Metabolic Adverse Events in Patients With Mental Illness Treated With Antipsychotics: A Primary Care Perspective

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This article was supported by Bristol-Myers Squibb (Princeton, N.J.) and Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan). Editorial support for the preparation of this manuscript was provided by Ogilvy Healthworld Medical Education (London, United Kingdom) and funding was provided by Bristol-Myers Squibb (Princeton, N.J.).

Dr. Stewart has received grant/research support from Pfizer and honoraria from Bristol-Myers Squibb, Pfizer, AstraZeneca, and Janssen; has served on the speakers or advisory boards of Janssen; and is a stock shareholder of Janssen and Pfizer. Mr. Whitehead is an employee of Otsuka America Pharmaceutical, Inc. Dr. Baker is an employee and stock shareholder of Bristol-Myers Squibb. Dr. Balf has no other financial affiliations to report.

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Background: Individuals with mental illness are at a higher risk of medical mortality than the general population, primarily due to an increased risk of cardiovascular disease. There are a number of modifiable metabolic risk factors associated with some atypical antipsychotics that warrant careful monitoring and treatment in both psychiatric and primary care practice if the risk of cardiovascular disease is to be effectively reduced.

Data Sources: Previous guidelines have focused on awareness of metabolic risk factors in psychiatry, yet few articles have appeared in the primary care–focused journals. We present pragmatic guidelines that focus on monitoring metabolic abnormalities in primary care based on established guidelines, including joint recommendations 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, and the Mount Sinai conference.

Data Synthesis: All patients receiving atypical antipsychotic agents associated with metabolic adverse events should be routinely monitored for weight gain and abnormalities in blood glucose and lipid levels. Effective communication and collaboration between mental health and primary care services and better access to primary care screening and treatment for individuals with mental health problems are needed.

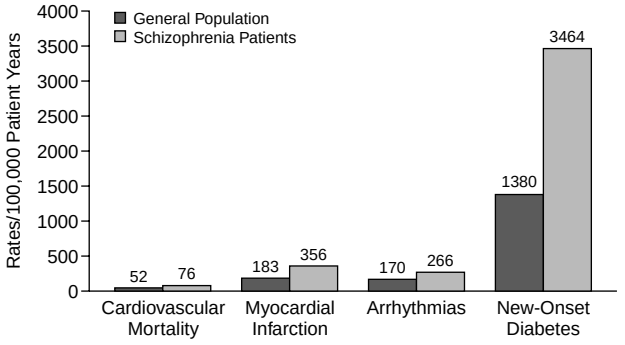
Conclusion: There is a clear need for awareness among primary care physicians, particularly as metabolic effects of atypical antipsychotics such as blood pressure and glucose and lipid levels are possibly best monitored in a primary care setting.

(Prim Care Companion J Clin Psychiatry 2008;10:15–24)

It is becoming increasingly acknowledged that individuals with mental illness are at higher risk of medical mortality than the general population, in addition to the increase in unnatural deaths (e.g., suicide, accident). A meta-analysis of mortality data from studies in patients with schizophrenia has shown that there is a significant increase in overall mortality, with a standardized mortality ratio of 1.51 compared with the general population.[1] Similar increases in overall and cardiovascular mortality have been observed in patients with affective disorders, including unipolar depression and bipolar disorder.[2,3] This article will briefly review the evidence for the association between atypical antipsychotic medications and modifiable risk factors associated with cardiovascular disease that are common in those with mental illness. The article will focus on the role of the primary care physician in monitoring and managing metabolic parameters in individuals with mental illness, and how the risk of cardiovascular disease can be effectively reduced.

The most common cause of natural death in patients with schizophrenia is cardiovascular disease, accounting for 34% of male deaths and 31% of female deaths, again significantly higher than the risk in the general population.[1] More worrying are results from a recent large, national survey conducted in the United Kingdom that showed a 3-fold risk of coronary heart disease in persons with severe mental illness < 50 years old compared with the control group without mental illness.[4] Figure 1

Figure 1. Risk of Cardiovascular and Metabolic Events in Patients With Schizophrenia and in the General Population (commercially insured U.S. population)[a]



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illustrates the increased risk of cardiovascular and metabolic events in patients with schizophrenia compared with the general population. Thus, careful monitoring of cardiovascular risk factors and appropriate treatment for those with increased risk are emerging needs in the care of individuals with psychiatric disorders.

Atypical antipsychotics were developed to overcome extrapyramidal side effects associated with the use of typical antipsychotics at clinically effective doses, and this has led to widespread use since their introduction over a decade ago. Despite these benefits, the use of atypical antipsychotics has also been associated with reports of dramatic weight gain, diabetes, and atherogenic lipid profiles.[6] Metabolic side effects, combined with the close association of these factors with cardiovascular disease, led the American Diabetes Association (ADA), the American Psychiatric Association (APA), the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity to hold a joint conference in November 2003 to develop a consensus on the relationship between antipsychotic drugs and obesity and diabetes.[6] This, combined with consensus guidelines for physical health monitoring in schizophrenia published in the same year,[7] has led to an increasing focus on the monitoring and treatment of these risk factors in psychiatry. Furthermore, atypical antipsychotics, as a class, carry a warning regarding the risk of hyperglycemia and diabetes as required by the U.S. Food and Drug Administration (FDA), although there are different levels of risk associated with each agent.

We suggest that the growing use of atypical antipsychotics makes it necessary that primary care clinicians are aware of all patients who fall in the ever-expanding range of conditions for which antipsychotic treatment is used. A number of atypical agents are approved for use in schizophrenia and bipolar disorder, and aripiprazole has recently been approved as adjunctive treatment to antidepressant therapy in adults with major depressive disorder. Furthermore, in a large sample of Medicaid patients, 64% of adults were receiving an antipsychotic for an off-label indication,[8] while in a second large study, 77% of youths receiving an antipsychotic did not have a diagnosis of a psychotic disorder.[9] Even if they are not the primary prescribers of these medications, there is an urgent need for better understanding of the standard of care as it relates to metabolic monitoring of patients taking atypical antipsychotics. The need for better awareness in primary care is highlighted by the finding that few articles in this area have been published in primary care–focused journals. A MEDLINE search of the literature (1976, when first detected, to July 14, 2007) for publications addressing the issue of atypical antipsychotics and metabolic abnormalities identified 107 publications in the psychiatric literature compared with only 7 in primary care journals. A further 14 articles in the pharmacology literature, 5 articles in the endocrinology literature, and 1 each in the basic research and nursing literature were identified.

Here, we present pragmatic guidelines that focus on monitoring metabolic abnormalities in primary care, providing a convergence of established guidelines. We hope this article will help to turn awareness into action and build a treatment alliance between psychiatry and primary care that will ultimately result in improved patient care.

METABOLIC DISTURBANCES AND DISEASE-STATE RISK

Patients with schizophrenia and bipolar disorder are at an increased risk of abnormal glucose metabolism and metabolic disorders.[10–12] While the increased metabolic risk may be related to the impact of the condition on lifestyle and nutrition, it is also possible that there is a direct pathophysiologic link between mental illness and disturbed glucose regulation. For example, a study in antipsychotic-naive patients with first-episode schizophrenia showed that the prevalence of impaired fasting glucose tolerance was significantly greater than in healthy controls matched for age, sex, diet, and exercise ($p < .02$).[13] Mean fasting plasma glucose, insulin, and cortisol levels were also significantly increased in the patients with schizophrenia ($p < .05$).[13]

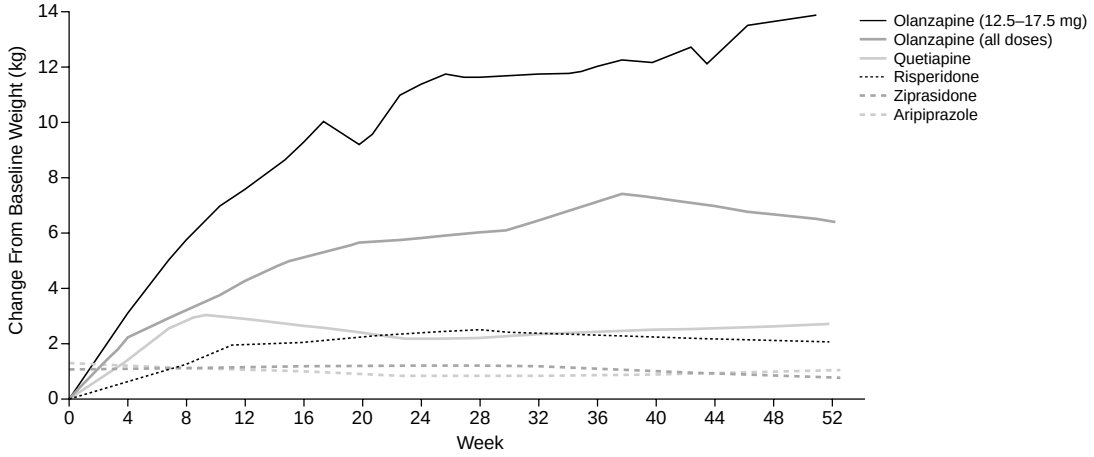
Weight gain and abdominal obesity are important risk factors for insulin resistance and dyslipidemia. It was therefore initially thought that weight gain was an important cause of antipsychotic-related metabolic disturbance until it was discovered that some atypical antipsychotic agents like olanzapine and clozapine can increase insulin resistance and triglyceride levels without associated weight gain.[10,14,15] While some atypical antipsychotic agents may have more direct adverse effects on glucose

Table 1. Physical Health Side Effects of Commonly Used Antipsychotics[a,b]

Drug	Side Effect						Specific Risks
	Weight Gain	Glucose Abnormalities	Lipid Abnormalities	QTc Prolongation	Prolactin Elevation	Sedation	
Clozapine	+++	+++	+++	0	0	+++	Agranulocytosis, seizures, and myocarditis
Olanzapine	+++	+++	+++	0	0	+	
Risperidone	++	++	++	0	+++	+	
Quetiapine	++	++	++	+	0	++	Cataracts
Ziprasidone	0	0	0	++	0	0	Rash
Aripiprazole	0	0	0	0	0	+	
Paliperidone	++	0	0	0	++	+	
Haloperidol	+	+	+	0 (+ if IV)	+	++	Dystonia risk in young

[a]Based on Lehman et al.[16]
[b]0 = no risk or rarely causes side effects at therapeutic dose, + = mild or occasionally causes side effects at therapeutic dose, ++ = sometimes causes side effects at therapeutic dose, and +++ = frequently causes side effects at therapeutic dose.
Abbreviation: IV = intravenous.

Figure 2. Mean Weight Change in Patients Receiving Antipsychotic Agents[a]



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metabolism, independently of any effects on body weight,[6] the relationship of abdominal obesity to insulin resistance suggests that weight gain is still an important signal for potential metabolic disturbance, and rapid weight increases after initiation of antipsychotic therapy are an important indication of potential increased metabolic risk. Thus, weight gain and increased triglyceride levels are easily measured early signals of potential adverse metabolic effects of atypical antipsychotic agents.

Atypical Antipsychotic Agents and Weight Gain

Weight gain is a well-established side effect of treatment with antipsychotic therapy. However, there is evidence to suggest significant differences between the weight gain liabilities of the atypical antipsychotics (Table 1 and Figure 2). Of these agents, clozapine and olanzapine are generally associated with the greatest impact on body weight during both shorter- and longer-term therapy.[17–20] The incidence of clinically significant weight gain in studies of clozapine and olanzapine is also similar, with 20% of patients receiving either agent experiencing weight gain ≥ 10% with treatment lasting from 10 weeks to 12 months.[21,22] Data suggest that risperidone has an intermediate effect on weight in the short term,[17] and quetiapine appears to have a short-term weight gain potential similar to that of risperidone.[23]

By comparison, the newer antipsychotic agents, aripiprazole and ziprasidone, are associated with minimal weight gain.[17,24] The newest FDA-approved agent, paliperidone extended release, the active metabolite of risperidone, has the same weight gain profile as its parent drug.[25]

Although a comprehensive discussion of the weight gain potential of the typical agents is beyond the scope of this review, it should be noted that they are also associated with weight changes ranging from a reduction of 0.39 kg

with molindone to an increase of 1.08 kg and 3.19 kg with haloperidol and thioridazine, respectively.[17]

Atypical Antipsychotic Agents and Abnormal Glucose Regulation

In addition to their effects on body weight, clozapine and olanzapine are also associated with abnormal glucose regulation. First, case reports of spontaneously reported adverse events have suggested that new-onset type 2 diabetes and diabetic ketoacidosis occurred more frequently in patients receiving olanzapine and clozapine, with relatively fewer cases with risperidone and quetiapine treatment.[26–29] The primary care clinician must be aware that even though diabetic ketoacidosis rarely occurs in type 2 diabetics, it is becoming more common in the setting of olanzapine and clozapine treatment,[26,28] and patients are generally younger.[30] The time from initiation of antipsychotic therapy to onset of newly diagnosed diabetes, documented by glucose or glycohemoglobin levels, was generally short and occurred within the first 3 months of starting therapy for 56% of clozapine patients,[26] 47% of olanzapine patients,[28] 48% of risperidone patients,[27] and 41% of quetiapine patients (6-month data).[29] Time from initiation of antipsychotic therapy to onset of newly diagnosed diabetes tended to be less for patients experiencing exacerbation of existing disease, with 64%, 84%, 71%, and 86% of clozapine,[26] olanzapine,[28] risperidone,[27] and quetiapine[29] cases, respectively, occurring within 3 months of initiation. Interestingly, a high proportion of new-onset diabetes cases occurred in young patients within 6 months of initiating antipsychotic therapy.[26,28] This finding is in agreement with analysis of health care data from the Veterans Health Administration that has shown the elevated risk of diabetes to be highest in younger patients (< 45 years) with schizophrenia.[31]

Additional evidence for the differential association between atypical antipsychotics and risk of insulin resistance, hyperglycemia, and type 2 diabetes comes from both database analyses and controlled clinical trials.[32] Evidence is strongest for olanzapine and clozapine, suggesting that both treatments are associated with an increased risk of diabetes, while evidence for risperidone is less extensive, suggesting that treatment with risperidone is not associated with a consistent increased risk of developing diabetes.[32] Findings with quetiapine are contradictory and offer relatively less reassuring evidence concerning the relationship between quetiapine treatment and diabetes risk. [32]

Initial studies suggest that aripiprazole and ziprasidone do not adversely effect blood glucose regulation.[32,33] Furthermore, in addition to their favorable metabolic profiles, recent evidence suggests that antipsychotic-related metabolic disturbances can be reversed following a switch to either aripiprazole or ziprasidone.[34,35] In a recent case series evaluation of patients who underwent extensive metabolic evaluation following initiation of aripiprazole, there was a significant reduction in fasting glucose, fasting insulin, insulin resistance index, and serum lipid levels after 3 months of treatment.[34] In addition, all 7 cases of recent-onset diabetes were reversed.[34] Similarly, patients switching to ziprasidone due to antipsychotic-related metabolic disturbances while taking previous medication experienced improvements in serum glucose levels, as well as improvements in weight and lipid levels after 6 months of treatment.[35]

Although the effects of certain atypical antipsychotics on weight gain can be used to explain the effects of these agents on glucose regulation, there is also direct evidence that drug effects are independent of adiposity. For example, in 1 study increased insulin resistance was observed in patients receiving clozapine and olanzapine, independent of adiposity, while patients taking risperidone had similar levels as patients receiving typical antipsychotics.[36]

The association of certain atypical antipsychotics with insulin resistance has important implications for monitoring, as patients with insulin resistance may present with normal glucose levels as the pancreas attempts to maintain glucose homeostasis. However, insulin resistance and compensatory hyperinsulinemia can produce elevated triglyceride levels, emphasizing the importance of ongoing lipid monitoring.

Atypical Antipsychotic Agents and Dyslipidemia

Patterns of dyslipidemia in patients receiving atypical antipsychotics mirror those of abnormal glucose metabolism, although the data are generally less consistent, perhaps reflecting the significant role of adiposity and body weight in lipid metabolism. Numerous studies in patients receiving clozapine have shown that treatment is associated with increased levels of triglycerides,[32] and increased cholesterol levels have also been reported in some studies.[37,38] Similarly, olanzapine is commonly associated with increased levels of triglycerides and cholesterol in most, but not all, studies.[32] Data for risperidone and quetiapine are generally less consistent, although do suggest that effects are less than those observed with clozapine and olanzapine.[32] Nevertheless, pooled data from 3- to 6-week placebo-controlled schizophrenia trials report 23% of patients experienced elevated triglyceride levels and 16% of patients experienced elevated total cholesterol levels with quetiapine therapy.[39] Any increase in cholesterol levels has significant health implications, as a 10% increase in cholesterol levels is associated with a 20% to 30% increase in the risk of coronary heart disease.[40] There is no evidence to suggest that aripiprazole and ziprasidone have any adverse effects on lipid parameters,[32] and initial data with paliperidone extended release also suggest no adverse effects on serum lipids.[25]

THE TREATMENT GAP

Despite the higher morbidity and mortality rates from cardiovascular disease in patients with mental illness than in the general population and the increased risk of metabolic disturbance in individuals taking some atypical agents, individuals with mental health problems often have limited access to appropriate primary care screening and treatment for important metabolic conditions associated with cardiovascular disease risk. Findings from the large Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study have shown that rates of nontreatment in schizophrenia ranged from 30% for diabetes up to 62% for hypertension and up to 88% for dyslipidemia.[41] In particular, nonwhite women were particularly at risk with higher rates of undertreatment for diabetes and dyslipidemia compared with their male counterparts.[41] Perhaps more alarming is that metabolic monitoring of bipolar patients apparently was not included in the original design of the large Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial.[42] The STEP-BD trial was designed in response to a National Institute of Mental Health initiative seeking a public health intervention model that could generate externally valid answers to treatment effectiveness questions related to bipolar disorder.[42] Together these findings support the need for improvements in awareness, health screening, and monitoring in the psychiatric population by both mental health and primary care services. An additional finding of the CATIE study was that weight gain was a major reason for treatment discontinuation in patients with schizophrenia.[43] Thus, better monitoring and awareness also have the potential to improve treatment compliance.

Social and economic factors also contribute to the treatment gap between the mentally ill and the general population. Changes in psychosocial variables can have a huge impact on access to care, as individuals with schizophrenia and bipolar disorder often have difficulties maintaining employment, and health care insurance coverage can be variable.[44]

The Case of Mr. A

Mr. A is a 35-year-old white man diagnosed with bipolar I disorder since age 25 years. Over the past 10 years, he has been treated by a psychiatrist with various mood stabilizers (e.g., lithium, carbamazepine, valproate) yielding mixed results. His most recent manic episode occurred 10 months ago, after which he was treated with an atypical antipsychotic, and his manic symptoms have been stabilized satisfactorily.

Mr. A has come to his primary care physician for a matter unrelated to his bipolar I disorder; however, it is noticed that his weight has increased from 180 lb to 250 lb since he was prescribed the atypical antipsychotic. Mr. A complains about the weight gain and asks his physician if anything can be done to address it. The physician has not received any psychiatric or medication history from Mr. A's psychiatrist.

This case illustrates the type of patient who may commonly present in the primary care setting and highlights some interesting questions: What, if any, actions should the primary care physician take to address this patient's concerns about weight gain in light of the relative success in treating his manic symptoms? Should any additional tests be conducted to evaluate potential metabolic complications that Mr. A might be developing? The following review of guidelines for monitoring and treatment of metabolic disturbances in primary care will hopefully help to address some of these questions and provide recommendations for Mr. A's ongoing care.

MONITORING AND TREATMENT OF METABOLIC DISTURBANCES IN PRIMARY CARE

Recommendations, such as those issued by the Mount Sinai Conference[7] or the statement issued by the ADA in association with other bodies,[6] clearly state that monitoring of metabolic parameters is essential in patients with mental illness if their cardiovascular health is to be improved. A summary of combined recommendations for the frequency of monitoring is given in Table 2.

Effective monitoring of metabolic disturbances requires effective communication between mental health and primary care services.[7] While mental health care must clearly give due consideration to physical health monitoring, especially when related to side effects of prescribed antipsychotic medications, metabolic abnormalities such as blood pressure and glucose and lipid level monitoring are possibly best monitored in a primary care setting.[7] In addition, guidelines currently recommend that metabolic disturbances in individuals with mental illness should be treated in a primary care setting should they arise during the course of mental health care screening.[6,7] It is therefore paramount that primary care physicians are as aware of the recommendations for monitoring in this population as their mental health colleagues, especially as coordination of services will be key to successful care.

Key baseline parameters to be assessed prior to initiating antipsychotic medications include family history of metabolic conditions, weight and height, waist circumference, plasma glucose level, blood pressure, and lipid profile.[6,7] Together, these measurements allow evaluation of obesity, prediabetes, and dyslipidemia, prompting appropriate treatment where required (Table 3).[6,7] Follow-up assessments are recommended frequently after initiating or changing antipsychotic therapy and at regular intervals thereafter.[6,7] Coronary heart disease lifestyle risk factors such as poor diet, lack of exercise, and

Table 2. Summary of Recommendations for Ongoing Monitoring of Patients Taking Atypical Antipsychotics[a]

Variable	Baseline	Every Visit for First 6 Months	4 Weeks	8 Weeks	12 Weeks	4 Months	Every 3 Months	Every 4 Months	Annually	Every 2 Years	Every 5 Years
Personal/family history	A								A		
Ethnicity	M[b]										
Smoking status	M[c]										
Weight	A, M		A	A	A		A				
Body mass index	A, M	M[d]					M				
Waist circumference	A, M								A		
Blood pressure	A				A				A		
Fasting plasma glucose	A, M				A	M			A, M		
Signs and symptoms of diabetes	A, M								M		
Lipid profile	A				A					M	A
ECG (if ↑QTc risk factors)	M										
Prolactin/sexual side effects	M								M		

[a]Based on American Diabetes Association et al.[6] and Marder et al.[7]
[b]Ethnicity should be considered at baseline, as being a member of a high-risk ethnic population (black, Hispanic American, Native American, Asian American, Pacific Islander) increases the risk of diabetes.
[c]Clinicians should inquire about smoking status, as this contributes to an increased risk for cardiovascular morbidity and mortality. Patients who smoke should be referred to smoking cessation programs.
[d]Patients who are seen at intervals of more than 1 month should be instructed to self-monitor and to notify the prescribing physician if they gain more than the number of pounds corresponding to an increase in 1 body mass index unit.
Abbreviations: A = American Diabetes Association-American Psychiatric Association recommendations, ECG = electrocardiogram, M = Mount Sinai Conference.

Table 3. Summary of Treatment Recommendations for Metabolic Risk Factors in Patients With Mental Illness[a]

	Guideline	
Metabolic Risk Factor	ADA-APA	Mount Sinai
Increased weight		
Specialist referral	✓	
Medication switch	✓	✓
Closer monitoring		✓
Dietary advice	✓	
Exercise advice	✓	
Weight management program	✓	✓
Adjunctive medication		✓
Impaired glucose tolerance/diabetes		
Referral	✓	PCP/internist
Medication switch	✓	
Dyslipidemia		
Referral	Specialist referral	PCP
Medication switch	✓	
Cholesterol-lowering drug		✓

[a]Based on American Diabetes Association et al.[6] and Marder et al.[7]
Abbreviations: ADA = American Diabetes Association, APA = American Psychiatric Association, PCP = primary care provider.

smoking, often more prevalent in the mentally ill population, are also important baseline considerations.

WEIGHT GAIN AND OBESITY

As individuals with mental illness are more likely to be overweight or obese than the general population, weight should be routinely monitored in all patients, especially in those receiving treatment with atypical antipsychotic medications associated with weight gain.[6,7] While it is especially important for psychiatrists to carefully monitor weight gain after switch or initiation of antipsychotic medication, body weight and/or body mass index should be continually monitored at intervals of 3 months. All patients should be encouraged to monitor their own weight and report any weight change to their mental health care provider or primary care provider.[6,7]

From a primary care perspective, patients with weight gain resulting in a body mass index increase of 1 unit should be considered to be in need of intervention.[6] However, it may also be practical to consider clinically significant weight gain, commonly defined as an increase of ≥ 7%, as a need for intervention.[45] Guidelines recommend use of weight management programs, as well as general advice on diet and exercise.[6,7] Physicians should also advise patients to contact their mental health care provider to consider a medication switch if weight gain continues or other interventions prove unsuccessful.[6,7]

DIABETES

Recommendations for the frequency of monitoring for the development of abnormal glucose regulation are generally consistent between the ADA and Mount Sinai guidelines, with both recommending that monitoring should be done at baseline and then at 3 to 4 months after starting antipsychotic therapy. The usual diagnostic test for diabetes, as recommended by the ADA, is the fasting plasma glucose test (≥ 126 mg/dL), and it is also recommended for screening for diabetes in individuals with schizophrenia.[6] Fasting glucose levels between 100 mg/dL and 125 mg/dL are indicative of prediabetes and should also be closely monitored. Although the Mount Sinai guidelines[7] suggest measurement of glycated

hemoglobin (e.g., hemoglobin A1c) if a fasting test is unfeasible in a mental health care setting, the ADA recommendations for screening in the general population[5] advise against the use of glycated hemoglobin due to its relative insensitivity as a screening measure. In a primary care setting, fasting plasma glucose level is therefore preferable.[6] In addition to blood glucose monitoring, it is also key for psychiatrists and primary care physicians to explicitly look for the signs and symptoms of diabetes, especially if patients are also experiencing weight gain or are receiving antipsychotics associated with weight gain.[6] Individuals with mental illness receiving antipsychotics should be screened for diabetes annually.[6,7]

Primary care providers, or a clinician experienced in treating diabetes, should assume responsibility for the treatment and monitoring of patients with test results that suggest the possibility of diabetes, and patients reporting signs or symptoms of diabetes should undergo prompt evaluation and treatment where necessary following the latest ADA guidelines.[46] Referral to an ADA-approved diabetes self-management program is also suggested, if available.[6]

DYSLIPIDEMIA

A fasting lipid profile is recommended at baseline and 3 months after treatment initiation of antipsychotic medication by the APA and then every 5 years for those patients with a normal lipid profile. Although screening every 5 years is recommended by the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines in asymptomatic individuals, those with mental illness are at increased risk of coronary heart disease as a group, regardless of antipsychotic medication, and as such we believe they should undergo more frequent monitoring. Therefore, routine monitoring may be more appropriate as recommended by the Mount Sinai guidelines (i.e., every 2 years for normal low-density lipoprotein [LDL] cholesterol levels and every 6 months for LDL cholesterol levels > 130 mg/dL). The fasting lipid profile should include measurement of total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides.

For patients developing dyslipidemia while on antipsychotic therapy, the ADA recommends considering switching to an atypical agent not associated with significant weight gain or diabetes.[6] When considering the need for intervention, it should be taken into account that the risk of cardiovascular disease does not depend on the cut-off score, but rather there is a continuous increase in risk as lipid levels increase.[47] For example, if a patient's triglyceride levels increase by 40 mg/dL, his or her risk of cardiovascular events is much higher, even if the level does not increase above the 150 mg/dL threshold.

Treatment of individuals identified with abnormal lipid levels should also follow guidelines recommended by the NCEP, with LDL levels being the primary focus of intervention due to their close association with atherosclerosis.[48] The goal of treatment is an LDL level < 100 mg/dL in patients with coronary heart disease or risk equivalents. For patients with multiple risk factors, as patients with psychiatric illness are likely to be, the target should be < 130 mg/dL.[48] When necessary, patients should receive lipid-lowering medication and lifestyle advice. While monitoring of lipid levels should be carried out in a mental health setting in patients receiving treatment with atypical antipsychotics, treatment of dyslipidemia is primarily the responsibility of primary care providers, highlighting the need for good communication between primary care and mental health care services. However, the Mount Sinai guidelines do suggest treatment within the mental health care setting for patients without access to primary care services.

Elevated triglyceride levels, when combined with low HDL cholesterol levels and only slight elevation in LDL cholesterol levels, are often associated with insulin resistance and should be considered in patients presenting with this characteristic pattern of lipid abnormalities.

METABOLIC SYNDROME AND MENTAL ILLNESS

Metabolic syndrome represents a cluster of metabolic symptoms including abdominal obesity, glucose intolerance, hypertension, and atherogenic dyslipidemia (elevated triglyceride and low HDL cholesterol levels). When occurring together, these symptoms substantially increase risk for cardiovascular disease and type 2 diabetes. Analysis of data from CATIE indicates that metabolic syndrome is highly prevalent in schizophrenia patients in the United States, occurring in 41% of patients when defined using NCEP-derived criteria.[49] When compared with age- and race-matched controls, individuals with schizophrenia are at significantly increased risk compared with the general population; men and women with schizophrenia were 138% and 251% more likely to have metabolic syndrome, respectively.[49] Similar higher prevalence rates have also been reported in Europe.[50] While less comprehensive data are available on the increased risk of metabolic syndrome in patients with bipolar disorder, data indicate that prevalence of the metabolic syndrome in these patients is also alarmingly high (30%).[11] Furthermore, metabolic syndrome is strongly associated with a poor self-rating of physical health and increased somatic preoccupation.[51]

Metabolic syndrome in those with mental illness clearly represents an enormous source of cardiovascular risk. From a primary care perspective, all symptoms of metabolic syndrome need to be monitored and managed effectively.[7]

ADDITIONAL PHYSICAL HEALTH SIDE EFFECTS OF ATYPICAL ANTIPSYCHOTIC TREATMENT

In addition to the metabolic side effects of certain atypical antipsychotic medications, other important physical health effects commonly associated with some atypical agents include prolongation of QTc intervals and prolactin elevation combined with associated sexual side effects (see Table 1). In the case of QTc intervals, the main study that resulted in the current guideline formulation showed that ziprasidone, from the atypical antipsychotics, resulted in a larger QTc prolongation than quetiapine, risperidone, and olanzapine, although the percentages of study patients displaying significant QTc prolongations were not as high as one might expect.[52] For the busy practitioner, it is useful to know that current guidelines recommend that patients who are to be treated with ziprasidone must have a baseline electrocardiogram if the following risk factors are present: known heart disease, a personal history of syncope, a family history of sudden death at an early age, or congenital long QT syndrome.[7] It is also useful to think of the possible interactions with potential QTc-prolonging drugs before prescribing quinolones, macrolides, cotrimoxazole, tricyclics, other antipsychotics, chloral hydrate, or diuretics. For example, the use of paliperidone causes a modest increase in QTc intervals and should be avoided in combination with other QTc-prolonging drugs. QTc-prolonging antipsychotics should be discontinued if the QTc interval is > 500 ms, and immediate communication with the mental health provider is recommended.

Although prolactin elevation is more commonly associated with typical antipsychotic agents, hyperprolactinemia is also seen with risperidone treatment. Both mental health and primary care providers should ask patients receiving treatment about symptoms associated with prolactin elevation, including questions about galactorrhea, menstruation regularity, and libido in women, as well as libido and erectile and ejaculatory function in men.[7] Inquiring about these symptoms of hyperprolactinemia is important since measurements of prolactin levels are highly variable by individual and not tightly correlated to overt symptoms. Measurement of plasma prolactin levels may be warranted, and prolactin elevation (> 100 ng/mL) or detection of symptoms of hyperprolactinemia merit consultation with the patient's mental health care provider regarding a medication adjustment. Should their symptoms or levels not resolve with a prolactin-sparing regimen, a full endocrinologic evaluation is indicated to rule out prolactinoma or pituitary tumors.

Recommendations for Mr. A

Mr. A's weight gain was significant during the relatively short treatment period and was a cause for concern. Addressing weight gain should be a priority. Managing weight gain in patients with severe psychiatric disorders is especially challenging,[53] and not all patients are able to follow dietary and lifestyle modifications. With this in mind, it may be beneficial to enlist the help of a family member or caregiver if one is available.[6,7] Advice on diet and exercise should be given, either directly or through weight management programs[6] such as Weight Watchers, which are now eligible for tax deduction, or through programs belonging to a specific employer or health insurance carrier. The weight loss plan should be realistic[53] (even 5%–10% weight loss has been shown to be metabolically beneficial) and mindful of the patient's situation. Switching medications to an efficacious antimanic agent with a favorable metabolic safety profile should be discussed directly with the treating psychiatrist and psychiatric care team,[6,7] highlighting the need for a collaborative approach to patient care. It is worth keeping in mind that, while metabolic disturbances are deleterious in the long run, hasty unilateral discontinuations of psychotropics carry the risk of severe, sometimes lethal, psychiatric decompensations. Steps should also be taken at a primary care level to address weight gain. If medication switching and dietary advice prove insufficient, adjunctive treatment to reduce weight gain may become an option.[6,7] Again, consultation with the psychiatric care team is recommended, as some drugs (e.g., stimulants) may exacerbate psychiatric symptoms, whereas others have negligible interference with psychotropic medications (e.g., orlistat).

Regular monitoring for future metabolic disturbances should be part of Mr. A's ongoing care plan, and treatment should be provided by the primary care team should any issues be detected.

CONCLUSIONS

Primary care professionals have an important part to play in the physical health care of people with mental illness, as they are well positioned to monitor metabolic disturbances and should do so regularly. While psychiatrists and other mental health care providers have a role in physical health monitoring, they should not do so in isolation. Long-term treatment requires careful clinical monitoring over time to become the standard of care in both mental and primary health care, thus ensuring that patients get the same level of medical care available to the general population. With careful collaboration and awareness between services, the impact of medical comorbidity on cardiovascular disease mortality in patients with mental illness can be reduced.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), molindone (Moban), olanzapine (Zyprexa), orlistat (Xenical), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal).

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