drugs. First-generation antipsychotic drugs are now used rarely to treat schizophrenia in the United States but are often used in less developed countries.

Second-generation antipsychotic drugs were initially thought to have better side-effect profiles than first-generation medications. However, problems with second-generation antipsychotic drugs quickly became evident; side effects include drug-induced weight gain and its complications. Therefore, professional organizations developed consensus guidelines for baseline assessment and monitoring of patients prescribed antipsychotic drugs (Table 1).[4] The FDA (US Food and Drug Administration) directed all manufacturers of second-generation antipsychotic drugs

to warn prescribers and patients of the potential for these drugs to induce hyperglycemia (high blood sugar) and diabetes mellitus (diabetes), which are often associated with weight gain.

METABOLIC PROBLEMS AND THE METABOLIC SYNDROME

Metabolic problems of greatest concern pertain to the body's ability to properly manage (1) glucose and (2) lipids (their storage, consumption, and conversion to metabolically useful chemicals). Glucose dysregulation includes high blood sugar that can progress to diabetes. Dysregulation of lipid (fat) metabolism, commonly referred to as "high cholesterol," may be called dyslipidemia. Although most people who experience metabolic disturbances also experience being overweight or obese, metabolic dysregulation can occasionally occur without weight gain. Excess weight/obesity, hyperglycemia/diabetes, dyslipidemia, cigarette smoking, and lack of physical activity are well-established risk factors for the development of CAD. When symptoms develop in CAD, the condition is called CHD.

Atypical Antipsychotic Drugs And Metabolic Disturbances (see Table 2)

Atypical antipsychotics currently available in the United States (in order of market approval) are: clozapine (1990), risperidone (1994), olanzapine (1996), quetiapine (1997), ziprasidone (2000), aripiprazole (2001), and paliperidone [the main active metabolite of risperidone] (2006). These agents are also available in Europe. Atypical antipsychotics available in Europe but not in the United States are amisulpride, melperone, sertindole, sulpiride, and zotepine. Atypical antipsychotic drugs differ in their potential to cause metabolic adverse effects.[5,6]

Weight Gain

Weight gain usually results from increased appetite—a common side-effect of many atypical antipsychotic drugs—and subsequent excessive food consumption. Antipsychotic agents differ in their potential to cause weight gain. Risk of weight gain is greatest for those taking clozapine and least for ziprasidone (Table 2).[5] For other antipsychotic drugs, the risk can be "quantified" for short-term use with olanzapine having high risk, quetiapine and possibly zotepine having moderate risk, and risperidone, sertindole, amisulpride, aripiprazole, and ziprasidone having mild risk. The estimated mean weight gain over 1 year is about 1 kg (2.2 lbs) with aripiprazole and ziprasidone, 1.5 kg (3.3 lbs) with amisulpride, 2 - 3 kg (4.4 - 6.6 lbs) with quetiapine and risperidone, and over 6 kg (13.2 lbs) with olanzapine and clozapine.[7,8] With long-term use, differences in weight-gain are less pronounced. There can be significant individual differences in weight gain based on the type and amount of foods consumed. The risk and extent of weight gain are much higher in younger first-episode psychosis patients with no previous exposure to antipsychotic drugs compared with patients in long-term treatment. Therefore, young adults experiencing psychosis for the first time are at greater risk for weight gain due to medication effect.[9]

Glucose Dysregulation and Diabetes

Atypical antipsychotic drugs pose varying degrees of risk for high blood sugar levels that usually develop slowly over several years and can progress to diabetes mellitus (Table 2). Diabetes commonly follows drug-induced weight gain. However, olanzapine and clozapine may directly induce glucose dysregulation in the absence of weight gain. Very rarely, hyperglycemia may develop rather suddenly within several weeks of starting an antipsychotic drug. The potential risk is high with olanzapine and clozapine,

Table 1. Consensus Guidelines for Baseline Assessment and Monitoring of Patients Receiving Atypical Antipsychotic Medications (More Frequent Assessments May Be Warranted Based on Clinical Status)[4]

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history*	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

**Personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease*

Table 2. Relative Likelihood of Metabolic Disturbances with Atypical Antipsychotic Medications[5,6]

Medication	Weight Gain	Glucose Metabolism Abnormalities	Dyslipidemia	Metabolic Syndrome
Amisulpride	Low	Low	Low	—
Aripiprazole	Low	Low	Low	Low
Clozapine	High	High	High	High
Melperone	—	—	—	—
Olanzapine	High	High	High	High
Paliperidone	—	—	—	—
Risperidone	Medium	Medium-to-low	Low	Medium
Sulpiride	—	—	—	—
Quetiapine	Medium	Medium-to-low	High	High
Sertindole	Low	—	—	—
Ziprasidone	Low	Low	Low	Low
Zotepine	Medium	—	—	—

medium for quetiapine and low for risperidone, aripiprazole, and ziprasidone. Young female patients with normal weight at baseline who gain weight rapidly appear to be particularly prone to this complication.

Effects on Lipids

The administration of atypical antipsychotic drugs may result in elevated lipids, including reduced "good cholesterol" (HDL – high density lipoproteins) and elevated "bad cholesterol" (cholesterol, triglycerides, and LDL – low density lipoproteins). The risk is high with clozapine, olanzapine, and quetiapine and relatively lower with risperidone and amisulpride. Ziprasidone and aripiprazole are least likely (or unlikely) to cause unhealthy cholesterol. The lipid profiles of patients who switched to one of these agents from another antipsychotic drug may actually improve.[5] Weight gain associated with atypical antipsychotic drug administration may explain unhealthy cholesterol levels in most cases, but occasionally this disturbance occurs without weight gain.

TREATMENT WITH ANTIPSYCHOTIC DRUGS

Schizophrenia is a chronic and disabling condition. Taking antipsychotic drugs is usually needed to control the symptoms of this condition to improve functioning and quality of life. Therefore, if medications are prescribed, the potential adverse metabolic effects of antipsychotic drugs should not prevent someone from taking these medications. Instead, effort should be made to minimize the potential side effects of these medications.

Young adults who begin taking antipsychotic drugs should be screened for various metabolic and CHD risk factors at baseline and periodically thereafter. Professional organizations provide guidelines (Table 1). As discussed above, different atypical antipsychotic drugs vary in their potential to cause adverse metabolic effects. Because antipsychotic drugs differ little, if any, in their efficacy in treating schizophrenia, a person who has personal risk factors for CHD at baseline or a strong family history of these risk factors should not take a medication associated with high metabolic complications. People treating their schizophrenia with antipsychotic medications should work closely with their primary care physician or their health care provider to monitor any early signs of metabolic disturbances (e.g., rapid or persistent weight gain) after starting an antipsychotic drug. Periodic monitoring of blood pressure, glucose and lipids should also be conducted by the psychiatrist or family physician. If metabolic worsening occurs, patients and their health care providers should work together sooner rather than later to change treatment to an antipsychotic drug with a lower metabolic risk.

Healthy lifestyle interventions are essential to counter adverse metabolic effects of antipsychotic drugs and metabolic problems or risk factors that may be present before starting an antipsychotic drug. Healthy lifestyle habits include eating a balanced diet and getting regular exercise. Health care providers should offer education and support, but sometimes patients benefit most from the services of a dietician and/or exercise therapist. Cigarette smoking is a well-established risk factor for CHD, so people with schizophrenia who smoke should discuss with their healthcare provider the options that are available to help them quit smoking. Alcohol or substance use may also adversely affect the course of schizophrenia. If many lifestyle changes are needed, they should be incorporated at a pace that is comfortable and manageable. Patients should make sure they get the right people on their healthcare team and support system to help them go through this – no one can do it alone!

CONCLUSION

People with schizophrenia are at risk for metabolic problems, CHD, and early cardiac death. Unhealthy lifestyle factors and potential metabolic complications of antipsychotic drugs contribute to these risks. Antipsychotic drugs differ in their metabolic risk, so individuals with schizophrenia should consult their health care providers in selecting the best and safest medication for them. Unfortunately, despite available treatment guidelines, baseline assessment and regular monitoring for metabolic problems are not that common. Therefore, it is important for patients to initiate the conversation about medication safety with their health care providers if necessary.

Adoption of a healthy lifestyle is the most effective way to diminish the risk of metabolic problems, CHD, and early mortality. People with schizophrenia should enlist the help of friends, family, and health professionals to support them in making the changes they need to live a happy, healthy, productive life.

REFERENCE LIST

1. Newcomer, J. W., & Hennekens, C. H. (2007). Severe mental illness and risk of cardiovascular disease. *Journal of the American Medical Association, 298,*1794-1796.
2. Saha, S., Chant, D., & McGrath, J. (2007). A Systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Archives of General Psychiatry, 64*(10), 1123-1131.
3. Meyer, J. M., & Stahl, S. M. (2009). The metabolic syndrome and schizophrenia. *Acta Psychiatrica Scandinavica, 119,* 4-14.
4. American Diabetes Association American Psychiatric Association, American Association of Clinical Endocrinologists, & North American Association for the Study of Obesity. (2004). Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care, 27,* 596-601.
5. Hasnain, M., Vieweg, W. V. R., Fredrickson, S. K., Beatty-Brooks, M., Fernandez, A., & Pandurangi, A. K. (2009). Clinical monitoring and management of the metabolic syndrome in patients receiving atypical antipsychotic medications. *Primary Care Diabetes, 3,* 5-15.
6. Hasnain, M., Fredrickson, S., Vieweg, W., & Pandurangi, A. (2010). Metabolic syndrome associated with schizophrenia and atypical antipsychotics. *Current Diabetes Reports, 10,* 209-216.
7. Leadbetter, R., Shutty, M., Pavalonis, D., Vieweg, V., Higgins, P., & Downs, M. (1992). Clozapine-induced weight gain: Prevalence and clinical relevance. *American Journal of Psychiatry, 149,* 68-72.
8. Newcomer, J. W., & Haupt, D. W. (2006). The metabolic effects of antipsychotic medications. *Canadian Journal of Psychiatry, 51,* 480-491.
9. Álvarez-Jiménez, M., González-Blanch, C., Crespo-Facorro, B., Hetrick, S., Rodríguez-Sánchez, J. M., Pérez-Iglesias, R., & Vázquez-Barquero, J. L. (2008). Antipsychotic-induced weight gain in chronic and first-episode psychotic disorders: *A systematic critical reappraisal. CNS Drugs, 22,* 547-562.

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