SPECIAL EDITION

PRACTICAL ISSUES *in* PSYCHIATRY

A SUPPLEMENT TO

Current PSYCHIATRY

APRIL 2005

Pharmacotherapy of schizophrenia and bipolar disorder with coexisting medical illness

FREE 1.5 CME credits

Based on a live satellite broadcast presented by Distance Learning Network on **December 9, 2004**, and developed by CURRENT PSYCHIATRY.

A DIALOGUE BETWEEN

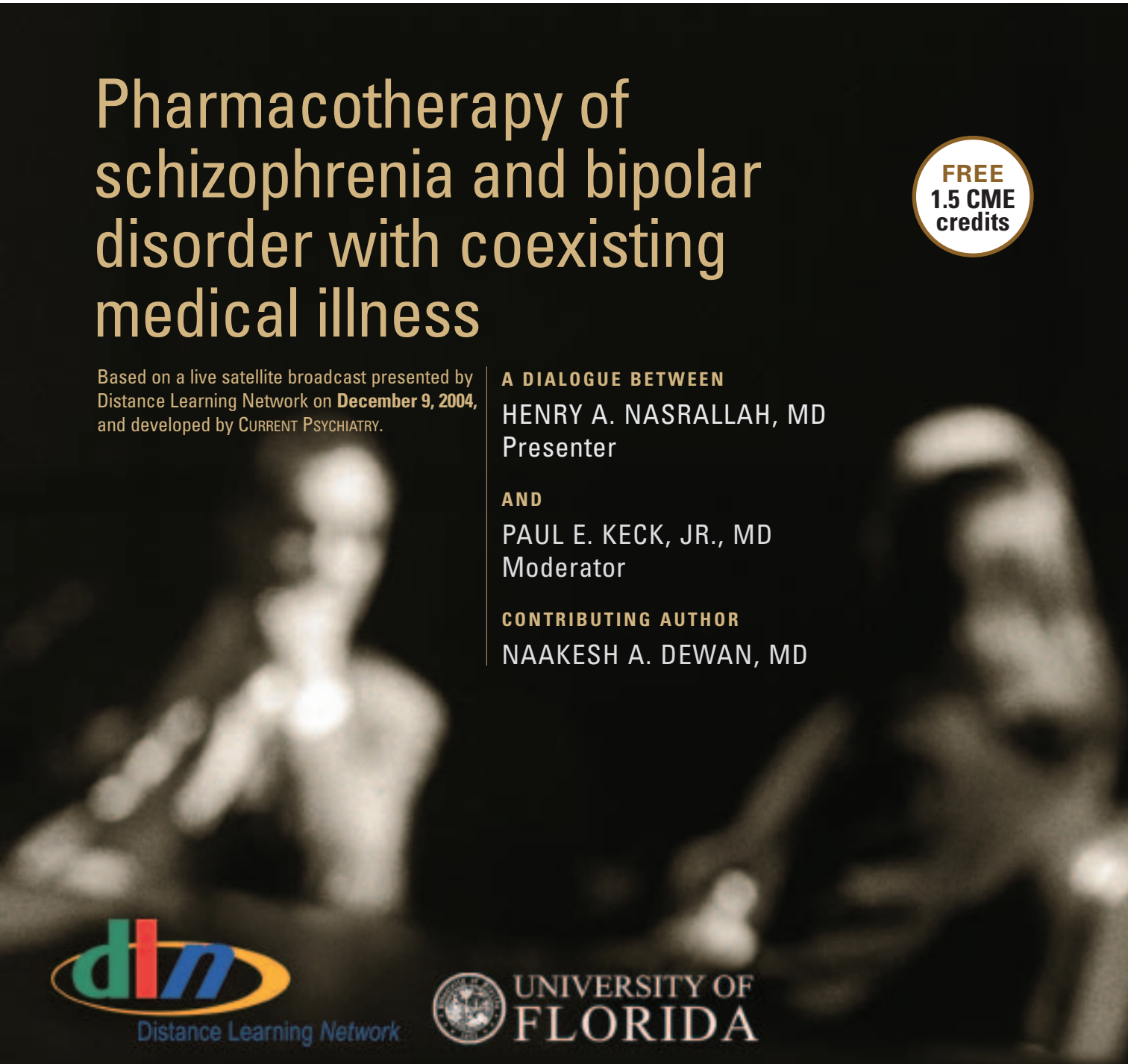
HENRY A. NASRALLAH, MD
Presenter

AND

PAUL E. KECK, JR., MD
Moderator

CONTRIBUTING AUTHOR

NAAKESH A. DEWAN, MD



dln Distance Learning Network

UNIVERSITY OF FLORIDA

Supported by an unrestricted educational grant to Distance Learning Network, Inc. from Bristol-Myers Squibb and Otsuka America Pharmaceutical.

SPECIAL EDITION

Pharmacotherapy of schizophrenia and bipolar disorder with coexisting medical illness

Needs assessment: Medical ailments often co-occur with schizophrenia and bipolar disorder and contribute to the increased morbidity and mortality in those disorders. Cardiovascular disease, cancer, chronic obstructive pulmonary disease (COPD), metabolic disorders, and human immunodeficiency virus (HIV) are examples of medical conditions commonly found in individuals with schizophrenia or bipolar disorder. Besides suicide—which accounts for a high proportion of deaths in bipolar disorders and schizophrenia—heart disease, stroke, diabetes, COPD, and HIV are significantly more prevalent in those 2 psychiatric brain disorders than in the general population.

In addition to increasing mortality, medical conditions can complicate the management of schizophrenia and bipolar disorder, especially the pharmacotherapeutic aspects. Yet, there are very few published guidelines for the treatment of psychosis or mood disorders in the presence of medical comorbidities. Practically all controlled clinical trials exclude patients with coexisting medical morbidities and, thus, offer little guidance for practitioners treating medically ill schizophrenia and bipolar patients. In this activity, rational guidelines for the appropriate use of antipsychotics, mood stabilizers, and antidepressants in the presence of medical conditions will be discussed. Optimal drug selection will reduce adverse effects, minimize medical illness exacerbations, avert potential drug-drug interactions, and maximize both medical and psychiatric stability in schizophrenia and bipolar disorder with coexisting medical conditions.

Learning objectives: At the end of this educational activity, participants should be able to:

1. Discuss the evidence and clinical guidelines regarding the optimal use of antipsychotics to treat psychosis in patients with cardiovascular disease (CVD), obesity, cancer, HIV, and lung disease
2. Recognize the evidence and clinical guidelines regarding the optimal use of mood stabilizers to treat manic and depressive symptoms in patients with CVD, obesity, cancer, HIV, and lung disease
3. Apply the evidence and clinical guidelines regarding the optimal use of antidepressants in the treatment of depressive symptoms in patients with CVD, obesity, cancer, HIV, and lung disease

Audience: Psychiatrists and other health care professionals who manage patients with bipolar disorder or schizophrenia

Program release date: April 2005

Expiration date: April 2007

Accreditation statement / credit designation: Distance Learning Network, Inc. is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Distance Learning Network, Inc. designates this educational activity for a maximum of 1.5 hours of category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit he/she actually spent in the educational activity.

The University of Florida College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity is approved for 1.5 contact hours (0.15 CEUs) in states that recognize ACPE. To receive credit you must attend the entire session and complete the evaluation form. The University of Florida College of Pharmacy will provide statements of Continuing Education Credit within four weeks after the session. (012-999-04-340-H01)

Distance Learning Network, Inc. has been approved as a provider of continuing education in nursing by the Utah Nurses Association, which is accredited as an approver of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation. The participant will be awarded 1.8 contact hours of credit for attendance completion of supplemental materials.

Distance Learning Network, Inc. is approved by the American Psychological Association to offer continuing education for psychologists. Distance Learning Network, Inc. maintains responsibility for the program. The participant will be awarded 1.5 contact hours of credit for attendance and completion of supplemental materials.

Commercial Support: This activity has been supported by an unrestricted educational grant to Distance Learning Network, Inc. from Bristol-Myers Squibb and Otsuka America Pharmaceutical.

Co-sponsor Statement: This activity is co-sponsored by Distance Learning Network, Inc. and the University of Florida Colleges of Medicine and Pharmacy.

Conflict of Interest Financial Disclosure: As a sponsor accredited by the ACCME, it is the policy of Distance Learning Network, Inc. to require the disclosure of the existence of any significant financial interest or any other relationship a faculty member or a sponsor has with the manufacturer(s) of any product discussed in an education presentation. The presenters reported the following:

Dr Dewan reports that he is on the speakers' bureaus for Eli Lilly and Company, Janssen Pharmaceutica Products, L.P., and Pfizer Inc. Dr Dewan does not intend to discuss unapproved/investigative use of commercial products/devices.

Dr Keck reports that he receives grants/research support from Abbott Laboratories, the American Diabetes Association, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, GlaxoSmithKline, Elan Corporation, Eli Lilly and Company, Janssen Pharmaceutica Products, L.P., Merck & Co., Inc., the National Institute of Mental Health, the National Institute of Drug Abuse, Organon Pharmaceuticals USA Inc., Ortho-McNeil, Pfizer Inc., the Stanley Medical Research Institute, and UCB Pharma. He is on the advisory boards of Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Corcept Therapeutics, GlaxoSmithKline, Janssen Pharmaceutica Products, L.P., Jazz Pharmaceuticals, Inc., Eli Lilly and Company, Novartis Pharmaceuticals, Ortho-McNeil, Pfizer Inc., UCB Pharma, Shire US Inc., and Wyeth. He reports no other commercial relationships. Dr Keck does not intend to discuss unapproved/investigative use of commercial products/devices.

Dr Nasrallah reports that he receives grants/research support from AstraZeneca Pharmaceuticals, Janssen Pharmaceutica Products L.P., and Pfizer Inc. He is a consultant to Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Janssen Pharmaceutica Products, L.P., and Pfizer Inc. He is on the advisory boards of Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Janssen Pharmaceutica Products, L.P., and Pfizer Inc., and is on the speakers' bureaus for Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Janssen Pharmaceutica Products, L.P., and Pfizer Inc. He reports no other commercial relationships. Dr Nasrallah does intend to discuss unapproved/investigative use of commercial products/devices.

FACULTY

NAAKESH A. DEWAN, MD
President
Center for Mental Healthcare Improvement
Clearwater, Florida

PAUL E. KECK, JR., MD
Vice Chair for Research
Professor of Psychiatry, Pharmacology, and Neuroscience
Department of Psychiatry
University of Cincinnati College of Medicine
Mental Health Care Line and General Clinical Research Center
Cincinnati Veterans Affairs Center
Cincinnati, Ohio

HENRY A. NASRALLAH, MD
Associate Dean
Professor of Psychiatry, Neurology, and Neuroscience
University of Cincinnati College of Medicine
Cincinnati, Ohio

Current PSYCHIATRY

Introduction

Patients with schizophrenia or bipolar disorder often have serious co-occurring medical illnesses such as cardiovascular disease, respiratory disease, asthma, chronic obstructive pulmonary disease, diabetes, obstructive sleep apnea, obesity, cancer and human immunodeficiency virus infection/acquired immune deficiency syndrome.[1,2] Thus, psychiatrists must manage both the psychiatric disorder and preexisting or emerging medical conditions, some of which are often treatment-related.

Further, schizophrenia and bipolar disorder are associated with behaviors and lifestyle issues that increase the risk for serious medical conditions. Obesity, binge eating, substance abuse, smoking, lack of exercise, and poor nutrition are widespread among patients with psychiatric disorders.[3,4]

This publication is based on *Pharmacotherapy of Schizophrenia and Bipolar Disorder With Coexisting Medical Illness*, a live presentation distributed via satellite broadcast by Distance Learning Network on December 9, 2004. It has been adapted by *Current Psychiatry*. Here, internationally known experts in the fields of schizophrenia and bipolar disorder provide practical strategies to help clinicians effectively meet the needs of patients with serious psychiatric disorders and a variety of medical conditions associated with significant morbidity and mortality. This publication will provide general guidelines regarding these important clinical issues.

We hope you find this material useful in your practice.

Naakesh A. Dewan, MD
Paul E. Keck, Jr., MD
Henry A. Nasrallah, MD

References

1. Kilbourne AM, Cornelius JR, Han X, et al. Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disord*. 2004;6:368-373.
2. Meyer JM, Nasrallah HA, eds. *Medical Illness and Schizophrenia*. Washington, DC: American Psychiatric Publishing; 2003.
3. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship with historical illness variables in 288 patients with bipolar disorder. *Am J Psychiatry*. 2001;158:420-426.
4. Green AI, Canuso CM, Brenner MJ, Wojcik JD. Detection and management of comorbidity in patients with schizophrenia. *Psychiatr Clin North Am*. 2003;26:115-139.

Psychiatric disorders and medical comorbidities

A growing problem with severe implications for worldwide health

Naakesh A. Dewan, MD

The number of patients who experience both psychiatric disorders and medical comorbidities is significant and likely to increase. In 1990, psychiatric diseases represented more than 10% of the worldwide disease burden. The percentage is expected to increase to 15% by 2020.

Severity weights for various disorders also underscore the impact on function associated with psychiatric illnesses. The World Health Organization (WHO) reported that active psychosis had a disease severity equivalent to that of quadriplegia (0.70 to 1.00).[1] Unipolar major depression, blindness, and paraplegia received ratings of 0.50 to 0.70. As a comparison, rheumatoid arthritis and angina received ratings of 0.12 to 0.24 while mild mental retardation and Down syndrome received a rating of 0.36 to 0.50.

Psychiatric illness occurs frequently in persons who have cardiovascular disease, diabetes, and chronic obstructive pulmonary disease—conditions cited by the WHO as the leading sources of disease burden in established market economies (**TABLE 1**).[1] Patients with psychiatric disorders are likely to abuse alcohol and to smoke, and because of smoking, they are at risk for lung and upper respiratory cancers.

Thus, serious psychiatric disorders exist with equally serious medical comorbidities. To effectively treat both psychiatric disorders and coexisting medical conditions, psychiatrists need to better understand drug-to-drug, drug-to-disease, and disease-to-disease interactions in patients with existing or emerging medical comorbidities. They need to consider such comorbidities when selecting appropriate pharmacotherapy. They must monitor the safety of selected agents, particularly as multiagent pharmacotherapy becomes increasingly common. ■

Table 1
The worldwide disease burden

	Total (millions)	Totals (%)
All Causes	**98.7**	**9.0**
1. Ischemic disease	8.9	6.8
2. Unipolar major depression	**6.7**	**5.0**
3. Cardiovascular disease	5.0	4.7
4. Alcohol use	4.7	4.4
5. Road traffic accidents	4.3	4.4
6. Lung and UR cancer	3.0	3.0
7. Dementia and degenerative CNS	**2.8**	**2.9**
8. Osteoarthritis	2.7	2.7
9. Diabetes	2.4	2.4
10. COPD	2.3	2.3

UR, upper respiratory; CNS, central nervous system; COPD, chronic obstructive pulmonary disease

Source: Murry CJL, Lopez AD, eds.[1]

Current PSYCHIATRY

The challenge for psychiatrists

Issues in diagnosing and managing patients with psychiatric disorders and medical illnesses

A DIALOGUE BETWEEN
Henry A. Nasrallah, MD, and Paul E. Keck, Jr., MD

KECK: Henry, could you review the key issues we face in treating patients with schizophrenia or bipolar disorder who have preexisting or emerging treatment-related comorbid medical conditions?

NASRALLAH: The important questions for clinicians are:

- How do I manage schizophrenia or bipolar disorder without exacerbating a preexisting medical illness?
- How do I treat the medical illness without worsening the primary psychiatric disorder?
- How do I manage a patient with more than 1 medical comorbidity?
- How do I minimize adverse interactions between the psychotropic and nonpsychotropic medications prescribed to a given patient?

Clinicians need to remember that patients with either bipolar disorder or schizophrenia have higher standard mortality ratios (SMRs)—observed/expected deaths—from medical causes when compared with the general population. In patients with bipolar disorder, SMRs are 1.9 in men and 2.1 in women.[2]

People with various diseases who also have schizophrenia have higher SMRs. In those with

- Diabetes and schizophrenia, SMRs are 2.7 times those of the general population.
- Cardiovascular disease (CVD), cerebrovascular disease, coronary heart disease (CHD) and schizophrenia, SMRs are 2.3 times those of the general population.
- Respiratory diseases and schizophrenia, SMRs are 3.2 times those of the general population.
- Infectious diseases and schizophrenia, SMRs are 3.4 times those of the general population.[3]

Medical illnesses also develop with treatment. Diabetes, CVD, hyperlipidemia, and hyperprolactinemia may worsen with the weight gain associated with psychotropic agents.

Clinicians need to think about primary prevention or management of these comorbidities in addition to providing psychiatric treatment.

Medical comorbidities: The silent killers

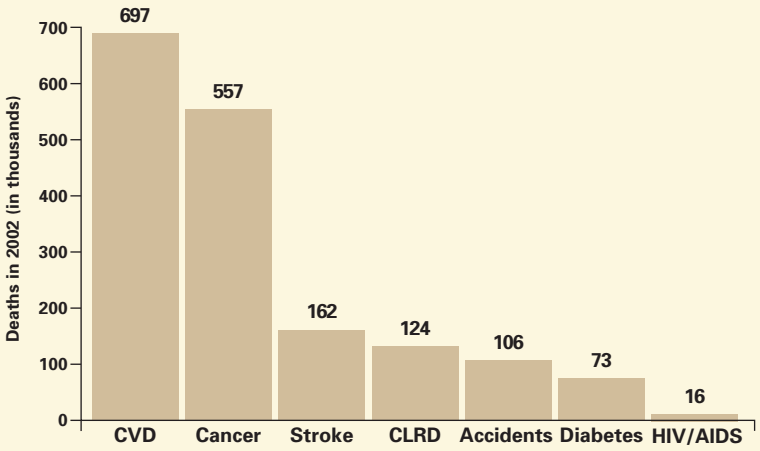
KECK: You raise a very important point. We always evaluate the risk of suicide in patients with serious psychiatric disorders. We need to be equally attentive to medical comorbidities, which function as "silent" killers. The significance of these comorbidities in patients with psychiatric disorders has been ignored in both the clinical and research settings.

NASRALLAH: Yes. Leading causes of death in the United States are shown in **FIGURE 1**.[4,5] These and other conditions are frequently associated with bipolar disorder or schizophrenia. Further, the presence of these psychiatric disorders increases the risk of mortality associated with some of these diseases.

KECK: Consequently, if we better manage medical conditions associated with bipolar disorder or

Figure 1

Causes of death in the United States



CVD, cardiovascular disease; CLRD, chronic lower respiratory disease; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome
Source: National Center for Health Statistics; Center for Disease Control and Prevention.[4,5]

schizophrenia, we might be able to prolong our patients' lives.

NASRALLAH: Absolutely. I tell our trainees that they must be physicians first and psychiatrists second: These illnesses can kill your patient. Even if you succeed in treating the psychosis, the patient will die young if these comorbidities are not managed.

KECK: We often face the problem of a psychiatric illness plus several co-occurring medical morbidities.

Patient behaviors and risk for comorbidities

NASRALLAH: We face an additional challenge as well: Many medical comorbidities stem from poor health-related behaviors. Let's briefly look at modifiable risk factors.

- 40% of persons with schizophrenia are obese, compared with 20% of the general populace. Overweight or obesity is a key risk factor for several diseases. Many factors lead to obesity, and lifestyle factors associated with psychiatric disorders play a part.
- 70% to 80% of people with schizophrenia smoke, compared with 25% in the general population. Smoking, too, is a risk factor for many illnesses.
- 47% of people with schizophrenia have a history of substance abuse.[6]

Our patients are often sedentary, have poor nutrition, and so on. These behaviors, too, add to the risk for several medical comorbidities.

KECK: Studies in patients with bipolar disorder also show a greater prevalence of obesity. In one investigation, 68% of patients with bipolar disorder were overweight; in another, 57% were overweight.[7,8] Weight status is associated with the number of previous depressive episodes; most weight gain has been shown to occur during acute treatment.

Additionally, our patients often are unable to obtain appropriate treatment. When they visit a primary care physician, they sometimes fail to delineate their symptoms in a clear-cut manner. The clinician may not know that the patient is experiencing an illness. Literature dating from reports by Kraepelin indicates that people with schizophrenia have a high pain threshold. This actually constitutes a risk for our patients: If you don't feel pain, you may not perceive that you have an illness, or you may delay seeking medical help.

Recent epidemiologic data also indicate that routine screening tests for such conditions as high cholesterol or breast cancer are less likely to be performed in patients with mental illness. Therefore, illnesses are likely to be diagnosed at a more pronounced stage.[9,10]

Other factors also affect treatment. For example, our patients are often underinsured. They tend not to report sexually transmitted diseases.

To make matters worse, preexisting, treatment-related, and behavior-related comorbidities occur within a very fragmented health care system. Many of our patients lack access to optimum primary care. In short, they are in jeopardy for a variety of reasons. ■

Cardiovascular disease and psychiatric disorders:
Strategies to reduce the risk for morbidity and mortality

KECK: Could we review specific comorbidities?

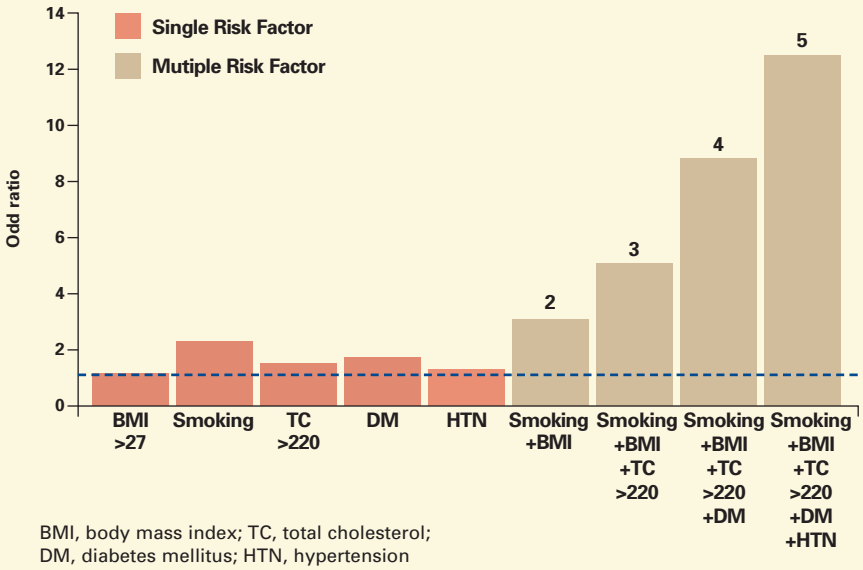
NASRALLAH: Certainly. Let's start with CVD, the number 1 killer in the United States. Risk factors include obesity, hypertension, smoking, dyslipidemia, and hyperglycemia.[11]

Death from CVD in patients with schizophrenia is 2 times higher than in the general population.[6] Further, CVD risk factors include conditions common in individuals with schizophrenia or bipolar disorder, such as obesity and smoking.

A brief review of data from the Framingham Study[12] indicates the importance of multiple risk factors for CVD. This study enrolled 2489 men and 2856 women aged 30 to 74 years and followed them for 12 years. A total of 383 men and 227 women developed CHD. As indicated in **FIGURE 2**,[12] the presence of a single risk factor increased the risk of CHD. However, the presence of multiple risk factors greatly elevated the risk. Clearly, our patients—who tend to smoke, be overweight, and have elevated cholesterol and blood pressure levels—are at the highest of risk.

Figure 2

Risk of cardiovascular disease and number of risk factors



BMI, body mass index; TC, total cholesterol; DM, diabetes mellitus; HTN, hypertension
Source: Wilson PW, et al.[12]

Table 2

Thymoleptic agents and cardiovascular events

Agents	Conduction	Coagulation	Blood Pressure
TCAs	Proarrhythmic	NA	↓
SSRIs	NA	Antiplatelet	NA
Venlafaxine	NA	NA	↑ at higher doses
Bupropion	NA	NA	↑ at higher doses
Lithium	Usually minor proarrhythmic	NA	NA
Valproate	NA	Interactions with warfarin	NA
Lamotrigine	NA	NA	NA

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor

Effect of psychotropic agents on CVD or CVD risk factors

NASRALLAH: In selecting the most appropriate agent for patients with

Table 3
Antipsychotic agents and cardiovascular effects

Agents	Conduction	Coagulation	Blood Pressure
TDZ, MDZ, SLP, PMZ, DRP	QTc ↑	NA	↓
Clozapine	Rare myocarditis	NA	Rare severe ↓↓
Olanzapine	NA	NA	↓
Risperidone	NA	NA	↓
Quetiapine	Mild QTc ↑	NA	↓
Ziprasidone	QTc ↑	NA	↓
Aripiprazole	NA	NA	↓

TDZ, thioridazine; MDZ, mesoridazine; SLP, sulpiride; PMZ, pimozide; DRP, droperidol

CVD or CVD risk factors, we need to consider the cardiovascular effects of available psychotropic agents. As shown in **TABLE 2**, the potential proarrhythmic effects of tricyclics are well established.[12]

A modest risk of increase in blood pressure is associated with venlafaxine and bupropion. Valproate may result in pharmacokinetic interactions with warfarin.

Antipsychotics have somewhat more substantial cardiovascular effects (**TABLE 3**). Thioridazine, mesoridazine, sulpiride, pimozide, and droperidol are associated with QTc prolongation. Quetiapine and ziprasidone also may pose minor risks. Additionally, these agents also produce some orthostatic hypotension. Although this effect is uncommon, it could be of significance for a patient with a history of cerebrovascular disease or CVD or one who is receiving medication that might lower blood pressure additively. ■

Smoking in persons with schizophrena or bipolar disorder:
Effect on patient health and potential need for dosing adjustments

NASRALLAH: Smoking is probably one of the most preventable causes of morbidity and mortality. Patients with schizophrenia smoke heavily.

Among people with schizophrenia, the prevalence of cigarette smoking has been estimated at 56% to 88% compared with the overall prevalence in the United States of 25%.[13] A variety of factors may be involved: People with schizophrenia may use tobacco to self-medicate. Abnormalities in the brain-reward pathways make them particularly vulnerable to tobacco and other drug use. Genetic and environmental factors independently associate with smoking and schizophrenia.

KECK: Similar estimates of overall prevalence of tobacco use have been estimated for persons with bipolar disorder.[14]

NASRALLAH: Additionally, patients who smoke more heavily are exposed to more toxicity. Clinicians should consider the potential role of smoking in their patients with diabetes and insulin resistance. We often think that these conditions are related to treatment medication, but we need also to consider the potential role of smoking and try to help our patients quit.

Management issues for clinicians

KECK: Smoking affects how some agents are metabolized. Patients who use tobacco may need more frequent monitoring of drug levels. Bipolar patients may require dosage adjustments during the maintenance phase of treatment. Tobacco use induces the CYP 1A2 enzyme system, which is involved in the

metabolism of olanzapine and clozapine as well as some conventional antipsychotics, such as haloperidol and chlorpromazine.[13] Further, patients who successfully stop smoking will most likely need dosage reduction of medications to decrease the likelihood of antipsychotic side effects.

Risperidone, quetiapine, ziprasidone, and aripiprazole are not likely to be affected by smoking cessation because the CYP 1A2 pathway is not involved. Similarly, antiepileptic agents are unaffected, with the exception of carbamazepine, a CYP 1A2 substrate inducer.[15] ■

Psychiatric disorders and obesity: Factors that affect treatment decisions

NASRALLAH: Obesity, like smoking, cuts across many of the conditions we encounter. Obesity or weight gain is associated with not only CVD but also the development of type 2 diabetes, gallbladder disease, osteoarthritis, dyslipidemia, obstructive sleep apnea (OSA), and breast, prostate, and colon cancers.[10,16,17] Psychotic and mood disorders represent independent risk factors for obesity. Individuals with mood and psychotic disorders exhibit a cluster of risk factors for being overweight or obese: sedentary lifestyle, binge eating disorder, and weight gain associated with pharmacological treatment.[18,19] Obesity-associated conditions such as disorders of glucose metabolism appear to be more prevalent in persons with bipolar disorder.[2]

KECK: Yes, the risk factors for obesity in patients with bipolar disorder also include severity and recurrence of depressive episodes (especially with atypical features), co-occurring binge eating disorder, alcohol abuse or dependence, family history of obesity, and pharmacotherapy.

Central nervous system agents and weight gain

KECK: Treatments for psychiatric disorders often cause weight gain and increase the risk for obesity and associated illnesses. We need to develop treatment approaches that improve patient outcomes. Our goal is remission of symptoms, but we need to be careful not to worsen other illnesses. Therefore, we need to consider which psychotropic medications cause weight gain and which do not.

Central nervous system (CNS) agents that present a risk of causing weight gain include antidepressants, antiepileptics (some of which are used for bipolar illness and schizophrenia, such as valproate), antipsychotics, including some old typical antipsychotics, and lithium (**TABLE 4**). Other agents have a much lower propensity for causing weight gain.

Table 4
CNS drug-induced weight gain

Drugs That May Promote Weight Gain	Drugs That Cause Little or no Weight Gain or Weight Loss
Antidepressants • Paroxetine • Mirtazapine • MAOIs, TCAs • SSRIs*	**Antidepressants** • Bupropion • Venlafaxine
Antiepileptic drugs • Valproate • Gabapentin	**Antiepileptic drugs** • Topiramate • Lamotrigine • Zonisamide
Antipsychotics • Clozapine, olanzapine, risperidone, quetiapine	**Antipsychotics** • Ziprasidone • Aripiprazole
Lithium	

*Weight gain mainly with paroxetine
CNS, central nervous system; MAOIs, monoamine oxidase inhibitors; TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors

Table 5

Pharmacotherapy aimed at counteracting antipsychotic–drug-induced weight gain

Drug (background)	Study Design	N	Mo	Weight Change (kg)
Amantadine (olanzapine)	Observational case series	38	12	-2.2
Orlistat (varied)	Open-label case	2	12	-3.3
Nizatidine (olanzapine)	Randomized, double-blind	175	4	ND
Metformin (varied)	Open-label	19	3	15 lost weight; 4 had slight gain or no change

ND, no difference compared with placebo
Source: Baruch R, et al; Morrison JA, et al; Anghelescu I, et al; Cavazzoni P, et al.[21-24]

Clinicians should note that a key issue is the risk of an individual patient having a substantial amount of weight gain. The treatment-associated incidence of weight gain totaling 7% or more compared with baseline body weight is shown in **FIGURE 3**.[20]

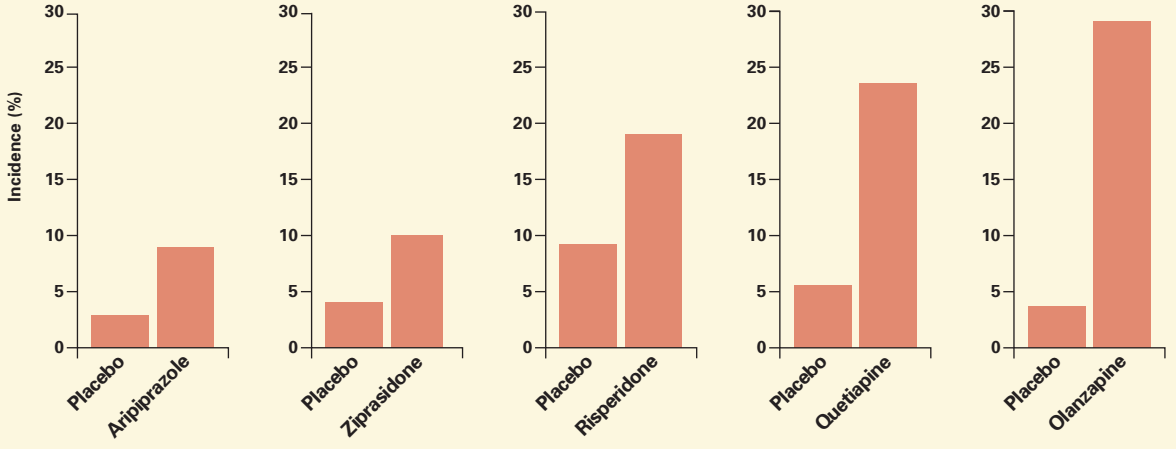
Recent trials (**TABLE 5**) have assessed the efficacy of agents that counteract the weight-gain effects of antipsychotic drugs.[21-24] Amantadine used with olanzapine produced a –2.2-kg weight change. Olanzapine in combination with nizatidine showed no effect. Orlistat in combination with various antipsychotic agents produced a –3.3-kg weight change. Metformin, used with various agents, produced inconsistent results.

Psychiatrists also need to monitor weight and weight gain. I systematically record the patient's body mass index (BMI) at each office visit (or at least monthly) to identify gradual increases. I intervene to prevent significant weight gain. I also measure waist circumference around the umbilicus by tape measure because central adiposity is the biggest risk factor for the metabolic syndrome. For patients who begin treatment with a high baseline BMI, I consider the need to prevent further weight gain through agent selection.

I remind patients about the importance of diet and exercise. I tell patients to try to walk at least 150 minutes a week. Just walking around the block for half an hour is better than not exercising at all. ■

Figure 3

Clinically significant (≥7%) weight gain during antipsychotic treatment



Source: Physicians' Desk Reference®.[20]

The metabolic syndrome and diabetes:
Implications for patients with psychiatric disorders

KECK: A key risk for our patients is metabolic syndrome, a cluster of abnormalities that include abdominal obesity, elevated triglycerides, low high-density lipoprotein cholesterol, elevated blood pressure, and elevated fasting glucose (**TABLE 6**). The condition is often called "prediabetes" and is defined by the presence of 3 symptoms, although presence of any 1 constitutes a risk factor.[25] Clearly, we need to monitor these risk factors.

Bipolar disorder and schizophrenia are independent risk factors for type 2 diabetes. Incidence of diabetes may be 2 to 3 times higher in our patients than in the general population. Other conditions we've discussed—obesity, smoking, and the metabolic syndrome—increase the risk for diabetes as well; and CVD is the leading cause of death in persons with diabetes.[26]

Table 6
The metabolic syndrome

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

HDL-C, high-density lipoprotein cholesterol
Source: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.[25]

Screening recommendations

KECK: Recently published guidelines provide concrete recommendations for diabetes risk-factor screening, management, and, where appropriate, referral of patients for additional treatment.[27] They outline a plan that can help us function first as physicians and second as psychiatrists (**TABLE 7**).

The American Diabetes Association has put forth consensus recommendations to help clinicians determine how frequently to monitor patients who receive antipsychotic drugs (**TABLE 8**).[28]

Table 7
Screening recommendations for diabetes risk factors

At initial assessment, clinicians should evaluate the following:

- Age: All adults aged 45 years or older should be screened for diabetes. If findings are normal, screening should be repeated at 3-year intervals.
- Screening at a younger age or more frequently is advisable for patients who have the following risk factors:
  - Overweight or obese, weighing 20% or more over ideal body weight
  - Central body adiposity
  - First-degree relative with diabetes
  - High-risk ethnic group, particularly Hispanic, African American, or Asian
  - Having delivered a baby heavier than 9 lb
  - History of gestational diabetes in patient or patient's mother
  - Blood pressure ≥ 140/90 mm Hg
  - HDL < 35 mg/dL
  - Triglycerides ≥ 250 mg/dL
  - Previous impaired fasting glucose or impaired glucose tolerance

Source: Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.[27]

Obesity as a risk factor for diabetes

KECK: The fact that obesity is a risk factor for diabetes has been demonstrated in many studies. As BMI increases, there is a dramatic increase in the risk of type 2 diabetes (**FIGURE 4**).[29]

NASRALLAH: Yes, in **FIGURE 4**,[29] the Y axis illustrates that people who are highly obese have 60 times the risk for diabetes as do people with a normal BMI.

Table 8

Patient follow-up to counteract antipsychotic drug-induced weight gain

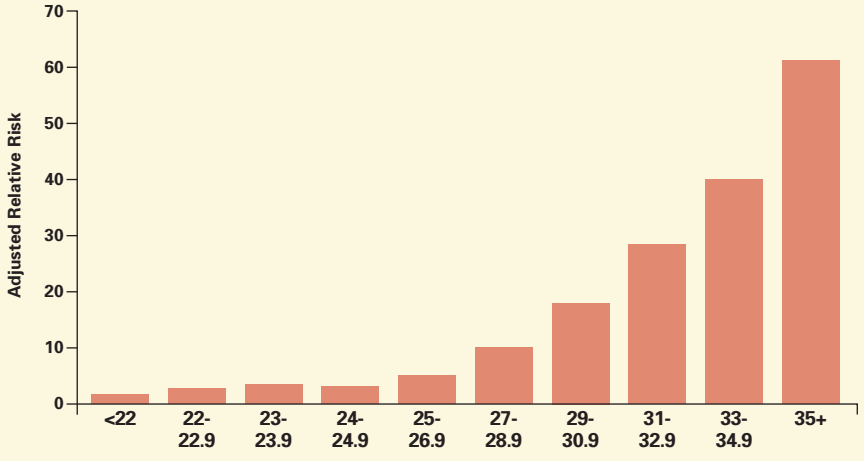
	Start	4 wk	8 wk	12 wk	3 mo	12 mo	5 y
Personal/ family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting glucose	X			X		X	
Fasting lipid profile	X			X			X

More frequent assessments may be warranted based on clinical status.
BMI, body mass index

Source: American Diabetes Association, et al.[28]

Figure 4

Body mass index and relative risk of type 2 diabetes



In women aged 35-55 years in 1976; data adjusted for age.
Source: Colditz GA, et al.[29]

KECK: Right. These are quantum jumps in risk. Thank you for emphasizing that.

NASRALLAH: The metabolic experts strongly urge that we switch our patients when they gain 5% of their baseline body weight—generally referred to as the switch threshold—because it's important not to reach the 7% increase.

KECK: Yes, we also need to pay attention to the patient who gains a pound a week or more at the initiation of treatment. What do we do for that individual? If diet and exercise—the usual lifestyle changes—aren't helpful or the patient isn't compliant, we have a limited number of medicines that have been studied or reported in trials. We need research in these areas.

Selection of antipsychotic agents

KECK: The effects of antipsychotic drugs on weight gain, lipid profile, and risk of diabetes are described in **TABLE 4**. In clinical trials, ziprasidone and aripiprazole have shown the least propensity to produce weight gain, presumably because these agents do not stimulate appetite. An intermediate risk of weight gain occurs with risperidone and quetiapine, and the greatest overall risk occurs with olanzapine and clozapine.

The increased risk of weight gain is thought to translate into an elevated though indirect risk for associated diabetes (**FIGURE 4**).[29] The relation of antipsychotic drugs, weight gain, and diabetes, as put forth by a recent consensus development conference, is shown in **TABLE 9**.[28] ■

Genetics, lifestyle, risk, and cancer:
A complex relationship with effects on patient outcomes

NASRALLAH: We have briefly mentioned the consequences of excess weight in terms of risk for CVD, the metabolic syndrome, and insulin resistance. Significantly, although heart disease is the number 1 killer in the United States, cancer is number 2. Obesity is a factor in both diseases. In cancer, obesity is mainly associated with colon and prostate cancer in men and breast, ovarian, and endometrial cancers in women. It is also associated with cancer of the kidney.

Behavior-based risk factors for cancer are common in people with schizophrenia. They include higher alcohol consumption, which increases the risk of certain types of cancer, especially in the oral cavity, esophagus, and liver. Alcohol consumption is also associated with breast and endometrial cancer.

Tobacco use is notoriously associated with lung cancer as well as cancer of the lips, tongue, pharynx, and esophagus.

People who have bipolar disorder or schizophrenia also tend to have sedentary lifestyles, elevating the risk for colon cancer.

Many of our female patients have low parity, associated with higher rates of cancers of the oral cavity, pharynx, esophagus, liver, larynx, breast, endometrium, and kidney.

To put the cancer risk into perspective, let's look at the relative risk of various cancers in people with schizophrenia, as compared to the general population (**TABLE 10**).[30,31] The slight overall increase in relative risk, 1.17, can be attributed to a few cancers: lung, pharyngeal, endometrial, gallbladder, and rectal. The number of cancers are higher in persons with schizophrenia than in the general population.

Is schizophrenia cancer-protective?

NASRALLAH: Studies have shown that first-degree relatives of patients with schizophrenia have a statistically significantly lower rate of cancer overall. In one evaluation, siblings of individuals with schizophrenia had a risk of cancer of 0.89 (95% confidence interval [CI], 0.83–0.94) and parents of people with schizophrenia had a risk factor of 0.91 (95% CI, 0.89–0.93).[30]

The reasons for this cancer-protective effect are unclear. Possibly, the biology of schizophrenia may include accelerated apoptosis, or cell death. As a result, cancer cells may be destroyed when they become mitotic. Unfortunately, accelerated apoptosis may also result in excessive loss of brain tissue during psychosis.[30]

It has been proposed that the genetically based protective factors associated with schizophrenia are not manifested in patients with schizophrenia as a result of an increased likelihood of smoking, obesity, alcohol use, and poor dental hygiene.

KECK: So it's a benefit to have the traits that seem to be protective against cancer, but not the illness.

Table 9

Consensus development conference on antipsychotic drugs and obesity and diabetes

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Colzapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/-	-	-
Ziprasidone*	+/-	-	-

\+ Increase effect
\- No effect
D, discrepant data
*Newer drugs with limited long-term data
More frequent assessments may be warranted, based on clinical status
Source: American Diabetes Association, et al.[28]

Table 10

Relative risk of various cancers in patients with schizophrenia

A large Finnish study showed the following:	SIR	
Overall	1.17	(95% CI, 1.09–1.25)
Lung cancer	2.17	(95% CI, 1.78–2.60)
Pharyngeal cancer	2.60	(95% CI, 1.25–4.77)
Endometrial cancer	1.75	(95% CI, 1.19–2.48)
Gall bladder cancer	2.07	(95% CI, 1.03–3.70)
Rectal cancer	2.60	(95% CI, .13–.75)
The 1986 National Mortality Follow-up Survey reported:		
Overall cancer risk in schizophrenia (OR)		
	.59	(95% CI, .38–.93)

SIR, standard incidence ratio; CI, confidence interval; OR, unadjusted odds ratio
Source: Lichtermann D, et al; Cohen M, et al.[30,31]

NASRALLAH: Yes, a carrier is protected from cancer but possibly perpetuates the gene for schizophrenia.

Studies suggest that patients with schizophrenia may experience delays in cancer diagnosis and receive inadequate treatment.

Substantial clinical experience notes that coadministration of psychotropic drugs with chemotherapeutic agents does not result in complications, although most psychotropic drugs are metabolized in the liver and are protein bound. Dose adjustments may be necessary if the chemotherapeutic drug affects the metabolism of a psychotropic agent or if the patient is debilitated. No systematic research has been undertaken concerning the use of clozapine with chemotherapeutic drugs toxic to white blood cells.

NASRALLAH: Conventional antipsychotics and risperidone result in hyperprolactinemia, particularly at higher doses. Whether this causes cancer remains uncertain. During any long-term follow-up of patients with chronic mental illness, significant substance abuse and multiple medical problems occur, making the cause of cancer extremely difficult to determine with certainty. The relation between prolactin release and cancers has been investigated extensively; only a very weak association has been confirmed. Still, investigations continue.

KECK: We have a theoretic basis and a small amount of preclinical data to suggest that prolactin may promote breast cell and endometrial cancer growth. To date, however, we have no compelling evidence that hyperprolactinemia is, by itself, a major risk factor for breast cancer.

NASRALLAH: Yes. We do know that hyperprolactinemia causes sexual dysfunction. But we can't, with certainty, say that it can increase the risk of cancer. ■

Management of asthma and COPD:
Treatment strategies in patients with psychiatric disorders

NASRALLAH: In patients with schizophrenia, cigarette smoking is probably the single most important risk factor for developing pulmonary disease, including asthma, chronic obstructive pulmonary disease (COPD), OSA, and lung cancer.

Persons with mood or anxiety disorders seem to have higher rates of asthma diagnosis compared with the general population. We have no evidence that the incidence or prevalence of asthma is greater in people with schizophrenia or bipolar disorder than in the general population. However, many patients with bipolar disorder or schizophrenia do have asthma and need to receive the right treatment.

When asthma co-occurs with schizophrenia, we see significant increases in morbidity and mortality, mainly related to the challenges regarding access to and compliance with treatment. This is of great concern because asthma can be fatal without the correct medication. People with schizophrenia may discontinue antipsychotics, relapse, and neglect their asthma.[32] They may lack access to proper treatment. Interestingly, one study showed that theophylline—which has a low therapeutic index and is dangerous in overdose—is more commonly used in patients with schizophrenia than are inhaled leukotrine β-agonists, which have a better safety and efficacy profile.[33]

KECK: There are additional concerns regarding agents used for asthma: Sympathomimetics could exacerbate or destabilize the illness and lead to sleep disruption. People with schizophrenia often are prescribed antidepressants for depressive symptoms, so there is a potential drug-to-drug interaction between sympathomimetics and noradrenergic reuptake inhibitors. Patients with bipolar disorder who are prescribed theophylline may experience lithium toxicity, as both agents are renally cleared.

NASRALLAH: Yes. What do you do to protect bipolar patients with serious asthma who take steroids?

KECK: I maximize mood stabilizers to the highest tolerated level. I may also add a second antimania drug as needed, prophylactically.

NASRALLAH: But asthma can kill you in a minute.

KECK: Absolutely, so it's essential to achieve a balance.

NASRALLAH: Let's look at COPD, rampant in many of our patients because of smoking. It is important to distinguish between COPD and asthma in patients with pulmonary symptoms: The treatment of each condition is different. Steroids are usually helpful in asthma, but not in COPD, which usually is accompanied by emphysema and chronic bronchitis. The best treatment is to stop smoking, but this is very difficult to accomplish. Nevertheless, COPD in patients with schizophrenia is serious because COPD reduces the amount of oxygen that reaches the brain, resulting in hypoxemia and hypercarbia.

Agent selection for patients with COPD

NASRALLAH: For COPD, we use inhaled anticholinergics, especially for treatment of people with chronic bronchitis with cough and sputum production. These agents do not cross the blood–brain barrier, which is a benefit. Inhaled β-agonists are useful in the treatment of chronic bronchitis and emphysema, but they may cause activation and anxiety in some patients, so we must be alert to psychiatric symptoms that appear during treatment.

KECK: Corticosteroids are the most commonly implicated drugs in triggering mania.

NASRALLAH: Patients with COPD can become delirious if their lung function deteriorates, which is a potential effect of a simple upper respiratory infection. This is very difficult to diagnose, particularly in an outpatient setting, because you have delirium

Table 11

Antipsychotic selection in schizophrenia complicated by pulmonary disease

Comorbid Condition	Sedation	Weight Gain	EPS Liability
Asthma	Avoid	–	Avoid
COPD	Strongly avoid	Avoid	Avoid
OSA	Strongly avoid	Strongly avoid	Avoid
Respiratory dyskinesia	Avoid	Avoid	Strongly avoid
Acute dystonia	–	–	Strongly avoid

EPS, extrapyramidal symptoms; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea

superimposed on psychosis. Further, in patients with already compromised lung function associated with COPD, sedating medications can blunt their respiratory drive and should be used only when no other choice is available (**TABLE 11**).

Mental health clinicians should be alert to any sudden change in mental status in a patient with COPD. The use of blood gases is indicted in such settings, especially when accompanied by a change in the pattern of cough and sputum production. ■

Obstructive sleep apnea:
Symptoms may be difficult to identify in psychiatric patients

NASRALLAH: Obstructive sleep apnea is marked by intermittent obstruction of the upper airway during sleep, which produces repetitive hypoxia—oxygen levels can drop from 90% or 95% to 70%. The patient experiences reflexive and frequent awakening to re-oxygenate. Some people do have primary sleep apnea, but the condition is usually secondary to obesity. In such cases, the abdominal fat actually pushes on the airways and causes breathing problems. Often, when they awake, they snack, furthering weight issues.

During the day, these patients may exhibit symptoms of lethargy, depression, and cognitive impairment. They don't exercise and have difficulty at work. It may be dangerous for them to perform such necessary tasks as driving a car.

Sleep apnea is underrecognized in people with schizophrenia. Daytime sleepiness may be attributed to medication effect rather than OSA symptoms. Typically, there is no bed partner to report snoring. Patients are less likely to be referred for polysomnography. Left untreated, OSA can worsen cognition and lead to treatment-resistant symptoms, including aggression and assaultive behavior. Additionally, OSA is also associated with elevated anemia obesity.

The prevalence of OSA was evaluated in a study of 364 psychiatric patients referred to a sleep center. Patients with schizophrenia were 2 times more likely to be diagnosed with OSA than were patients with other psychiatric disorders.[34] Patients with schizophrenia also tend to have more severe OSA, as rated by the Respiratory Disturbance Index criteria.

OSA: A byproduct of weight gain?

NASRALLAH: It is possible that chronic antipsychotic treatment—associated with weight gain—may actually begin the cycle: Chronic antipsychotic treatment may be considered a major risk factor for both obesity and OSA in patients with schizophrenia.

KECK: We see interesting data about OSA in patients with bipolar disorder. About 15 years ago, Steve Strakowski and other investigators noticed rapid cycling in patients with unstable bipolar I illness. When their dosage of mood stabilizers was increased, the patients gained more weight and developed OSA, which was not initially diagnosed. The sleep disturbance destabilized the mood disorder; more mood stabilizers were prescribed. Only when the OSA was diagnosed and treated was the cycle broken—primarily through weight loss. It was a fascinating case of an iatrogenic cause of a secondary medical problem that worsened the primary psychiatric illness.

NASRALLAH: It's so hard to diagnose OSA. As you said, frequent awakenings and bipolar disorder constitute a partial sleep deprivation that can trigger hypomania in a normal person. In someone with bipolar disorder, it can progress to mania.

Agent selection to avoid potential side effects

NASRALLAH: In patients with COPD, serious OSA, asthma, or respiratory dyskinesia, agents that can worsen hypoventilation and hypoxemia as well as weight gain associated with extrapyramidal symptoms (EPS), should be avoided (**TABLE 11**).

In patients with EPS, acute dystonic reaction can occur in the glottis or larynx and, rarely, result in acute laryngeal spams, Parkinsonian muscle rigidity, or dyskinesia of the respiratory muscles. ■

HIV/AIDS and persons with chronic mental illness:
Comparatively high prevalence among the mentally ill

NASRALLAH: In 2001, 800,000 adults and adolescents in the United States had been diagnosed with AIDS; more than half of that number had died. Risk for human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) is greatest in the 5-H groups: homosexual men, heroine users, Haitians, hemophiliacs, and health care workers, who tend to be infected by their patients.[35]

Table 12

Interactions of antipsychotics and antiretroviral medications

	Amprenavir	Ritonavir; Lopinavir/ Ritonavir	Fluconazole	Trimethoprim
Clozapine	↑	↑↑		
Risperidone		↑↑		
Olanzapine		↓		
Ziprasidone	NA	NA	NA	NA
Quetiapine			↑	
Aripiprazole	NA	NA	NA	NA

Serious mental illness, especially schizophrenia, bipolar I, and recurrent depression, are considered risk factors for HIV because of such patients' higher rates of unsafe sex and injection drug use. Overall, the prevalence of HIV among the chronically mentally ill has been estimated at between 4% and 20%, 10 to 80 times the US prevalence of 0.4%. Additionally, there is a low rate of adherence to treatment in this population.[36,37]

Interactions between antipsychotics and antiretroviral medications do occur, as shown in **TABLE 12**, although we have little data.

There are concerns in terms of QT interval prolongation associated with the use of thioridazine or mesoridazine with trimethoprim and in terms of possible QT prolongation with the use of mesoridazine and fluconazole. ■

Summary

NASRALLAH: When we consider common medical illnesses that result in significant morbidity and mortality, we find that schizophrenia and bipolar disorder are frequently associated with these conditions. Additionally, risk factors in which psychotic patients frequently engage (eg, smoking, obesity, unsafe sex,

drug abuse) can exacerbate these co-occurring medical disorders.

Careful selection of the appropriate psychotropic agent is critical to avoid worsening the medical condition. Optimum agent selection is also essential to avert pharmacokinetic interactions with medications being taken for a coexisting medical condition. ■

References

1. Murray CJL, Lopez AD, eds. *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020.* Cambridge, Mass: Harvard University Press (on behalf of the World Bank and the World Health Organization); 1996.
2. Osby U, Brandt L, Correia N, Ekbom A, Sparen P. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry.* 2001;58:844-850.
3. Osby U, Correia N, Brandt L, Ekbom A, Sparen P. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophr Res.* 2000;45:21-28.
4. National Center for Health Statistics. Centers for Disease Control and Prevention Web site. Available at: http://www.cdc.gov/nchs/faststats/deaths.htm. Accessed February 2, 2005.
5. Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report.* 2002;14:1-40.
6. Kaplan HI, Sadock BJ, Grebb JA. *Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences, Clinical Psychiatry.* 7th ed. Baltimore, Md: Lippincott Williams & Wilkins; 1994.
7. Fagiolini A, Buysse DJ, Frank E, Houck PR, Luther JF, Kupfer DJ. Tolerability of combined treatment with lithium and paroxetine in patients with bipolar disorder and depression. *J Clin Psychopharmacol.* 2001;21:474-478.
8. McElroy SL, Frye MA, Suppes T, et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. *J Clin Psychiatry.* 2002;63:207-213.
9. Goldman LS. Medical illness in patients with schizophrenia. *J Clin Psychiatry.* 1999;60(suppl 21):10-15.
10. Jeste DV, Gladsjo JA, Lindamer LA, Lacro JP. Medical comorbidity in schizophrenia. *Schizophr Bull.* 1996;22:413-430.
11. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report.* Bethesda, Md: National Institutes of Health; 1998. NIH Publication 98-4083.
12. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97:1837-1847.
13. George TP, Vessicchio JC, Termine A. Nicotine and tobacco use in schizophrenia. In: Meyer JM, Nasrallah HR, eds. *Medical Illness and Schizophrenia.* Washington, DC: American Psychiatric Publishing; 2003:81-98.
14. Ziedonis D, Williams JM, Smelson D. Serious mental illness and tobacco addiction: a model program to address this common but neglected issue. *Am J Med Sci.* 2003;326:223-230.
15. Prior TI, Baker GB. Interactions between the cytochrome P450 system and the second-generation antipsychotics. *J Psychiatry Neurosci.* 2003;28:99-112.
16. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* 2000;23(suppl 1):S4-S19.
17. Bray GA. Risks of obesity. *Endocrinol Metab Clin North Am.* 2003;32:787-804.
18. McIntyre RS, McCann SM, Kennedy SH. Antipsychotic metabolic effects: weight gain, diabetes mellitus, and lipid abnormalities. *Can J Psychiatry.* 2001;46:273-281.
19. Malhotra S, McElroy SL. Medical management of obesity associated with mental disorders. *J Clin Psychiatry.* 2002;63(suppl 4):24-32.
20. *Physicians Desk Reference®.* Montvale, NJ: Thomson PDR; 2004;685,1034,1764,2597.
21. Baruch R, Poulin M, Thakur A, Karagianis J. Amantadine induces weight loss in patients treated with olanzapine. Paper presented at: XIth Biennial Winter Workshop on Schizophrenia; February 24-March 1, 2002; Davos, Switzerland.
22. Morrison JA, Cottingham EM, Barton BA. Metformin for weight loss in pediatric patients taking psychotropic drugs. *Am J Psychiatry.* 2002;159:655-657.
23. Anghelescu I, Klawe C, Benkert O. Orlistat in the treatment of psychopharmacologically induced weight gain. *J Clin Psychopharmacol.* 2000;20:716-717.
24. Cavazzoni P, Tanaka Y, Roychowdhury SM, Breier A, Allison DB. Nizatidine for prevention of weight gain with olanzapine: a double-blind placebo-controlled trial. *Eur Neuropsychopharmacol.* 2003;13:81-85.
25. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.
26. Geiss LS, Herman WH, Smith PJ. Mortality in non-insulin-dependent diabetes. In: Harris MI, Cowie CC, Stern MP, et al, eds. *Diabetes in America.* 2nd ed. Washington, DC: National Institutes of Health, US Department of Health and Human Services; 1995:233-257. DHHS publication no. (NIH) 95-1468.
27. Expert Committee on the Diagnosis and Classification of Diabetes

Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2003;26(suppl 1):S5-S20.

28. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care.* 2004;27:596-601.
29. Colditz GA, Willett WC, Stampfer MJ, et al. Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol.* 1990;132:501-513.
30. Lichtermann D, Ekelund J, Pukkala E, Tanskanen A, Lonnqvist J. Incidence of cancer among persons with schizophrenia and their relatives. *Arch Gen Psychiatry.* 2001;58:573-578.
31. Cohen M, Dembling B, Schorling J. The association between schizophrenia and cancer: a population-based mortality study. *Schizophr Res.* 2002;57:139-146.
32. Joseph JS, Blais L, Ernst P, Suissa S. Increased morbidity and mortality related to asthma among asthmatic patients who use major tranquillisers. *BMJ.* 1996;312:79-81.
33. Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma: A randomized, controlled trial. *Ann Intern Med.* 1999;130:487-495.
34. Winkelman JW. Schizophrenia, obesity, and obstructive sleep apnea. *J Clin Psychiatry.* 2001;62:8-11.
35. Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report.* 2001. Available at: http://www.cdc.gov. Accessed February 2, 2005.
36. Cournos F, Empfield M, Horwath E, et al. HIV seroprevalence among patients admitted to two psychiatric hospitals. *Am J Psychiatry.* 1991;148:1225-1230.
37. Rosenberg SD, Trumbetta SL, Mueser KT, et al. Determinants of risk behavior for human immunodeficiency virus/acquired immunodeficiency syndrome in people with severe mental illness. *Compr Psychiatry.* 2001;42:263-271.

CME Questions
Posttest Answer Form

Please circle the correct answer for each question.

1. The following medical disorders may co-occur in a patient with schizophrenia or bipolar disorder and may complicate pharmacotherapy with antipsychotics, mood stabilizers, or antidepressants:
   a) Diabetes
   b) Human immunodeficiency virus
   c) Chronic obstructive pulmonary disease
   d) Sleep apnea
   e) All of the above

2. A coexisting medical illness may complicate the treatment of psychiatric disorders as follows:
   a) Psychotropics may exacerbate the co-occurring medical illness
   b) The medication being taken for the medical illness may worsen the psychiatric symptoms
   c) There may be pharmacokinetic interactions between the psychotropic agent and the pharmacotherapy of the medical illness
   d) All of the above

3. Significant weight gain with some atypical antipsychotics may increase the risk of the following medical disorders:
   a) Cardiovascular disease
   b) Breast and colon cancer
   c) Dyslipidemia
   d) Diabetes
   e) Obstructive sleep apnea
   f) a, c, and d
   g) All of the above

4. Sedating psychotropic drugs should be avoided in patients with coexisting chronic obstructive pulmonary disease or asthma.
   a) True
   b) False

5. The lowest risk of metabolic complications in patients with schizophrenia or bipolar disorder is associated with which of the following antipsychotics?
   a) Risperidone
   b) Ziprasidone
   c) Aripiprazole
   d) Quetiapine
   e) Olanzapine
   f) All of the above
   g) b and c

6. Obstructive sleep apnea in an obese person with schizophrenia may worsen which of the following features of schizophrenia?

   a) Negative symptoms
   b) Cognitive deficits
   c) Bizarre dreams
   d) All of the above
   e) a and b only
   f) None of the above

7. Ritonavir inhibits the HIV medication cytochromes p450 2D6 and p450 3A4 and induces cytochrome p450 1A2. Therefore, when given to patients receiving atypical antipsychotics, the following consequences are likely:

   a) Clozapine and quetiapine serum levels would increase
   b) Olanzapine serum levels would decrease
   c) Risperidone serum levels would increase
   d) All of the above
   e) a and b only

8. Prevalence of human immunodeficiency virus among the chronically mentally ill has been estimated between 4% and 20% which is 10 to 80 times the US prevalence of .4%.

   a) True
   b) False

9. Risk factors for obesity in bipolar disorder include all but the following:

   a) Severity and recurrence of depressive episodes (especially with atypical features)
   b) Co-occurring binge eating disorder, alcohol abuse/dependence
   c) Family history of obesity
   d) Hemophilia

10. Schizophrenia patients were 2 times more likely to receive a diagnosis of OSA relative to other psychiatric disorders.

    a) True
    b) False

Program Evaluation

Distance Learning Network, Inc. and the University of Florida Colleges of Medicine and Pharmacy thank you for your participation and would appreciate your comments regarding the quality of the information presented. Please circle the appropriate answer for each question below, using the following scale:

a. Strongly agree **b.** Agree **c.** Disagree **d.** Strongly disagree **e.** Does not apply

1. The program objectives were fully met.	**a**	**b**	**c**	**d**	
2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.	**a**	**b**	**c**	**d**	
3. The educational activity has enhanced my professional effectiveness and improved my ability to:					
a. Treat/manage patients	**a**	**b**	**c**	**d**	**e**
b. Communicate with patients	**a**	**b**	**c**	**d**	**e**
c. Manage my medical practice	**a**	**b**	**c**	**d**	**e**
4. The information presented was without promotional or commercial bias.	**a**	**b**	**c**	**d**	
5. The program level was appropriate.	**a**	**b**	**c**	**d**	
6. Do you intend to change your clinical practice as a result of the information presented in this CME program?	**Yes**		**No**		

Comments:

7. Suggestions regarding this material, or recommendations for future presentations

Registration Form

PLEASE PRINT CLEARLY

Name (last) (first)

Street address

City **State** **Zip**

Telephone **Fax**

Email

Degree initials **Specialty**

Affiliation

Signature **Actual time spent in this activity** (hours) (minutes)

Type of Credit Certificate Requested: (please check one)

❑ AMA ❑ ACPE ❑ UNA Nursing ❑ CE-Psychologists ❑ Certificate of Attendance

For the Physician's Recognition Award (PRA), you can claim only the time you actually spent on this educational activity. This cannot exceed the 1.5 hours designated as the maximum allowable credit for this supplement.
To receive credit, you must mail this form, the program evaluation, and the completed posttest answer form to:

Distance Learning Network, Attn: Chris Crestani, P.O.Box 1111, State College, PA 16804
Phone: (800) 326-9166 or (814) 466-7808; **Fax:** (814) 466-7509

SPECIAL EDITION

PRACTICAL ISSUES *in* PSYCHIATRY

A SUPPLEMENT TO

Current PSYCHIATRY

APRIL 2005

Pharmacotherapy of schizophrenia and bipolar disorder with coexisting medical illness