

# Metabolic Syndrome and Mental Illness

John W. Newcomer, MD

## Abstract

Patients with mental illnesses such as schizophrenia and bipolar disorder have an increased prevalence of metabolic syndrome and its components, risk factors for cardiovascular disease and type 2 diabetes. Although the prevalence of obesity and other risk factors such as hyperglycemia are increasing in the general population, patients with major mental illnesses have an increased prevalence of overweight and obesity, hyperglycemia, dyslipidemia, hypertension, and smoking, and substantially greater mortality, compared with the general population. Persons with major mental disorders lose 25 to 30 years of potential life in comparison with the general population, primarily due to premature cardiovascular mortality. The causes of increased cardiometabolic risk in this population can include nondisease-related factors such as poverty and reduced access to medical care, as well as adverse metabolic side effects associated with psychotropic medications, such as antipsychotic drugs. Individual antipsychotic medications are associated with well-defined risks of weight gain and related risks for adverse changes in glucose and lipid metabolism. Based on the medical risk profile of persons with major mental illnesses, and the evidence that certain medications can contribute to increased risk, screening and regular monitoring of metabolic parameters such as weight (body mass index), waist circumference, plasma glucose and lipids, and blood pressure are recommended to manage risk in this population. Treatment decisions should incorporate information about medical risk factors in general and cardiometabolic risk in particular. In addition to the implications for individual clinicians, the problem of disparity in meeting healthcare needs for persons with mental illness in comparison with the general population has become an important public policy concern, with recent recommendations from the National Association of State Mental Health Program Directors and the Institute of Medicine. This article provides an overview of cardiometabolic risk in patients with major mental illness and describes steps for risk reduction.

(*Am J Manag Care. 2007;13:S170-S177*)

Patients with major mental illnesses such as schizophrenia and bipolar disorder have increased risks of morbidity and mortality compared with the general population, with a 25- to 30-year shorter life span due primarily to premature cardiovascular disease (CVD) (eg, myocardial infarction [MI], stroke).<sup>1-4</sup> Key modifiable risk factors that contribute to excess morbidity and mortality include cardiometabolic factors, such as overweight and obesity, dyslipidemia, diabetes, hypertension, and smoking.<sup>1-4</sup> Although these risk factors are present within the general population,<sup>5</sup> epidemiologic data suggest that patients with major mental illnesses have an increased prevalence of some or all of these risk factors.<sup>6</sup> Treatment with psychotropic medications, including second-generation, or atypical, antipsychotic medications, can also be associated with adverse metabolic effects.<sup>7</sup>

This article provides an overview of cardiometabolic risk in patients with mental disorders such as schizophrenia and bipolar disorder, and associated increases in morbidity and mortality. Potential treatment-related effects are also discussed, along with considerations for managing risk.

## Metabolic Syndrome: Definition and Risks

Metabolic syndrome has been used to describe a grouping of cardiometabolic risk factors associated with insulin resistance, including<sup>8</sup>:

- Abdominal obesity
- Atherogenic dyslipidemia
- Elevated blood pressure (BP)
- Glucose intolerance
- Prothrombotic state
- Proinflammatory state

These metabolic risk factors are associated with the development of CVD, including coronary heart disease (CHD) and cerebrovascular disease, as well as type 2 diabetes mellitus (T2DM). **Table 1** presents clinical criteria established by the National Cholesterol Education Program (NCEP) to define the metabolic syndrome.<sup>9</sup>

**Address correspondence to:** John W. Newcomer, MD, Professor of Psychiatry, Psychology and Medicine, Medical Director, Center for Clinical Studies, Washington University School of Medicine, 660 S Euclid, St Louis, MO 63110. E-mail: newcomerj@wustl.edu.

**Disclosure:** Dr Newcomer has received grant/research support from the National Institute of Mental Health, the National Alliance for Research on Schizophrenia and Depression, the Sidney R. Baer Jr. Foundation, Janssen, Pfizer, Bristol-Myers Squibb, and Wyeth, and is a consultant for the following: Janssen; Pfizer; Bristol-Myers Squibb; AstraZeneca; GlaxoSmithKline; Organon; Solvay; Wyeth; consultant to litigation: Compact Clinicals.

Abdominal obesity and related increases in insulin resistance are important factors that can contribute to excess morbidity and mortality.<sup>8</sup> Obesity can lead to insulin resistance, or a reduced tissue sensitivity to insulin actions, which is associated with the development of other CVD risk factors, including dyslipidemia, prothrombotic and proinflammatory states, and diabetes.<sup>1,10,11</sup> The association between increasing body mass index (BMI) and cardiovascular risk and mortality is well established.<sup>8-12</sup> Central adiposity (ie, visceral abdominal adiposity) is particularly associated with insulin resistance<sup>12</sup> and increased risk for T2DM and CVD.

### Cardiometabolic Risk in Mental Illness: Morbidity and Mortality

The prevalence of cardiometabolic risk factors is higher among patients with mental illness than in the general population.<sup>1,6</sup> Most studies of metabolic syndrome or individual metabolic risk factors have been conducted in patients with schizophrenia or depression, but the evidence is consistent with more limited information for other serious mental disorders, such as bipolar disorder.<sup>6,13,14</sup> Specifically, increased rates of insulin resistance and diabetes have been reported in association with schizophrenia and depression, including limited observations in unmedicated patients.<sup>14</sup> Hypothesized contributing factors include smoking, poor nutrition, poverty, urbanization, and sedentary lifestyle,<sup>13</sup> as well as adverse effects associated with psychotropic medications that include some of the second-generation antipsychotics (see **Cardiometabolic Risk and Antipsychotic Agents** below).<sup>7</sup>

**Reduced access to medical care.** Another potential contributor to the medical risk observed in mental health patients involves access to medical care. A review of community-based mental healthcare of patients with schizophrenia, major depression, dysthymia, bipolar disorder, anxiety disorder, panic disorder, obsessive-compulsive disorder, or alcohol abuse found significant limitations in the treatment of these patients.<sup>15</sup> The reduced availability of healthcare services, combined with socioeconomic factors that make it difficult for some patients to work, retain healthcare insurance, and pursue care complicate the identification and

**Table 1. NCEP Clinical Criteria for Metabolic Syndrome\***

Risk Factor	Defining Level
Abdominal obesity	Waist circumference
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
BP	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL

\*Metabolic syndrome is diagnosed when ≥3 risk factors are present.  
NCEP indicates National Cholesterol Education Program; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure.  
Source: Adapted with permission from Reference 9.

treatment of comorbid medical conditions. In addition, specialization among healthcare professionals may result in reduced attention to overall medical health (ie, a psychiatrist may focus solely on treatment for bipolar disorder, but may not monitor for cardiometabolic risk factors).<sup>15</sup>

**Cardiometabolic risk.** Patients with mental illnesses such as schizophrenia and bipolar disorder have a higher prevalence of cardiometabolic risk factors compared with the general population. Obesity, hyperglycemia, smoking, and dyslipidemia are key modifiable risk factors for CVD and diabetes that are all more prevalent among patients with schizophrenia and bipolar illness.<sup>7</sup>

**Impact of reduced primary and secondary prevention on mortality.** Patients with major mental illnesses such as schizophrenia and bipolar disorder have a substantially higher risk of death compared with the general population. A study of Medicare patients admitted to the hospital for treatment of MI indicated that patients with comorbid mental illness of any type had an increased 1-year mortality rate of approximately 19%.<sup>16</sup> Overall, the life expectancy of patients with major mental disorders is substantially shorter compared with the general population. An early study indicated that patients with schizophrenia had a 20% shorter life span

compared with the general population.<sup>1</sup> A more recent US study, however, indicated an even greater reduction in life span for those with major mental illness. This study examined age-adjusted death rates, standardized mortality ratios, and years of potential life lost for public mental health clients compared with the general population in 6 states over a period of several years. Patients with mental illness died at substantially younger ages than the general population. For those states in which both inpatient and outpatient data were available, the mean number of potential years of life lost for patients with major mental illnesses ranged from 25 to 30 years compared with the general population.<sup>2</sup> CHD was the leading cause of death among patients with mental illness in all 6 states, similar to the ranking of heart disease in the general population for each state and for the United States as a whole, but with earlier cardiac death in the mentally ill.

### Screening and Treatment Recommendations

Modifiable and nonmodifiable risk factors can contribute to overall cardiometabolic risk. It is important to assess modifiable risk factors in individual patients to evaluate patient risk of cardiovascular and metabolic diseases.<sup>1</sup> The association between mental illness and increased cardiometabolic risk, particularly the association between psychiatric medications and risk, suggests a role for psychiatrists and other mental healthcare clinicians in monitoring risk and in assessing risk in relation to prescribing antipsychotic medications. Modifiable risk factors that should be evaluated at or near baseline and serially after prescription of antipsychotics include:

- weight
- BMI
- waist circumference
- fasting plasma lipids (total, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol, and triglycerides)
- fasting and/or postload (or perhaps postprandial) plasma glucose
- BP

Patients who smoke should be instructed to quit and should be provided with support, including counseling and smoking cessation aids. Laboratory parameters should be monitored periodically, pay-

ing particular attention to changes in any value after initiation of a new antipsychotic agent.<sup>1</sup>

Weight gain associated with atypical antipsychotic agents generally occurs within the first few months after initiation and may not stabilize for more than a year.<sup>6</sup> The American Diabetes Association (ADA) recommends weight monitoring at 4, 8, and 12 weeks after initiating a change in antipsychotic therapy, and quarterly thereafter. A weight gain of  $\geq 5\%$  of baseline weight may signal the need to switch to a different atypical antipsychotic agent. In addition to monitoring by physicians, patients should be encouraged to track their own weight and waist circumference.<sup>6</sup>

Similar recommendations for weight, glucose, and lipid monitoring come from the Mount Sinai Conference, which brought together psychiatrists, endocrinologists, and other medical experts to develop guidelines for the routine monitoring of adult schizophrenia patients receiving antipsychotic therapy.<sup>17</sup> These guidelines do, notably, recommend that patients with schizophrenia should be considered at high risk for CHD. Therefore, based on the NCEP guidelines, their lipid profile might need to be monitored more frequently (ie, every 2 years for normal LDL-C levels, and every 6 months for LDL-C  $>130$  mg/dL) than is recommended by the ADA/American Psychiatric Association consensus statement. The Mount Sinai guidelines suggest that fasting glucose or glycated hemoglobin (A1C) could be used for glucose monitoring, whereas the ADA recommendations for screening in the general population advise against the use of A1C because of its relative insensitivity as a screening measure.

The introduction of regular routine monitoring should allow for the early detection of changes in these important risk factors, and so improve the overall long-term health of patients with schizophrenia and other mental illnesses.

Confirmed laboratory values that exceed defined criteria (Table 1) should result in intervention, including therapeutic lifestyle change, consideration of changes in potentially contributory psychotropic medications, and referral to a primary care provider or an appropriate specialist. Coordination of care between psychiatric and primary care providers is essential under these circumstances. After measurement at or near baseline,

fasting plasma glucose, lipid levels, and BP should be assessed at least 3 months after initiation of antipsychotic medication. Thereafter, quarterly measurement of weight and annual monitoring of plasma glucose, lipid levels, and BP is recommended.<sup>6</sup> Patients who develop abnormal glucose and lipid profiles should be evaluated promptly, even if no symptoms are noted.

### Access to Care

Patients with major mental illnesses should enjoy access to medical care similar to persons in the general population, but there is strong evidence of disparities in the level of healthcare provided to persons with mental illnesses compared with the general population. The World Health Organization has suggested that persons with mental disorders have a right to healthcare comparable to that received by the general population.<sup>18</sup> Recent well-controlled studies indicate, however, that persons with mental illnesses receive reduced levels of healthcare.<sup>19</sup> In addition to reductions in primary prevention,<sup>16</sup> persons with mental health conditions receive less secondary care.<sup>19</sup>

### Cardiometabolic Risk and Antipsychotic Agents

Patients with schizophrenia and bipolar disorder are commonly prescribed antipsychotic agents. First-generation antipsychotic use has decreased as the use of second-generation antipsychotics, also known as atypical antipsychotics, has risen substantially over the past decade. Randomized clinical trials have demonstrated the efficacy of second-generation antipsychotic medications in controlling a broad range of symptoms, and their tolerability with regard to neurologic adverse events, such as drug-induced Parkinsonism, is improved compared with first-generation agents.<sup>20,21</sup> Second-generation antipsychotic agents, however, like first-generation agents, have been observed to induce weight gain that varies in magnitude across individual agents (Table 2).<sup>4</sup>

Related in part to their propensity to induce weight gain, some second-generation antipsychotic agents have been associated with an increased risk for dyslipidemia and diabetes.<sup>4</sup> Initial case reports of new-onset diabetes, ketoacidosis, hyperglycemia, and dyslipidemia, as well as exacerbation of existing

diabetes and dyslipidemia, in patients treated with antipsychotics prompted evaluation of the relationship between these medications and metabolic effects.<sup>7,22</sup> The effects of antipsychotic agents on weight is important, because increasing adiposity can contribute to increasing cardiometabolic risk.<sup>6,8</sup> In addition to affecting metabolic risk through increased adiposity, some antipsychotics may also have direct effects on metabolic risk.<sup>7</sup>

Pharmacoepidemiologic studies in healthcare databases overall suggest increased risk for incident diabetes and dyslipidemia in treated patients compared with nonpatient groups, with a variable pattern of differential risk across agents but relatively consistent evidence of increased risk with clozapine and olanzapine.<sup>7</sup> A number of these reported observational analyses have used large administrative or health plan databases to test the strength of the association between treatment with specific antipsychotic medications and the presence of diabetes.<sup>23-39</sup> Their common approach has been to identify the association within a database between the use of specific antipsychotic medications and the presence of  $\geq 1$  surrogate indicator of diabetes (eg, prescription of an oral hypoglycemic medication, relevant *International Classification of Diseases, Ninth Revision [ICD-9]* codes). A recent new-user cohort study in a large national sample of US Veterans Health Administration patients with schizophrenia, but without preexisting diabetes, involved 15 767 patients who initiated use of olanzapine, risperidone, quetiapine, or haloperidol after at least 3 months with no antipsychotic prescriptions. Over 1 year of observation using Cox proportional hazards regression adjusting for potential confounders, with haloperidol use as the reference condition, diabetes risk was increased with new use of olanzapine (hazard ratio [HR], 1.64; 95% confidence interval [CI], 1.22-2.19), risperidone (HR, 1.60; 95% CI, 1.19-2.14), or quetiapine (HR, 1.67;

■ **Table 2.** Atypical Antipsychotics and Weight Gain

Highest Weight Gain Risk	Moderate Weight Gain Risk	Minimal Weight Gain Risk
Clozapine	Risperidone	Ziprasidone
Olanzapine	Quetiapine	Aripiprazole

Source: Adapted with permission from Reference 4.

95% CI, 1.01-2.76).<sup>40</sup> Overall, approximately two thirds of these studies report findings suggesting that drugs associated with greater weight gain were also associated with an increased risk for diabetes compared with no treatment, conventional treatment, or a drug associated with less weight gain. The other one third of studies reported to date have generally detected either no difference between groups or a nonspecific increase in the association for all treated groups compared with untreated controls. However, these studies have a number of methodologic limitations, including relying on surrogate markers for the presence of diabetes, without direct measures of metabolism.

To clarify these findings, a recent meta-analysis<sup>41</sup> of 14 studies (11 retrospective, 5 case-control)<sup>24-28,30,32-39</sup> examined the association of diabetes incidence among patients treated with atypical antipsychotics compared with conventional or no antipsychotic treatment. All of the included studies were retrospective analyses of existing databases, with 11 retrospective cohort studies representing the vast majority of patients (n = 232 871) and 5 case-control studies (n = 40 084) of large healthcare plans (eg, Medicaid, Blue Cross/Blue Shield, Veterans Affairs). Six studies (n = 122 270) included only patients with schizophrenia diagnoses, whereas 10 studies included patients with various psychotic illnesses (n = 150 685). Data were available for clozapine, olanzapine, quetiapine, and risperidone. Meta-analyses of the association of diabetes incidence among patients treated with atypical antipsychotics were performed using conventional antipsychotics or no antipsychotic treatment as the comparator groups. All odds ratios (ORs), relative risks, and HRs included in the meta-analyses were adjusted for a variety of covariates, the most common of which were treatment duration, age, and sex. These analyses indicated that clozapine was consistently associated with an increased risk of diabetes (vs conventionals: OR, 1.37; 95% CI, 1.25-1.52; vs no antipsychotics: OR, 7.44; 95% CI, 1.59-34.75). Olanzapine was also associated with increased risk for diabetes (vs conventionals: OR, 1.26; 95% CI, 1.10-1.46; vs no antipsychotic: OR, 2.31; 95% CI, 0.98-5.46). Neither risperidone (vs conventional: OR, 1.07; 95% CI, 1.00-1.13; vs no antipsychotic: OR, 1.20; 95% CI, 0.51-2.85) nor quetiapine (vs convention-

al: OR, 1.22; 95% CI, 0.92-1.61; vs no antipsychotic: OR, 1.00; 95% CI, 0.83-1.20) was associated with an increased diabetes risk. The results of these quantitative analyses of the association between atypical antipsychotic use and incident diabetes in large real-world databases suggest that the risk of diabetes varies among atypical antipsychotics, ranging from increases in risk relative to multiple comparators to no increase in risk for diabetes relative to any tested comparator.

Lambert et al<sup>42</sup> also examined the risk of hyperlipidemia among individuals with schizophrenia taking second-generation antipsychotics (clozapine, olanzapine, quetiapine, risperidone) compared with those taking conventional antipsychotics. A case-control study of MediCal claims data was conducted within a monotherapy inception cohort of patients who had 12 weeks' exposure to the drugs. Hyperlipidemia was defined by diagnostic claim (ICD-9: 272.1-272.4)<sup>43</sup> or prescription claim for antilipidemic agents, with hyperlipidemic patients matched by sex and age ( $\pm 3$  years) to patients who did not develop hyperlipidemia. Risk of hyperlipidemia associated with antipsychotic exposure was assessed by conditional logistic regression, controlling for age, ethnicity, prior diabetes or hypothyroidism, and exposure to other medications that increase risk of hyperlipidemia. Analyses were repeated with 24- and 52-week retrospective exposure periods. For the 12-week exposure period, olanzapine (OR, 1.20; 95% CI, 1.08-1.33) increased the risk of developing hyperlipidemia compared with other second-generation antipsychotic medications. Exposure to clozapine (OR, 1.16; 95% CI, 0.99-1.37), risperidone (OR, 1.00; 95% CI, 0.90-1.12), or quetiapine (OR, 1.01; 95% CI, 0.78-1.32) did not increase risk. Statistical tests comparing the 4 second-generation antipsychotics to one another revealed that the OR for olanzapine was greater than that for risperidone ( $P = .002$ ). Although the OR for clozapine was significant at 24 weeks (OR, 1.22; 95% CI, 1.03-1.45), increasing the exposure period to 24 or 52 weeks did not otherwise change the results. The authors concluded that compared with conventional antipsychotics, exposure to olanzapine and perhaps to clozapine increased the risk of hyperlipidemia among schizophrenia patients.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study is a major,



ongoing National Institute of Mental Health-sponsored prospective trial designed to assess the efficacy of the second-generation antipsychotic agents olanzapine, quetiapine, risperidone, and ziprasidone, with perphenazine included as a representative first-generation agent. The trial consisted of 1493 patients with schizophrenia at 57 sites in the United States. The primary outcome measure, time to all-cause discontinuation, combines patients' and clinicians' judgments of efficacy, safety, and tolerability in a global effectiveness measure that reflects their evaluation of therapeutic benefits in relation to "undesirable effects."<sup>44</sup> Secondary outcome measures include assessment of the reasons for discontinuation; for example, lack of efficacy or intolerability due to side effects, the latter including weight gain and metabolic disturbances.

Phase 1 results were published in September 2005. Patients taking olanzapine gained more weight than patients taking any other medication studied (mean weight gain, 2 lb/month), and 30% of patients in the olanzapine group gained  $\geq 7\%$  of their baseline body weight (vs 7%-16% of patients in the other groups;  $P < .001$ ). Olanzapine-treated patients also showed the greatest increases in total cholesterol (mean increase,  $9.7 \pm 2.1$  mg/dL), plasma triglycerides (mean increase,  $42.9 \pm 8.4$  mg/dL), and A1C (mean increase,  $9.7 \pm 2.1$  mg/dL), with statistically significant differences between treatment groups in each of these indices.<sup>44</sup>

CATIE phase 2 results were published in April 2006. Patients from phase 1 chose to enter 1 of 2 secondary phases. In phase 2T, which was intended to focus on tolerability issues, patients were randomized from their phase 1 treatment to olanzapine, quetiapine, risperidone, or ziprasidone<sup>45</sup> (ziprasidone was added after 24% of phase 2 enrollment had occurred). In phase 2E, intended to focus on efficacy, patients were randomized to clozapine, olanzapine, quetiapine, or risperidone.<sup>46</sup>

Of the 1493 patients eligible for phase 2 of CATIE, 444 chose to enroll in phase 2T. In CATIE phase 2T, 27% of patients randomized to olanzapine experienced a  $>7\%$  weight gain versus 13% of patients for risperidone, 13% for quetiapine, and 6% for ziprasidone ( $P = .009$ ). Olanzapine-treated patients again gained more weight than patients in the other groups (mean,  $1.3 \pm 0.6$  lb/month;  $P < .001$ ), and showed the greatest exposure-adjusted mean

increases in total cholesterol ( $17.5 \pm 5.2$  mg/dL), triglyceride ( $94.1 \pm 21.8$  mg/dL), and A1C ( $0.97\% \pm 0.3\%$ ), with statistically significant differences between treatment groups in each of these indices. Risperidone showed a mean weight loss ( $-0.2 \pm 0.4$  lb/month), with mean exposure-adjusted increases in blood glucose ( $6.9 \pm 5.8$  mg/dL) and A1C ( $0.49\% \pm 0.3\%$ ) and mean exposure-adjusted decreases in triglycerides ( $-5.2 \pm 21.6$  mg/dL) and total cholesterol ( $-3.1 \pm 5.2$  mg/dL). Quetiapine showed a mean weight gain of  $0.1 \pm 0.6$  lb/month, with mean exposure-adjusted increases in blood glucose ( $1.2 \pm 6.0$  mg/dL), A1C ( $0.61\% \pm 0.3\%$ ), triglycerides ( $39.3 \pm 22.1$  mg/dL), and total cholesterol ( $6.5 \pm 5.3$  mg/dL). Ziprasidone showed a mean weight loss ( $-1.7 \pm 0.5$  mg/dL), with mean exposure-adjusted increases in blood glucose ( $0.8 \pm 5.6$  mg/dL) and A1C ( $0.46\% \pm 0.3\%$ ), and mean exposure-adjusted decreases in triglycerides ( $-3.5 \pm 20.9$  mg/dL) and total cholesterol ( $-10.7 \pm 5.1$  mg/dL).<sup>45</sup>

Only 99 patients entered CATIE phase 2E (9% of those eligible), which may indicate reticence on the part of patients or their treating physicians to risk randomization to clozapine. Changes in weight, total cholesterol, triglycerides, and A1C were not significantly different across treatment groups in this arm of the study.<sup>46</sup> The failure to detect differences in this study arm may be attributable to the small sample size and/or a selection bias toward patients with a history of extensive prior treatment, including treatment with a high-weight-gain agent such as olanzapine, given that this arm of the study was intended for those who had experienced insufficient treatment efficacy.

Clinicians should provide ongoing monitoring for patients treated with antipsychotic agents. According to the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes, screening measures should include baseline assessment of personal and family history as well as baseline and follow-up monitoring of weight (ie, BMI), waist circumference, BP, fasting plasma glucose, and fasting lipid profile.<sup>6</sup>

## Conclusion

Persons with mental illnesses have an increased prevalence of cardiometabolic risk factors that impact morbidity and mortality. Treatment with psychotropic medications can be essential to the

quality of life for persons with mental disorders, but, in some cases, with some medications, treatment can increase cardiometabolic risk. A prudent approach to caring for persons with major mental illnesses involves monitoring cardiometabolic risk, including measurement of baseline and serial indicators for risk during antipsychotic treatment. It is advisable to involve patients in monitoring key indicators of risk, including weight and waist circumference, and to intervene when risks increase, including consultation with primary care providers and specialists. Future efforts should include ensuring continuity of care between psychiatric and general medical needs, and ensuring that persons with mental disorders have equal access to healthcare services.

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**Acknowledgment:** Dr Newcomer received an honorarium from Pfizer Inc in connection with the development of this manuscript. Editorial support was provided by Ascend Healthcare and funded by Pfizer Inc.

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