FREE 4.0 CME CREDITS

SUPPLEMENT TO

ANNALS OF
CLINICAL PSYCHIATRY

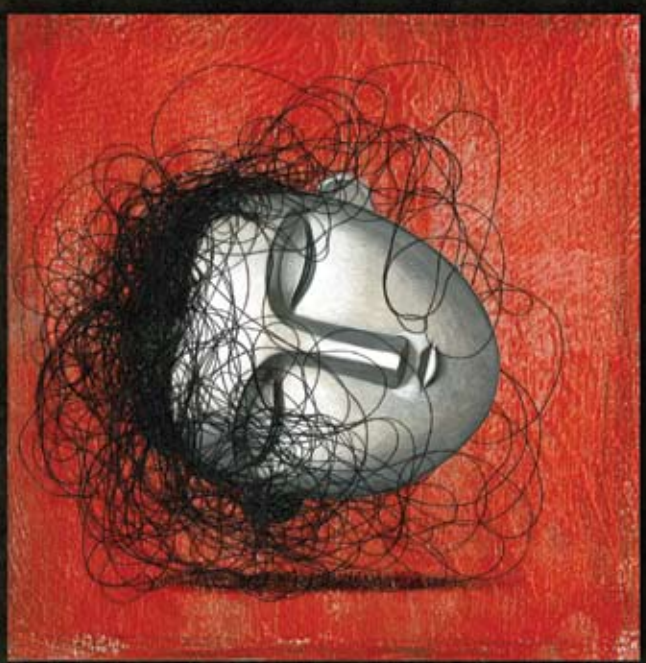
Available at www.aacp.com

Vol 20 No 4S • December 2008

Diagnosing and managing psychotic and mood disorders

CASE 1
Treatment-resistant psychosis

CASE 2
Psychosis with bipolar mania



CASE 3
Bipolar depression with anxiety

CASE 4
Unipolar vs bipolar depression

© JON KRAUSE FOR CURRENT PSYCHIATRY

Faculty

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

DONALD W. BLACK, MD
Professor of Psychiatry
University of Iowa Carver College of Medicine
Iowa City, Iowa

JOSEPH F. GOLDBERG, MD
Associate Clinical Professor of Psychiatry
Mt Sinai School of Medicine
New York, New York
Silver Hill Hospital
New Canaan, Connecticut

DAVID J. MUZINA, MD
Vice Chair for Research & Education
Associate Professor of Medicine
Cleveland Clinic Department of Psychiatry
& Psychology
Cleveland, Ohio

STEPHEN F. PARISER, MD
Professor of Psychiatry, Obstetrics and Gynecology
Medical Director, Psychiatry Clinics
Medical Director, Neuropsychiatry
Ohio State University College of Medicine
Columbus, Ohio

RELEASE DATE: DECEMBER 1, 2008
EXPIRATION DATE: DECEMBER 1, 2009

LEARNING OBJECTIVES

After reviewing this material, clinicians should be better able to:

- Achieve early and accurate diagnosis of patients with mood disorders
- Utilize available screening tools effectively
- Understand the mechanisms of action, hepatic effects, and other metabolic effects of available agents and their potential impact on treatment
- Develop an effective treatment plan that includes monotherapy or combination therapy
- Select the most appropriate agent(s) for short- and long-term treatment to meet individual patient needs

TARGET AUDIENCE

Psychiatrists, primary care physicians, and other health care professionals who treat patients with psychotic and mood disorders

CME ACCREDITATION

The University of Cincinnati designates this educational activity for a maximum of 4.0 *AMA PRA Category 1 credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity. This CME activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of the University of Cincinnati College of Medicine. The University of Cincinnati College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

FINANCIAL DISCLOSURES AND CONFLICTS OF INTEREST

According to the disclosure policy of the University of Cincinnati, faculty, editors, managers, and other individuals who are in a position to control content are required to disclose any relevant financial relationships with the commercial companies related to this activity. All relevant relationships that are identified are reviewed for potential conflicts of interest. If a conflict of interest is identified, it is the responsibility of the University of Cincinnati to initiate a mechanism to resolve the conflict(s). The existence of these interests or relationships is not viewed as implying bias or decreasing the value of the presentation. All educational materials are reviewed for fair balance, scientific objectivity of studies reported, and levels of evidence.

The faculty has reported the following:

• **Dr Nasrallah** reports that he is on the advisory board of Abbott, AstraZeneca, Cephalon, Janssen, Pfizer, and Vanda Pharmaceuticals; is a consultant for AstraZeneca, Janssen, Pfizer, and Vanda Pharmaceuticals; receives grants from AstraZeneca, Forest Laboratories, Janssen, Otsuka America Pharmaceutical Inc., Pfizer, Roche, and sanofi-aventis; and is on the speakers bureau of AstraZeneca, Janssen, and Pfizer.

• **Dr Black** reports that he is a consultant for Forest Laboratories and Jazz Pharmaceuticals and receives grant(s) from Forest Laboratories.

• **Dr Goldberg** reports that he is on the advisory board, speakers bureau, and serves as a consultant for AstraZeneca, Eli Lilly & Co, and GlaxoSmithKline.

• **Dr Pariser** reports that he receives grants from Pfizer and is on the speakers bureau of AstraZeneca, GlaxoSmithKline, and Pfizer.

• **Dr Muzina** reports that he is on the advisory board of AstraZeneca and Bristol-Myers Squibb; and is on the speakers bureau of AstraZeneca, Bristol-Myers Squibb, Pfizer, Sepracor, and Wyeth.

Planning Committee: Kay Weigand, University of Cincinnati; and Kristen Georgi, Charles Williams, and Katherine Wandersee for Dowden Health Media have disclosed no relevant financial relationship(s) with any commercial interests.

Off-label/unapproved agents discussed: Lithium, valproate, and carbamazepine are not approved by the FDA for the treatment of schizophrenia; lithium is not approved for the treatment of suicidality; topiramate, sibutramine, and metformin are not approved for the treatment of antipsychotic-induced weight gain; quetiapine is not approved for the treatment of generalized anxiety disorder; and venlafaxine is not approved for the treatment of obsessive compulsive disorder.

A list of FDA-approved drugs mentioned in this activity appears on page S31.

ACKNOWLEDGEMENT

This CME activity was developed through the joint sponsorship of the University of Cincinnati and Dowden Health Media. It was edited and peer reviewed by ANNALS OF CLINICAL PSYCHIATRY and CURRENT PSYCHIATRY.

UNIVERSITY OF Cincinnati

STATEMENT OF SUPPORT

This CME activity is supported by an educational grant from AstraZeneca.

Contents

INTRODUCTION

HENRY A. NASRALLAH, MD
PROGRAM CHAIR
UNIVERSITY OF CINCINNATI COLLEGE OF MEDICINE
CINCINNATI, OHIO

The diagnosis and management of psychotic and mood disorders is an evolving process and an important topic for continuing medical education. To facilitate a dialogue on the identification and treatment of psychotic and mood disorders, we have invited 4 expert faculty members to present actual patient cases. The learning objectives of this CME program are: (1) to achieve early and accurate diagnosis of patients with psychotic and mood disorders, using effective screening tools as needed; (2) to determine the most appropriate monotherapy or combination therapy for short- and long-term treatment; and (3) to review the mechanisms of action and metabolism of medications used for these conditions.

Each case presentation is followed by a panel discussion in which the collective experience of all of the faculty lends further practical insights into the nuances of management of such patients in both inpatient and outpatient settings. In particular, these cases underscore the importance of being alert to critical clues in a patient's history or the family's history.

In the first presentation, Donald Black, MD, discusses the case of a 54-year-old man with presumed chronic schizophrenia who was first diagnosed at age 17. Because the illness was not disabling at first, he went on to receive a BA degree in comparative literature. However, his compliance with treatment over the years was poor, and he continued to deteriorate despite treatment with first-generation and, subsequently, second-generation antipsychotic medications. The patient also suffered periodically from depressive symptoms. Most recently, he had been receiving injections of haloperidol and long-acting risperidone, but he refused the injections 10 days before being brought to the emergency room with disorganized thinking, tangential speech, paranoid and sexual delusions, auditory hallucinations, and hostility.

The second case, presented by Joseph Goldberg, MD, concerns a 20-year-old man on medical leave from his freshman year in college. The young man was being hospitalized for treatment of acute psychosis. In the emergency room, he claimed a terrorist

organization was trying to recruit him as an operative. Secret messages, he said, were being sent to him from tree stumps, and that the patterns of trees recently felled held clues to future terrorist attacks. A year earlier, after the patient complained of trouble concentrating, another psychiatrist had diagnosed attention deficit disorder and depression, prescribing amphetamine/dextroamphetamine for the former and escitalopram for the latter. His family history includes an older brother, diagnosed with bipolar disorder, who committed suicide; a mother who has panic disorder; and a father who has been treated for recurrent episodes of depression.

Steven Pariser, MD, presents the third case—a 26-year-old professional woman with rapid onset of lethargy, fatigue, irritability, anxiety, and depression. She also voiced odd neurologic complaints, leading a previous psychiatrist to diagnose conversion disorder and prescribe venlafaxine, clonazepam, and bupropion. Seemingly overlooked was a history of recurrent anxiety and depression in her teen years, hospitalization for depression in her 20s, an acknowledgement of obsessional thinking, and a family history of bipolar illness.

A 20-year-old man is the focus of the fourth case, presented by David Muzina, MD, to whom the patient was referred by his primary care physician and psychologist for treatment of mood swings, anxiety, and confusion. He had been given sertraline and then venlafaxine, but discontinued both medications on his own. His symptoms began rather abruptly 14 months earlier, coinciding with an intense program of weight lifting and supplement use to change his self-described smallness. Profound, persistent sadness and feeling "dead inside" were his chief complaints, and they had led to a break-up with his girlfriend, which distressed him greatly and preoccupied his thinking. He also believed his parents were hiding from him the truth of a significant birth defect.

The program concludes with a faculty discussion of several pivotal issues in the management of mood disorders:

- Pitfalls to avoid during the diagnostic evaluation
- Pros and cons of monotherapy and combination therapy
- Mechanisms of action of available medications and implications for an effective treatment plan
- Suggestions for enabling patient compliance with prescribed regimens

We hope the insights you glean from this exchange of clinical issues will enhance and confirm your own thinking when diagnosing and treating patients with psychotic and mood disorders. ■

CASE 1

Treatment-resistant psychosis and schizophrenia

Presented by
DONALD W. BLACK, MD UNIVERSITY OF IOWA CARVER COLLEGE OF MEDICINE, IOWA CITY, IOWA

Treatment options for schizophrenia have included many new antipsychotic agents in recent years. Managing this condition can be especially complicated when the patient responds poorly to treatment and has ongoing problems with adherence.

Identifying information: Mr M, a 54-year-old divorced white male with a history of chronic schizophrenia, presents to the emergency department unkempt, agitated, paranoid, and combative.

Chief complaint: The patient claims his mother is planning to kill him and that she seduced him when he was a child.

History of present illness: Mr M developed symptoms of schizophrenia at age 17. His symptoms were milder early in the disease course. He attended college and earned a degree in comparative literature. Afterward, he was never able to hold gainful employment and eventually went on Social Security disability. He has had numerous previous hospitalizations (50 or more), with increasing frequency in the past 2 years. He has become increasingly combative. During a previous hospitalization Mr M assaulted a nurse. His medical management is currently handled in an assertive community treatment (ACT) program. In the past, he participated in a local mental health drop-in clinic where he could socialize and meet people, but he is now too paranoid to participate.

Medications and allergies: Because of ongoing adherence problems, Mr. M is required by the ACT program to receive depot antipsychotic medications by injection. His current antipsychotic regimen consists of haloperidol decanoate 100 mg per month, divalproex 1200 mg/d, and risperidone intramuscular injection 25 mg every other week. Ten days prior to this admission, he refused these injections. Side effects of his medication include pseudoparkinsonism, tardive dyskinesia, and erectile dysfunction. To control the pseudoparkinsonism symptoms, the patient takes trihexyphenidyl orally 5 mg bid. He previously received some benefit from clozapine but this was discontinued because the patient refused weekly blood draws due to their inconvenience and discomfort. Previous medication history includes carbamazepine, lithium, and probably many other agents during the 37-year course of his disease. Although he occasionally develops symptoms of depression and has threatened to kill himself, antidepressants have not led to consistent improvement and he is not currently taking any. He is a heavy smoker but has no other substance abuse history.

Family history: There is no family history of mental illness. The patient's immediate family members are high functioning and psychiatrically well. Mr M lives alone and his parents support him financially, help him with household tasks, and monitor his behavior. He maintains contact with his ex-wife, whom he met as an inpatient and who also has schizophrenia. She divorced him after he became abusive toward her.

Review of systems: Other than a cough related to his heavy smoking, he has no complaints.

Mental status: The patient is seen in the emergency department lying on a gurney, unshaven, smelly, with long greasy hair and multiple layers of clothing despite summer weather. He displays an angry and hostile affect and directs anger toward his mother, whom he accused of sexually molesting him in childhood. Although his vocabulary is advanced, his speech is filled with profanity. He is sexually preoccupied and complains loudly and bitterly about his erectile dysfunction. His target symptoms include disorganized thinking, tangential speech, paranoid and sexual delusions, auditory hallucinations, and hostility. The patient has prominent oral-buccal movements, of which he appears to be unaware, and has mild hand tremors and cogwheel rigidity. He has no insight, but understands that doctors believe he has schizophrenia.

Assessment: Chronic psychosis

Provisional diagnosis:

Axis I: Chronic schizophrenia, undifferentiated type
Axis II: None
Axis III: Erectile dysfunction, pseudoparkinsonism, tardive dyskinesia
Axis IV: Moderate stressors
Axis V: 25

Treatment plan: Mr M was admitted to the inpatient psychiatric unit under a court order obtained due to his medication noncompliance. Once admitted, he agreed to take the antipsychotics by injection and understood that he would not be discharged unless he agreed to receive them. He maintained, however, that he was illegally committed and that his mother was behind the plot. He was reminded of his legal right to appeal the commitment. He was discharged the next day, with a recommendation provided to the ACT program for close monitoring.

PANEL DISCUSSION

Is the diagnosis of schizophrenia accurate?

DR NASRALLAH: Although this patient bears many of the clinical stigmata of chronic, deteriorating schizophrenia, such as delusions and hallucinations, I might also consider a diagnosis of severe psychotic bipolar disorder. The rationale would include the patient's relatively better initial functioning during the first 5 years after onset, when he was able to obtain a college degree, and the presence of depression and suicidal ideation. In addition, his highly irritable mood with threats and his history of assault toward his ex-wife and the nurse might suggest a psychotic bipolar condition. A subset of bipolar patients have a prognosis similar to that of patients with schizophrenia.[1]

DR BLACK: I agree—his diagnosis has never been entirely clear. In the early stages of his illness, the clinicians believed it resembled bipolar disorder, but as it evolved into a chronic psychotic state his clinical diagnosis alternated between chronic schizophrenia and schizoaffective disorder, bipolar type, in which a mood disorder and schizophrenic symptoms are both present (**TABLE 1**).[2]

The patient seems to have episodic depressive symptoms that meet full syndromal criteria for depression, and at times he has manic traits such as becoming overexcited, rapid speech, grandiose ideas about being a famous writer or knowing famous people, and hypersexuality. Also, his treatment history has included trials of mood stabilizers, suggesting that clinicians treating him previously were picking up on these bipolar traits. The new symptom of becoming episodically assaultive is problematic because it will make it more difficult to place him in a residential care facility or nursing home.

DR PARISER: Psychotic symptoms are extremely common in bipolar disorder. In fact, among the Axis I disorders, bipolar may contribute as much or more to the psychotic symptom population as schizophrenia.[3]

In a patient like this who is not doing well, it is sometimes helpful to take a step back and start from "square one" with some additional diagnostic studies. These might include appropriate metabolic profiles, vitamin and testosterone levels, syphilis screening, and a neurologic exam, possibly including neuroimaging. I am aware of a psychotic patient who had a fixed delusional system for several years due to refractory tertiary syphilis. There are also cases in which magnetic resonance imaging studies reveal an undetected brain tumor or neurodegenerative disease. Although these tests are expensive, this patient's multiple admissions and treatment failure have come at a considerable cost, both financially and in terms of his personal pain and loss.

DR BLACK: That is a good point. In this case, the patient is enrolled in an ongoing longitudinal study of schizophrenia and has had periodic brain imaging studies.[4,5] There is nothing specific in those findings.

DR GOLDBERG: I imagine that treatment with mood stabilizers has been tried for this patient, alone or as adjuncts to the antipsychotics he has received. I am interested to know what his response has been to the mood stabilizers, including the divalproex he is currently taking.

DR BLACK: He has taken various mood stabilizers over the years, including lithium, carbamazepine, and divalproex sodium, yet it is unclear if he benefits from them. He has also had electroconvulsive therapy, but this was of limited benefit and so it has not been repeated.

Balancing efficacy and tolerability in antipsychotic treatment

DR NASRALLAH: Treatment refractoriness continues to be a problem for many of our patients with schizophrenia. For this patient, who tried many of the available agents

with limited success, tolerance and adherence have become overriding issues. One challenge in treating patients like this is to find the best balance between efficacy and side effects.

DR BLACK: Pseudoparkinsonism is Mr M's main adverse effect. Because he is so disturbed by this symptom, he is constantly demanding to have the dosages of his antipsychotic drugs reduced. The ACT team complied with this request, and his clinical deterioration appeared to follow. It accelerated further when he refused the injection scheduled 10 days prior to this admission.

DR MUZINA: Extrapyramidal effects are one of the greatest disadvantages to first-generation or "conventional" antipsychotics such as haloperidol, which he is receiving in combination with divalproex.[6] Tardive dyskinesia, which is present but not as troublesome to the patient, is a result of blocking D2 receptors, while erectile dysfunction is related to increased serum prolactin. Some atypical agents such as risperidone have a high propensity for elevating prolactin levels as well (**TABLE 2**).[7,8]

DR NASRALLAH: It is interesting that this patient has erectile dysfunction and tardive dyskinesia, because bipolar patients may be more prone to develop extrapyramidal effects than patients with schizophrenia.[9] It may be worthwhile to convince him to go back on clozapine. This agent has helped him in the past, and even if his diagnosis is actually that of psychotic bipolar disorder, clozapine is the only medication shown to be consistently efficacious in treating refractory bipolar patients with mania or even depression.[10] Another thought is that perhaps treating his erectile dysfunction would give him some incentive to return to the clozapine.

Adherence in patients with psychosis

DR BLACK: Mr M functioned better when he was taking clozapine previously. Unfortunately, his insight is so poor that he will not take any orally administered antipsychotic medication.

DR GOLDBERG: Problems with adherence are especially difficult to overcome in a patient with schizophrenia. Reported nonadherence rates for these patients in the literature are between 41% and 50%.[11] The effect of the disease on cognitive function inherently disrupts adherence. In order for patients to be adherent, they have to believe that the "pros" of taking a medication will outweigh the "cons."[12] For a patient like this, who has impaired judgment and paranoia and who has already "tried everything," it would be difficult to convince him that yet another medication change is going to make the difference for him.

DR PARISER: One of the pitfalls of dealing with very refractory patients is that eventually they wear on us as clinicians because we are at a loss for how to best treat them going forward.

DR BLACK: I agree. The patient is aware of this, and told me recently, "Everyone hates me here because I keep

TABLE 1 DSM-IV-TR criteria for schizoaffective disorder

A. Two (or more) of the following symptoms are present for the majority of a one-month period:

- Delusions
- Hallucinations
- Disorganized speech (eg, frequent derailment or incoherence)
- Grossly disorganized or catatonic behavior
- Negative symptoms (ie, affective flattening, alogia, avolition)

NOTE: Only one of these symptoms is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

AND at some time there is one of the following:

- Major depressive episode
- Manic episode
- Mixed episode

B. During the same period of illness, there have been delusions or hallucinations for at least two weeks in the absence of prominent mood symptoms.

C. Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness.

D. The disturbance is not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition.

SUBTYPES

Subtypes of schizoaffective disorder exist and may be noted in a diagnosis based on the mood component of the disorder:

Bipolar type

If the disturbance includes a

- Manic episode
- Mixed episode

Major depressive episodes usually, but not always, also occur in the bipolar subtype; however, they are not required for DSM IV diagnosis.

TABLE 2 Side effects associated with neuroreceptor blockade

RECEPTOR BLOCKED	SIDE EFFECTS
Alpha 1 adrenergic	Orthostatic hypotension, sexual side effects, nasal congestion
Muscarinic M1	Anticholinergic: constipation, blurring of vision, urinary retention
Histamine H1	Sedation and weight gain
Serotonin 5-HT2	Weight gain, increased appetite
Dopamine D2	Extrapyramidal effects (parkinsonism, dystonia, akathisia, tardive dyskinesia), elevated prolactin

Reprinted with permission from Mathews M, Muzina DJ. *Cleve Clin J Med.* Atypical antipsychotics: New drugs, new challenges. 2007;74:597-606. © 2007 Cleveland Clinic Journal of Medicine.

coming in." We assure him that it is not true and we do the best we can, but patients who are refractory do wear on mental health professionals. We tend to throw our hands up and ask, "What do we do now?"

Treatment goals and psychosocial planning

DR BLACK: The severity of Mr M's present condition warrants placement in a care facility because he is unable to adequately care for himself. In these facilities, oral drugs could be administered in a supervised setting and his psychotic condition would probably improve, as would his nutritional status and personal hygiene. Both are deteriorating despite his parents' attempts to provide care for him. Mr M currently refuses placement.

DR GOLDBERG: What are the treatment goals? At this point they may have less to do with trying to modify the patient's disease course and more to do with fundamental safety. His parents are getting older, so his psychosocial supports are dwindling. That strikes me as one of the critical pieces of psychosocial planning. In addition, I am concerned about his suicide risk over the next several years.

DR BLACK: He has been talking more about suicide recently and about being depressed.

DR GOLDBERG: I would be very concerned about this patient losing his social supports and about his risk of becoming homeless. To some extent, the D2 blockade he has from the medications may contribute to dysphoria and contribute to his demoralization and negativism.[13] Also, assuming he might have bipolar disorder rather than schizophrenia, I might consider introducing even a small dose of lithium into his regimen for its antisuicide effect. We are seeing a convergence of pharmacologic approaches in the treatment of schizophrenia and bipolar disorder, especially now that many atypical antipsychotics are approved for the treatment of both conditions.[14]

Conclusion

DR NASRALLAH: Given the refractory nature of this patient's condition and his relative success with this agent, I would suggest that he be put back on clozapine if possible. In addition, I would increase the dose of risperidone, which is currently insufficient at 25 mg biweekly, and discontinue the haloperidol. I think his symptoms may improve.

With mentally ill patients who have tried everything but continue to deteriorate and become more difficult to manage, the effect of wearing down the staff and caregivers is a major concern. "Starting over" and revisiting some treatment approaches may be an option, because medications that were not helpful in the past may be more appropriate for treating current symptoms. As the condition of a refractory patient worsens, treatment goals may need to be re-evaluated to determine if social supports are adequate and if the patient is becoming a greater risk to self or others. ■

REFERENCES

1. Tsuang MT, Woolson RF, Fleming JA. Long-term outcome of major psychoses. I. Schizophrenia and affective disorders compared with psychiatrically symptom-free surgical conditions. *Arch Gen Psychiatry* 1979;36:1295-301.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text revision*. Washington, DC: American Psychiatric Association; 2000.
3. Marneros A, Roettig S, Roettig D, et al. The longitudinal polymorphism of bipolar I disorders and its theoretical implications. *J Affect Dis* 2008;107:117-26.
4. Arndt S, Andreasen NC, Flaum M, et al. A longitudinal study of symptom dimensions in schizophrenia. Prediction and patterns of change. *Arch Gen Psychiatry* 1995;52:352-60.
5. Milev P, Ho BC, Arndt S, et al. Initial magnetic resonance imaging volumetric brain measurements and outcome in schizophrenia: a prospective longitudinal study with 5-year follow-up. *Biol Psychiatry* 2003;54:608-15.
6. Mathews M, Muzina DJ. Atypical antipsychotics: new drugs, new challenges. *Cleve Clin J Med* 2007;74:597-606.
7. Zhong KX, Sweitzer DE, Hamer RM, et al. Comparison of quetiapine and risperidone in the treatment of schizophrenia: a randomized, double-blind, flexible-dose, 8-week study. *J Clin Psychiatry* 2006;67:1093-103.
8. Halbreich U, Kahn LS. Hyperprolactinemia and schizophrenia: mechanisms and clinical aspects. *J Psychiatr Pract* 2003;9:344-53.
9. Yassa R, Nair V, Schwartz G. Tardive dyskinesia and the primary psychiatric diagnosis. *Psychosomatics* 1984;25:135-8.
10. Zarate CA Jr, Tohen M, Baldessarini RJ. Clozapine in severe mood disorders. *Compr Psychiatry* 1995; 56:411-7.
11. Lacro JP, Dunn LB, Dolder CR, et al. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry* 2002;63:892-909.
12. Copeland LA, Zeber JE, Salloum IM, et al. Treatment adherence and illness insight in veterans with bipolar disorder. *J Nerv Ment Dis* 2008;196:16-21.
13. Mizrahi R, Rusjan P, Agid O, et al. Adverse subjective experience with antipsychotics and its relationship to striatal and extrastriatal D2 receptors: a PET study in schizophrenia. *Am J Psychiatry* 2007;164:630-7.
14. Citrome L, Goldberg JF, Stahl SM. Toward convergence in the medication treatment of bipolar disorder and schizophrenia. *Harv Rev Psychiatry* 2005;13:28-42.

CASE 2

Psychosis with bipolar mania

Presented by
JOSEPH F. GOLDBERG, MD MOUNT SINAI SCHOOL OF MEDICINE, NEW YORK, NEW YORK; SILVER HILL HOSPITAL, NEW CANAAN, CONNECTICUT

In a young patient presenting with symptoms of psychosis, an accurate initial diagnosis is critical, as inappropriate treatment can significantly worsen the patient's condition and complicate future management. However, selecting the best initial therapy is not always straightforward, especially for patients whose condition involves mixed features.

Identifying information: Mr S, a 20-year-old single white male college student, was admitted for his second lifetime hospitalization for assessment of acute psychosis.

Chief complaint: "The timberline means death. Other people are suffering and it's my fault."

History of present illness: According to his roommate, Mr S has been isolating himself, failing to attend class, staying awake at night writing obscure essays, consuming only coffee and beer, and engaging in Internet gambling. In the month prior to admission he lost about $4,000 playing Texas Hold 'Em. When he did not return their phone calls for a week, his parents arrived at the dormitory and called their son's regular psychiatrist (Dr H), who advised them to bring him to the local emergency department. Upon admission the patient was intensely concerned that al-Qaeda was infiltrating the Internet and had chosen him as a military operative. He perceived secret messages being sent to him from tree stumps, and believed that the patterns in which they had been cut down ("the timberline") imparted clues about future terrorist attacks. He denied feeling depressed or euphoric and denied having suicidal thoughts or hallucinations.

Medications and allergies: Approximately one year earlier, Dr H had diagnosed Mr S with attention-deficit/hyperactivity disorder (ADHD) and depression. The patient was prescribed amphetamine/dextroamphetamine and escitalopram. At the time of admission, the patient apparently was not using the antidepressant but had an empty amphetamine bottle in his room. He claimed to have discontinued escitalopram use because of weight gain and erectile dysfunction.

Psychiatric history: At age 16, the patient was briefly treated by a therapist in response to declining grades and "moodiness." At age 19, soon after starting college, he was hospitalized after attempting to jump off a building while under the influence of alcohol. He returned to his parents' home and remained there on medical disability for the rest of the academic year.

Family history: The patient's older brother was diagnosed with bipolar disorder and completed suicide at age 28. The patient's father has recurrent episodes of depression and is treated with antidepressants. His mother has panic disorder and is treated with selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines.

Social history: Birth history is unremarkable, with full-term vaginal delivery. The patient achieved normal childhood milestones and was considered a popular child who had many friends. He excelled in school, especially in math and science, until his school performance began to decline inexplicably during his junior year in high school. He currently has no romantic or sexual relationships.

Physical examination: A urine toxicology screen was positive for amphetamine. Blood alcohol level was <10 mg/dL. Other routine laboratory results were normal.

Mental status examination: The patient appeared moderately overweight and disheveled, with unkempt, greasy long hair. He was at times motorically retarded and at other times excessively animated. He made little eye contact and seemed internally preoccupied, but was also easily distracted by background noises in the examining room. He responded to questions in a staccato, rapid-fire manner and was often difficult to interrupt. He described his mood as calm and mellow, but his affect was dysphoric. His thought processes were at times tangential, circumstantial, and illogical. His thought content was notable for paranoid delusions, grandiose delusions, and ideas of reference. He denied having hallucinations, suicidal thoughts, or homicidal thoughts. Formal assessment of his cognitive functioning was limited because of his distractibility and formal thought disorder. Insight was poor and judgment

was grossly impaired. The patient was admitted to the inpatient psychiatric unit.

Provisional diagnosis:

Axis I: Bipolar disorder, mixed episode, with psychotic features
- R/O amphetamine-induced psychosis
- R/O paranoid schizophrenia
- R/O schizoaffective disorder, bipolar subtype

Axis II: Deferred

Axis III: None

Problems with primary support group; problems with social environment; educational problems; problems with access to health care services

Axis V: 21

Treatment and continuation of case: During this hospitalization, the patient was initially treated with risperidone 1 mg bid and divalproex 750 mg/d. Because of persistent psychosis, the risperidone dose was increased to 4 mg bid and divalproex to 1500 mg/d (valproate level 74 mcg/dL). After achieving "modest improvement," the patient was discharged after 10 days and followed in an intensive outpatient program. However, he soon became grossly psychotic and was rehospitalized. He was agitated, sleepless, intrusive, and floridly paranoid. Divalproex was increased to 2000 mg/d (96 mcg/dL). Risperidone was discontinued due to lack of efficacy, and the patient was cross-tapered onto olanzapine, which was titrated to 40 mg/d. Within a week, the patient's psychotic symptoms resolved significantly and he was discharged.

At the one-month follow-up, the patient appeared sullen and depressed and had gained 18 pounds. The patient and parents wanted to know if he could discontinue his medications. The immediate concern of the staff was that the patient might discontinue treatment altogether if the weight gain was not effectively addressed.

PANEL DISCUSSION

Misdiagnosis in bipolar disorder

DR NASRALLAH: I must say I was rather surprised and dismayed by the misdiagnosis of ADHD and depression in this patient, given the very frank symptoms of psychotic mania that were evident, coupled with the many personal and family clues that this is bipolar disorder. This case is a good example of the findings from the National Depressive and Manic Depressive Association 2000 survey showing a nearly 70% misdiagnosis rate for this condition.[1] The average patient with bipolar disorder sees at least 4 different physicians, and one-third of these patients wait at least 10 years before receiving a correct diagnosis.

Obviously, any wrong diagnosis can lead to therapeutic misadventures. The treatment in this case—a stimulant and an antidepressant—was probably the worst possible combination for someone at the onset of bipolar disorder. In my judgment, it could well have contributed to his deterioration and exacerbation of his symptoms.

DR GOLDBERG: I share Dr Nasrallah's sentiments about the misdiagnosis, especially with the patient's family history of bipolar disorder and suicide in a first-degree relative. Antidepressant use has been shown to induce mania in susceptible patients, and those with a family history of bipolar disease have been shown to be particularly at risk.[2]

DR BLACK: The importance of taking a thorough family history cannot be overstated, particularly with bipolar disorder, since it is so familial compared to other conditions we treat. But there is evidence that bipolar disorder is frequently misdiagnosed as ADHD.[3] Not only is ADHD one of the "popular" diagnoses of the day, but the comorbidities of these conditions can add to the confusion, especially in younger patients.[4,5] In this case, however, there were plenty of clues pointing toward bipolar disorder.

DR PARISER: A related issue is that young people with hypomania, which is characteristic of bipolar II, also tend to be labeled as ADHD.[3]

Effects of stimulant use in bipolar disorder

DR BLACK: We might also consider the potential effects of the patient's stimulant use and possible abuse in terms of inducing or at least exacerbating the illness.

DR GOLDBERG: Yes, it is possible that he had a diathesis for bipolar disorder that may have been precipitated by overuse of the amphetamine. I would not say it was purely iatrogenic. Not only is acute mood destabilization problematic in bipolar disorder, but use of mood-destabilizing substances may also delay acute remission or contribute to treatment resistance.[6]

DR MUZINA: I see many patients, including some who are professional athletes, who exhibit this kind of bipolar–stimulant spectrum. Akiskal and others have sometimes labeled this as bipolar three-and-a-half, whereby subthreshold bipolar traits become complicated by stimulant abuse.[7,8] In the patient's premorbid history, were there any indications of hyperthymic or cyclothymic traits?

DR GOLDBERG: That is an interesting question. One indication may be his popularity—having a lot of friends and being fairly sociable and object-seeking—along with excelling academically. An interesting study based on an Israeli draft registry described high academic performance in army recruits as being one of the more robust cognitive predictors of patients who go on to develop bipolar illness.[9] Retrospectively, one could speculate that he may have some hyperthymic traits above the norm.

DR MUZINA: In addition, he may be continuing to use amphetamines obtained illegally or possibly through Internet prescription sites. That could be a potential confounding factor going forward.

Selection of antipsychotic therapy in bipolar disorder

DR NASRALLAH: It is possible that stimulant abuse contributed to the refractoriness of this patient's psychotic symptoms. He responded somewhat to the combination of risperidone and divalproex but then deteriorated rapidly after discharge. His initial valproate blood level was 74 mcg/dL, which suggests there is room for increasing the dose.[10] However, raising the valproate levels did not appear to be sufficient until the antipsychotic agent, olanzapine, was added.

DR GOLDBERG: It is reasonable to speculate that he might have responded better had the stimulants not been in the picture. Regarding the divalproex dosage, a study by Allen and colleagues on treatment of acute mania in the emergency department suggested that serum valproate levels closer to 94 mcg/dL were associated with better results.[10] People sometimes administer this drug cautiously, rather than loading it at 20 to 30 mg/kg, and starting at 750 mg is probably too low for a patient who is floridly manic.

With respect to risperidone, the patient was taking 8 mg/d for a few weeks, which may not have constituted an adequate trial. I think his decompensation after discharge was too rapid to attribute to nonadherence. I believe that the loss of structure and support from the hospital contributed to the return of his psychotic symptoms. Risperidone may not be a sufficiently broad-spectrum antipsychotic agent for him. When his condition deteriorated, olanzapine was chosen because of the perception that it may be a better choice after nonresponse to risperidone.

DR NASRALLAH: How should this patient's treatment proceed? Weight gain from olanzapine is a problem, and the patient also appears to be exhibiting symptoms of postmanic depression.

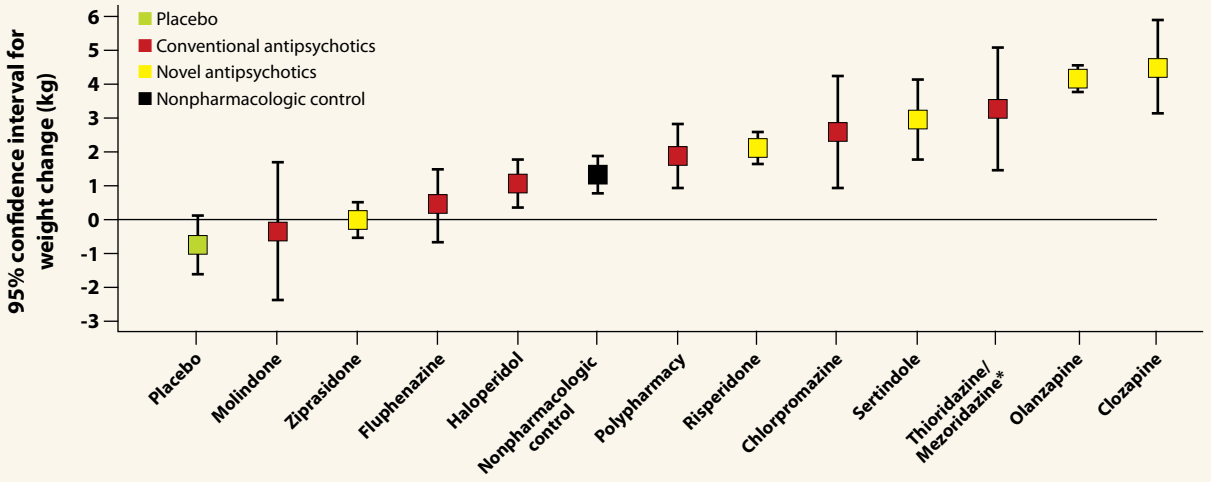
DR GOLDBERG: Adding fluoxetine to olanzapine, thereby creating an olanzapine-fluoxetine combination, would offer an FDA-approved option for the treatment of bipolar depression. In this instance, I instead opted to add lamotrigine, which is weight-neutral, in an effort to reduce the risk of the patient developing a full depressive episode.[11]

DR PARISER: Olanzapine is a very effective atypical antipsychotic, but weight gain is a major concern for many patients receiving this drug as well as clozapine. I have observed that many patients who gain weight tend to go off the medication, and those who do may not always admit that they are nonadherent (**FIGURE**).

Weight gain of 18 pounds in just one month signals the clear need for some type of intervention, whether that involves changing the olanzapine or divalproex, or adding other agents that might help to counteract psychotropic-induced weight gain, such as topiramate, sibutramine, or metformin.[12,13] Because obesity and chronic neuroleptic use are risk factors for sleep apnea in psychiatric patients, it might then be beneficial to conduct a sleep study.[14] Use of continuous positive airway pressure (CPAP) may improve his depression as well as his ability to lose weight.[15]

DR NASRALLAH: It is worth noting that this patient required about 40 mg of olanzapine, which is twice the upper limit of the recommended dose. One approach would be to substitute another atypical antipsychotic that has a lower potential for metabolic effects. One option is quetiapine, which is effective in treating psychosis and mania and also in treating bipolar depression.[16] In 2007, the manufacturer of olanzapine added a warning label to its prescribing information to indicate that olanzapine is more likely than other atypical antipsychotics to cause high blood sugar levels. However, it should also be noted that, according to the FDA, all atypical antipsychotics, including quetiapine, are thought to confer some risk for metabolic syndrome. Since 20 mg of olanzapine did not seem to resolve his symptoms, he may require a correspondingly high dose of

FIGURE Weight change with typical and atypical antipsychotics



95% confidence intervals for weight change after 10 weeks on standard drug doses, estimated from a random effects model

*Mezoridazine is no longer available in the United States.

Allison DB, et al. *Am J Psychiatry*. 1999;156:1686-1696; reprinted with permission from the American Journal of Psychiatry. © 1999 American Psychiatric Association.

quetiapine. Ziprasidone might be another consideration, particularly since the American Diabetes Association Consensus Development Conference perceives it as carrying among the lowest risks of causing metabolic dysregulation.[17] However, as yet there are no data with ziprasidone in treatment-resistant mania.

DR GOLDBERG: Switching from olanzapine to a different atypical antipsychotic carries the risk that other agents may not work as well, as we saw when this patient had previously been taking risperidone. Metabolic effects of therapy are difficult to predict, in part because so many outside factors can affect weight gain.[18] Many of the atypical antipsychotics are associated with metabolic changes such as weight gain. Olanzapine resulted in the greatest weight gain in the large-scale CATIE trial.[19] Risperidone was shown to be more weight-neutral, but was not effective in this patient. Ziprasidone is another agent that may be more weight-neutral.

DR BLACK: A study by Gupta and colleagues showed that patients switched from olanzapine to quetiapine actually lost some weight.[20] A possible advantage of using quetiapine might be its sedating properties, since this patient has a history of sleep problems. A study by Ketter to evaluate symptom improvement of bipolar depression and bipolar mania with quetiapine monotherapy looked at items on the Montgomery-Asberg Depression Scale (MADRS) and found a rapid and dramatic improvement in sleep quality related to overall MADRS improvement.[21] It seems to me that lithium and carbamazepine are rarely used anymore as initial therapy for bipolar disorder. I wonder whether either of these would be effective in this patient.

DR NASRALLAH: Lithium is well recognized for its protective effect against suicide.[22] With the history of suicide in a first-degree relative and this patient's own attempt a year ago, I would strongly advise selecting a therapy that may help reduce the risk of suicide, in addition to aggressively monitoring his depressive symptoms.

DR PARISER: Among the downsides of lithium therapy are its risk of causing cognitive impairment and tremor, both of which are likely to reduce adherence.[23,24]

DR NASRALLAH: Reducing depressive features in a patient with bipolar disorder helps minimize the risk for suicide, so an atypical agent with an antidepressant effect is another alternative. There are good data supporting the use of quetiapine in the treatment of bipolar depression.[25,26] Data on the effectiveness of using ziprasidone in bipolar depression are anticipated later this year.

DR PARISER: On the other hand, aripiprazole has had negative placebo-controlled findings in both the acute

treatment of bipolar depression and the prevention of bipolar depression, in contrast to the more favorable data for this agent as add-on therapy for unipolar depression.[27-30] In addition, the STEP-BD trial examined risperidone monotherapy and found a 4.6% response rate for treatment-resistant bipolar depression.[31]

DR MUZINA: As Dr Black mentioned, adding a second anticonvulsant to the divalproex that Mr S is already taking, such as carbamazepine, might be another option. For this patient, the antikindling effects from combined anticonvulsant therapy might be beneficial not only in terms of controlling the mixed-state withdrawal phenomena, but also in controlling cravings for stimulants or for activation and mood enhancement of the underlying temperament.

DR NASRALLAH: Speaking to the antikindling effect, one of the patient's early symptoms was waking up at night and writing lengthy, obscure essays about philosophical or religious issues. I have observed similar traits in patients with complex partial seizures in temporal lobe epilepsy. These seizures can go unnoticed unless the patient has an EEG. I would be interested to see the results of an EEG with nasopharyngeal leads under sleep-deprived conditions in this patient, to rule out complex partial seizures.

Conclusion

DR GOLDBERG: The patient's olanzapine therapy was discontinued and he was prescribed lamotrigine to stabilize his symptoms as well as topiramate to help counteract weight gain while continuing to monitor his metabolic profiles. To sum up the panel's recommendations, the best course for long-term treatment seems to be another atypical antipsychotic with a somewhat lower risk of metabolic side effects, relative to olanzapine, as well as an indication for treating bipolar depression to help lower the risk of suicide in this high-risk patient. ■

REFERENCES

1. Hirschfeld RMA, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry* 2003;64:161-74.
2. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. *Bipolar Disord* 2003;5:407-20.
3. Benazzi F. Bipolar disorder: focus on bipolar II disorder and mixed depression. *Lancet* 2007;369: 935-45.
4. Biederman J, Faraone S, Mike E, et al. Attention-deficit hyperactivity and juvenile mania: an overlooked comorbidity. *J Am Acad Child Adolesc Psychiatry* 1996; 35:997-1008.
5. Spencer TJ, Biederman J, Wozniak J, et al. Parsing pediatric bipolar disorder from its associated comorbidity with the disruptive behavior disorders. *Biol Psychiatry* 2001;49:1062-70.
6. Goldberg JF, Garno JL, Leon AC, et al. A history of substance abuse complicates remission from acute mania in bipolar disorder. *J Clin Psychiatry* 1999;60:733-40.
7. Camacho A, Akiskal HS. Proposal for a bipolar-stimulant spectrum: temperament, diagnostic validation and therapeutic outcomes with mood stabilizers. *J Affect Disord* 2005;85:217-30.
8. Winokur G, Turvey C, Akiskal H, et al. Alcoholism and drug abuse in three groups: bipolar I, unipolars, and their acquaintances. *J Affect Disord* 1998;50:81-9.
9. Reichenberg A, Weiser M, Rabinowiz J, et al. A population-based cohort study of premorbid intellectual, language, and behavioral functioning in patients with schizophrenia, schizoaffective disorder, and nonpsychotic bipolar disorder. *Am J Psychiatry* 2002;159: 2027-35.
10. Allen MH, Hirschfeld RM, Wozniak PJ, et al. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. *Am J Psychiatry* 2006;163:272-5.
11. Bowden CL, Calabrese JR, Ketter TA, et al. Impact of lamotrigine and lithium on weight in obese and nonobese patients with bipolar I disorder. *Am J Psychiatry* 2006;163:1199-201.
12. McElroy SL, Frye MA, Altshuler LL, et al. A 24-week, randomized, controlled trial of adjunctive sibutramine versus topiramate in the treatment of weight gain in overweight or obese patients with bipolar disorders. *Bipolar Disord* 2007;9:426-34.
13. Wu RR, Zhao JP, Guo XF, et al. Metformin addition attenuates olanzapine-induced weight gain in drug-naïve first-episode schizophrenia patients: a double-blind, placebo-controlled study. *Am J Psychiatry* 2008; 165:352-8.
14. Schwartz DJ, Karatinos G. For individuals with obstructive sleep apnea, institution of CPAP therapy is associated with an amelioration of symptoms of depression which is sustained long term. *J Clin Sleep Med* 2007;3:631-5.
15. Winkelman JW. Schizophrenia, obesity, and obstructive sleep apnea. *J Clin Psychiatry* 2001;62:8-11.
16 Thase ME. Quetiapine monotherapy for bipolar depression. *Neuropsychiatr Dis Treat* 2008;4:21-31.
17. American Diabetes Association, American Psychiatric Association, American Association for 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.
18. Citrome L, Vreeland B. Schizophrenia, obesity, and antipsychotic medications: what can we do? *Postgrad Med* 2008;120:18-32.
19. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353:1209-23.
20. Gupta S, Masand PS, Virk S, et al. Weight decline in patients switching from olanzapine to quetiapine. *Schizophr Res* 2004;70:57-62.
21. Ketter T. Rate of improvement across different symptom dimensions in bipolar disorder with quetiapine. Presented at the American Psychiatric Association 159th Annual Meeting; May 20-25, 2006; Toronto, Ontario, Canada.
22. Fountoulakis KN, Vieta E, Siamouli M, et al. Treatment of bipolar disorder: a complex treatment for a multi-faceted disorder. *Ann Gen Psychiatry* 2007; 6:27.
23. Mur M, Portella MJ, Martinez-Aran A, et al. Long-term stability of cognitive impairment in bipolar disorder: a 2-year follow-up study of lithium-treated euthymic bipolar patients. *J Clin Psychiatry* 2008;69: 712-9.
24. Gelenberg AJ, Jefferson JW. Lithium tremor. *J Clin Psychiatry* 1995;56:283-7.
25. Hardoy MC, Garofalo A, Mellino G, et al. Quetiapine as add-on treatment for bipolar I disorder: efficacy in preventing relapse of depressive episodes. *Clin Pract Epidemiol Ment Health* 2007;3:17.
26. Doree JP, Des Rosiers J, Lew V, et al. Quetiapine augmentation of treatment-resistant depression: a comparison with lithium. *Curr Med Res Opin* 2007;23:333-41.
27. Thase ME, Jonas A, Khan A, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. *J Clin Psychopharmacol* 2008;28:13-20.
28. Keck PE Jr, Calabrese Jr, McQuade RD, et al. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. *J Clin Psychiatry* 2006;67:626-37.
29. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2007;68:843-53.
30. Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 2008;28:156-65.
31. Nierenberg AA, Ostracher MJ, Calabrese JR, et al. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry* 2006;163:210-6.

CASE 3

Bipolar depression and anxiety

Presented by
STEPHEN F. PARISER, MD OHIO STATE UNIVERSITY MEDICAL CENTER, COLUMBUS, OHIO

Severe mood and anxiety symptoms coupled with somatic complaints led to an initial misdiagnosis in a perfectionistic young career woman. Careful assessment revealed a correct diagnosis of bipolar mixed disorder.

Identifying information: The patient is a 26-year-old single woman who was referred to me for evaluation of severe mood and anxiety symptoms.

Chief complaint: She had several somatic complaints, including lethargy and fatigue. She looked disheveled and was extremely irritable, anxious, and depressed.

History of present illness: Following an initial stellar career performance with a major national retailer, the patient began to falter precipitously in her work. She became agitated, lost interest in her appearance, and had difficulty concentrating. Due to her change in affect and functioning, her employer recommended that she have an evaluation at a prominent medical facility, where, because of odd neurologic and anxiety-related complaints, she was diagnosed with presumed conversion disorder and anxiety. She took a leave of absence from work and, later, was referred to me for reassessment of her condition.

Medications and allergies: The patient had been prescribed a regimen of venlafaxine XR 225 mg/d (for 12 weeks), clonazepam 1 mg bid, and bupropion SR 300 mg/d (for 1 year).

Psychiatric history: Beginning in her teens, the patient had experienced several episodes of anxiety and depression. In her early 20s, she was hospitalized for depression; there were no comorbid diagnoses made at that time, although she had symptoms of obsessive-compulsive disorder (OCD) at that time. She said she was a perfectionist and would count and check things repeatedly, and reported that she had obsessional thoughts. She had not experienced euphoria or any other typical symptoms of bipolar disorder. But, upon further questioning, she acknowledged feeling overstimulated and confirmed feeling tremendously irritable.

Medical history: The patient has always been in good physical health.

Family history: Her parents divorced when she was 12 years old. She was not close to her father, whom she described as moody and financially irresponsible. Further inquiry suggested that her father had bipolar disorder and her mother had been diagnosed with depression. A brother 2 years her senior was doing quite well.

Social history: The patient did well in high school and was popular. She attended a small college and majored in fashion merchandising. No alcohol or drug abuse was reported. There was no history of impulsively acting out.

Review of symptoms: The patient appeared depressed and exhibited psychomotor retardation. At the same time she was irritable and in angst. She had a very restricted affect, although she was at times tearful. There was no cognitive disability, but she complained of having difficulty focusing. She acknowledged a need to do things perfectly, which slowed her work.

Physical examination: Paresthesias of her legs and feet. The results of the laboratory workup showed macrocytosis and B_{12} deficiency.

Assessment: I concluded that the patient had bipolar mixed disorder and OCD. Her functional level was low, and there were many stressors in her life.

Provisional diagnosis:
Axis I: Bipolar disorder mixed; OCD
Axis II: Deferred
Axis III: B_{12} deficiency
Axis IV: Financial concerns, job issues, and chronic illness
Axis V: 40

Treatment plan: I slowly tapered and discontinued the venlafaxine and the clonazepam. I then prescribed quetiapine, lamotrigine, and sertraline, in that order to protect against mania, increasing the dose to 350 mg/d, at which time she began to sleep well and noted improvement in her irritability and distractibility. The lamotrigine dose was slowly increased to

200 mg/d and sertraline, slowly increased to 200 mg/d. The patient started B_{12} injections and her paresthesias stopped. I also conducted cognitive behavioral therapy to augment the medication. After 4 months, the patient looked and felt well and communicated effectively. Symptoms of OCD remitted and she returned to work. Even following continued conflicts with her supervisor and eventual resignation from her job, the patient remained optimistic about future opportunities.

PANEL DISCUSSION

Overstimulation as a diagnostic key

DR NASRALLAH: Focusing on symptoms without giving due consideration to a patient's history and family history can lead to a snap misjudgment and inappropriate treatment. Dr Pariser skillfully elicited from this patient her symptoms of irritability and overstimulation, which steered him to the bipolar spectrum.

DR PARISER: To confirm overstimulation, I often ask patients if they can identify with an image offered by the wife of a former bipolar patient who described him as "a gerbil on speed."

DR MUZINA: As I listened to your description of the patient, I wondered if perhaps she had some cluster B personality structure. This happens quite frequently and perhaps even in bipolar II patients. They may have more borderline histrionic and atypical personality traits than individuals with major depression.[1] Did personality structure enter into the differential diagnosis?

DR PARISER: The institution that saw her first certainly was focused on Axis II concerns. However, data show that many patients who have Axis I disorders, particularly those who are like this patient, may be mislabeled with personality disorders. Yet when the depressive disorder resolves, much of that concern disappears. This patient rarely took advantage of me—never called me inappropriately and always apologized for taking my time. When she lost her job, her level of independence was remarkable. She was also very insightful. The traits you aptly noticed in this situation cleared up when she felt better.

One problem in diagnosing a personality disorder is the prospect of lifelong management. In our mood disorders clinic, I encourage residents to withhold a diagnosis of personality disorder until we are secure in our assessment and until we've tried a rational treatment regimen. Once we label someone with a personality disorder, or even label them as being refractory with mood symptoms, it is easy to want to avoid them. Patients with mixed bipolar disorder are the ones I intuitively want to back away from.

Therapeutic agents for a dual diagnosis

DR GOLDBERG: With a working diagnosis of a mixed episode and an anxiety disorder, would using sertraline be redundant with the quetiapine? We published data last year showing that in a mixed episode, selective serotonin reuptake inhibitors (SSRIs) worsen mania symptoms and do not touch the depression.[2] Given data from studies of generalized anxiety disorder and quetiapine's ability to reduce anxiety symptoms in the context of depression, using this drug alone might be safer than augmenting with sertraline and be just as effective as the combination.

DR PARISER: That is a good point. A number of studies have also looked at cycle acceleration when antidepressants are used in augmentation.[3,4] When someone is protected with antimanics, the potential for this complication lessens. And sertraline is less likely to be a problem than the tricyclic antidepressants or clozapine.

DR GOLDBERG: In the pure depressed phase.

DR PARISER: This patient was on quetiapine for quite a while before I added sertraline, which I did because the lingering depressive and obsessional features were tremendously debilitating. As a rule, I, too, try to avoid using antidepressants in bipolar depression, especially in patients with mixed disorder. But in this situation, where there was frank comorbid OCD and not simply anxiety, the use of an SSRI seemed essential. This patient did benefit dramatically when sertraline was added. Her OCD symptoms improved.

DR NASRALLAH: The immediate combination therapy prescribed by her initial psychiatrist—venlafaxine, clonazepam, and bupropion—seemed unjustified. Trying one drug at a time makes more sense. With depression and anxiety we often use an SSRI that is indicated for both conditions. But I question the use of 2 antidepressants as well as a benzodiazepine; she could become physiologically tolerant to the latter. Especially since quetiapine, which you prescribed, is not only indicated for bipolar depression but also has strong anxiolytic effects.[5]

The other comment I have is that bupropion is the only antidepressant that is useless for anxiety. It is purely a norepinephrine-reuptake inhibitor. But venlafaxine would work. So giving bupropion for a year was totally unnecessary.

DR BLACK: However, presuming that Dr A felt the patient had OCD, the initial regimen doesn't necessarily sound bad. Venlafaxine, in at least one study, had anti-obsessional properties, and it is frequently combined with clonazepam. I often use bupropion to augment an anti-obsessional agent that is not sufficiently boosting the patient's mood.

I would also like to probe the patient's report of racing thoughts or feeling overstimulated. Many patients with OCD will say the same thing. When you explore it further, their racing thoughts turn out to be obsessions, basically. They use the term racing thoughts when it is really obsessional thinking. Do you think that might have been a possibility with this patient?

DR PARISER: She simply couldn't shut her mind off. She was highly irritable, distractible, and felt overstimulated. There were other clues to bipolar illness. She did have hypomanic episodes in the past but they were never dramatic enough for her to seek help. The family history was also suggestive.

Dr A, by the way, did not make a diagnosis of OCD. I am not interested in faulting anyone here, but data show that bipolar patients—having either agitated depression or mixed bipolar disorder—represent a large number of participants in studies. From the STEP-BD data we also know that when many of those patients entered the trial, they were suicidal or had suicidal ideation.[2] I am never 100 percent certain about anyone's diagnosis, but I thought it would be a huge risk not to treat her as though she had bipolar disorder or a mixed episode. If she did have a bipolar disorder and was given higher doses of venlafaxine or put on a tricyclic antidepressant, she could go into a terrible crisis.

I try to look at the comparative risks of treatment decisions. And I always ask my patients to go on the Web site of the National Institute of Mental Health (NIMH), where they can find useful information about bipolar disorder. I often avoid treating these patients the first time I see them, because once you start treatment for bipolar disorder, for most people it is a long haul.

DR BLACK: I had another question about the diagnosis of conversion disorder, presumably made on the basis of the patient's paresthesias and other somatic complaints. When that diagnosis is entertained, it is often wrong. There usually is some organic basis behind the complaints. When I see paresthesia, it is generally in a patient who meets the criteria for somatization disorder as well. There is no indication of that in this case except for the phrase "multiple somatic complaints."

DR PARISER: The initial psychiatrist actually told her she had conversion disorder.

DR BLACK: That seems inappropriate.

B_{12} deficiency can contribute to depression

DR PARISER: I certainly thought it was unhelpful. Fortunately, this patient had enough ego strength that the personality disorder diagnosis did not hurt her significantly. Her biggest concern was about her prospect of recovery. Seeing her reminded me of Shakespeare's line in *Measure for Measure*: "The miserable have only hope." When she realized we were going to look carefully at all factors—a gastrointestinal consult for the B_{12} deficiency; MRI for the headaches, and so forth—she began to get better and the symptoms went away. I think they were perhaps manifestations of the terrible agitation and anxiety, potential job loss, and financial ruin she was facing, and a huge sense of failure as compared with her brother who is very successful.

DR NASRALLAH: Dr Pariser, is it possible that her depression was due in large part to the B_{12} deficiency?[6]

DR PARISER: Yes, it is possible, but I don't know for sure. She had a long history of mood symptoms. At the point I saw her, she was on the verge of suicide. I had to treat her with that in mind, while also seeing that she got B_{12} supplementation.

DR NASRALLAH: How did you get her off clonazepam, which she had been taking for a year?

DR PARISER: Because she was not sleeping it was easy to convince her to try the quetiapine. She gradually saw the benefit it offered her. This is not just a symptomatic issue, because sleep disruption may also have helped perpetuate the illness. I have seen her now for more than a year. There has been progress, but it has been slow. The clonazepam taper went well once she was taking the quetiapine.

I would like to hear the group's thoughts on this: In my experience, it is harder to taper and eliminate

venlafaxine due to discontinuation syndrome than it is to taper and eliminate clonazepam. This patient was not taking a large dose of clonazepam and she had not been taking it for a long time. So, here is someone who is acutely distressed and I am concerned that venlafaxine may actually be making her worse. I proposed the idea of slowly tapering venlafaxine knowing that her symptoms could exacerbate from the discontinuation syndrome.[7]

Avoiding discontinuation syndrome

DR GOLDBERG: I agree, it is a double-edged sword. In stopping an antidepressant as part of treating a mixed state, you cannot discontinue venlafaxine as quickly as you do other agents. You want to stop the agent that is contributing to manic or hypomanic symptoms, but if you do it abruptly you can end up causing more problems (**TABLE**).

DR PARISER: I do not use venlafaxine much anymore for that very reason. Have any of you seen the same discontinuation symptoms with duloxetine?

DR NASRALLAH: Are you asking if duloxetine induces manic switching as much as venlafaxine?

DR PARISER: Yes, and whether duloxetine has the same likelihood of causing severe discontinuation symptoms as venlafaxine.

DR MUZINA: I do not know for sure if the data support it, but I have seen the same sort of continuation phenomena with venlafaxine, the new desvenlafaxine, and duloxetine. I take the same precautions with all of them.[8]

DR NASRALLAH: That is very interesting. What kind of withdrawal symptoms do you see? Is there an exacerbation of their depression, or other symptoms?

DR PARISER: I see sleep disruption, anxiety, and agitation.

DR MUZINA: And I can add headaches, nausea, vomiting, and flu-like symptoms.

DR BLACK: This is very much the same as what you see with the SSRI discontinuation syndrome.

DR MUZINA: I think it is worse.

DR PARISER: I agree, it is far worse. How do all of you treat the discontinuation syndrome?

TABLE Symptoms of SSRI discontinuation syndrome

TYPE	SYMPTOMS
Disequilibrium	Lightheadedness/dizziness, vertigo, ataxia
Sensory symptoms	Paresthesia, numbness, electric shock-like sensations
General somatic symptoms	Lethargy, headache, tremor, sweating, anorexia
Sleep disturbance	Insomnia, nightmares, excessive dreaming
Gastrointestinal symptoms	Nausea, vomiting, diarrhea
Affective symptoms	Irritability, anxiety/agitation, low mood

SSRI = selective serotonin reuptake inhibitor.

Reprinted with permission from Haddad PM. Antidepressant discontinuation syndromes. *Drug Safety.* 2001;24(3):183-197. © 2001 Adis International Ltd.

DR BLACK: Slowly, very slowly.

DR PARISER: I have a patient with bipolar disorder who is on 37.5 mg of venlafaxine, and she cannot get off that last 37.5 mg. Every time I try, discontinuation symptoms start. It is bizarre. Nobody needs to be on a dose as low as 37.5 mg of venlafaxine, but I have no choice and must allow her to continue.

DR GOLDBERG: The pharmacists complain, but I had a patient like that who would get nausea and headaches if we lowered the dose. We would open the capsule and dispense it in 4 ounces of water. She would take half and put the other half in the refrigerator. We kept lowering the dose that way. Some people may be very sensitive to subphysiologic doses; perhaps this is due to gastrointestinal or vestibular factors.

Conclusion

DR NASRALLAH: It is interesting that we have unanimity on the difficulty in withdrawing venlafaxine, and yet I have not come across many articles addressing the problem. Maybe it is time for a general review paper.

Let me raise a final point. Your patient's sensitivity to stress is obvious; it emanates from the case presentation. Even after you stabilized her, when she returned to work she still couldn't tolerate her boss, and resigned. Do you think cues in a person's work environment can have a triggering effect on his or her illness?

DR PARISER: Yes, I do. Once there is a wound, every encounter with salt is going to hurt. The anxiety of going back into that environment could provoke a reaction. But from everything I heard from the patient—if she is being straight with me, and I think she is—her boss was horribly difficult.

One of the issues she and I have talked about is whether it would be wise for her pursue something other than merchandising. I have encouraged her to think about that carefully; even with medical treatment, she could get into trouble again.

DR NASRALLAH: This has been a very interesting case of a patient with depression, anxiety, and somatic complaints, and how to simplify the medical regimen to cover all of these features. ■

REFERENCES

1. Joyce PR, Luty SE, McKenzie JM, et al. Bipolar II disorders: personality and outcomes in 2 clinical samples. *Aust NZ J Psychiatry* 2004;38:433-8.
2. Goldberg JF, Perlis RH, Ghaemi SN, et al. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. *Am J Psychiatry* 2007;164:1348-55.
3. Salvi V, Fagiolini A, Swartz HA, et al. The use of antidepressants in bipolar disorder. *J Clin Psychiatry* 2008;69:1307-18.
4. Paplos DF. Switching, cycling, and antidepressant induced effects on cycle frequency and course of illness in adult bipolar disorder: a brief review and commentary. *J Child Adolescent Psychopharmacol* 2003;13:165-71.
5. Calabrese JR, Keck PE, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry* 2005;162:1351-60.
6. Tiemeier H, van Tuijl HR, Hofman A, et al. Vitamin B12, folate, and homocysteine in depression: the Rotterdam Study. *Am J Psychiatry* 2002;159:2099-101.
7. Taylor D, Stewart S, Connolly A. Antidepressant withdrawal symptoms—telephone calls to a national medication helpline. *J Affect Disord* 2006;95:129-33.
8. Perahia DG, Kajdasz DK, Desaiah D, et al. Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder. *J Affect Disord* 2005;89:207-12.

CASE 4

Depression and anxiety: Distinguishing unipolar and bipolar disorders

Presented by
DAVID J. MUZINA, MD CLEVELAND CLINIC, CLEVELAND, OHIO

The use of steroids and supplements can complicate the clinical picture in a young man with mood swings, anxiety, and depression referred for psychiatric evaluation by his primary care clinician and a psychologist.

Identifying information: A 20-year-old single man was referred by his primary care physician and a psychologist for medical management of mood swings, anxiety, and confusion.

Chief complaint: The patient reported unremitting sadness that had lasted more than a year, and said that he generally felt "dead inside" or "like a zombie." He was often ruminative and irritable, with difficulty concentrating.

History of present illness: The young man's sadness and disagreeable sensations were relieved only for periods of 3 to 4 days when he felt more worried than sad. It was during these intervals of worry that he grew more ruminative, tired, and irritable, and said he could not "sort out" his thoughts.

The patient could not recall when he last felt well enough to have fun with friends. He ruminated about the past, often trying to change it in his mind and thereby causing himself to become confused about what was real and what he might have imagined to be real. In particular, he was preoccupied with the recent loss of a relationship with a girl, which began in high school. He blamed the loss on his moodiness. However, he also acknowledged that he briefly dated her younger sister, a short time after which the girlfriend abruptly stopped returning his calls, telling him it was payback for dating her sister. The patient spent a great deal of time online looking at his ex-girlfriend's MySpace social-interaction page, which only caused him to feel worse.

He blamed himself for everything that was wrong in his life and struggled with thoughts that people were talking and thinking about him negatively. Because he believed he was physically too small, he exercised regularly to stay in good shape.

Medications and allergies: The referring primary care physician and psychologist had prescribed sertraline 100 mg/d for 3 weeks. They then switched him to venlafaxine 225 mg/d, which he took for 4 to 5 weeks. However, the patient stopped taking both drugs on his own initiative because they made him feel numb, and he also thought they made him feel more depressed. In the week before the initial psychiatric evaluation, his father had given him some sleeping medications because he was often tense, keyed up, and unable to relax in the evenings and around bedtime. They did not help. Otherwise, this young man had not been taking any medications during the previous 6 months.

Psychiatric history: The patient had never been hospitalized and denied any suicidal or homicidal ideation. As mentioned, he sometimes thought he could undo the past by some ritualistic mental action.

The young man was an only child and spent a lot of time talking about this. He denied any history of childhood trauma. However, he held an unusual suspicion that his parents were hiding a birth defect from him, and that this defect was in some manner related to his current issues and difficulties. He did not give any more details about this suspicion, saying, "Every time I ask them about it, they tell me I'm crazy and just make a joke about it." His mother reported that it took about 10 years to conceive, but there were no complications with the pregnancy or delivery.

The patient received no intervention during the first 6 months of the current episode, when his family doctor was contacted. The doctor referred the patient to a psychologist for counseling, and the psychologist quickly referred him back to the doctor, believing that the young man needed a prescription for antidepressant medication.

His mother said he was drinking alcohol more regularly while on his medications, and that he was probably not fully compliant with the antidepressant regimens. He was never prescribed benzodiazepines for his anxiety and tension, apparently due to concern about abuse potential.

Medical history: The patient reported no medical problems connected with his mental symptoms, and he specifically denied any history of cardiovascular disease, seizures, or head injury.

Family history: The mother had been diagnosed with situational anxiety and depression and was taking fluoxetine. A paternal aunt was taking sertraline for a diagnosis of panic disorder. There was no known family history of schizophrenia, bipolar disorder, or suicide.

Social history: The patient had always been social, had no developmental delays, and performed well academically until his senior year in high school when his grades declined. He withdrew from friends and began experiencing anxiety and periods of sadness. It was during this time that he was working out more vigorously and using dietary supplements.

The patient still lived at home with his parents. Although he finished high school, he did not enroll in college. He had no specific plans for the future and was working part-time at a fast food restaurant.

Review of systems: He had not experienced panic attacks, excessive physical rituals or compulsions, nightmares, or flashbacks. He worried chronically in the past year, experiencing poor sleep, restlessness, and muscle tension.

On direct questioning, the patient denied hallucinations, thought insertion, or broadcasting. However, referential thinking did seem to weave through some of his history.

There were no clear periods of euphoria or classic manic symptoms. He often had been irritable and had a difficult time separating the irritability from the depression. Periodically, his anxiety rose above the daily baseline of tension and on-edge feelings to include confused thinking, which he described not as racing thoughts but as having many simultaneous thoughts that aggravated the tension and interrupted sleep.

The last 6 months were dominated by fragmented sleep, decreased appetite and libido, pervasive guilt with passive thoughts of death, but absolutely no suicidal ideation.

Substance use history: He rarely used alcohol, but admitted to drinking more heavily during his senior year of high school. He also denied any illicit substance abuse. He had used supplements purchased over the counter and online; however, he denied using injectable steroids. He would also augment his workouts with large amounts of energy drinks.

Although he denied current use of dietary supplements, he admitted to having done so in the past. He had used several herbal preparations as well as creatinine, protein supplements, and androstenedione that he would buy at nutrition stores or on the Internet to increase his testosterone levels and promote muscle growth. He conceded that he might have been more irritable, aggressive, and volatile while taking the supplements for his workouts. Though he claimed not to be using these supplements at present, he still had them and refused to discard them, saying he did not want to waste more than $300.

Physical examination: The patient was in good general health, clearly well-developed with increased muscle mass. Neurologic exam was unremarkable.

Mental status examination: This was largely within normal limits, although the patient exhibited a restricted affect when discussing his ex-girlfriend, in contrast to expected sadness or tearfulness. His thought process was logical, linear, and goal-directed. Cognitive testing, while limited to a brief Mini Mental State Exam, detected only some difficulty doing the serial seven test, but his effort was poor.

Assessment: The initial psychiatric impression was that while there were a number of diagnostic considerations, this young man most likely suffered from a mood disorder. Although he was never clearly manic, the presence of significant irritability and "crowded" thoughts along with the cyclical nature of his symptoms suggested Bipolar II disorder.

Provisional diagnosis:

Axis I: Bipolar disorder, mixed episode, with psychotic features
- R/O substance-induced mood disorder with psychotic features
- R/O paranoid schizophrenia
- R/O schizoaffective disorder, bipolar subtype

Axis II: Deferred

Axis III: None

Axis IV: Problems with primary support group; problems with social environment; educational problems; problems with access to health care services

Axis V: 21

Treatment: Baseline blood work, including thyroid function, heavy metals, metabolic panels, and toxicology screens were ordered. Although the patient's presentation and family history suggested mood disorder rather than

thought disorder, an MRI of the brain and projective testing were obtained to better evaluate a potential first-break psychosis. All test results were within normal limits.

The patient was referred to a 5-week mood disorders intensive outpatient program. Given the acute severity of his condition and the suspicion that he would require longer-term maintenance therapy for bipolar disorder, combination treatment with quetiapine (dosed up to 300 mg at bedtime during the first week) and lamotrigine (gradually titrated up to 200 mg/d over 5 weeks) was initiated.

PANEL DISCUSSION

DR NASRALLAH: The sudden onset of depression and anxiety in a previously well-adjusted young person can suggest several diagnostic possibilities and present a complicated clinical puzzle demanding careful exploration. Are there any comments on the initial steps in evaluating a referred patient such as this one?

DR PARISER: Having patients complete the Mood Disorder Questionnaire (MDQ) can be quite helpful, but it is important that they understand you are assessing symptoms experienced *during* an episode.[1] You are not asking them to report symptoms experienced randomly at different points in their lives.

Sometimes I also ask family members to fill out the MDQ as a means of recounting their observations of the patient. As long as I get consent from a patient in refractory cases, I will do everything I can to talk with one or more family members to help fill out the patient's history. These cases are very challenging.

DR BLACK: He has also been in therapy for 6 months. My experience in such cases is that it is hard for patients to describe the nature of the therapy, so I seldom know exactly what the therapist has been doing with them. After 6 months, it is either time to get a new therapist or to stop it altogether.

DR PARISER: That is a good point. How many obsessive-compulsive disorder patients have you discovered who are in dynamic therapy?

DR BLACK: Quite a few.

DR PARISER: Another important point this raises is that we should do our own therapy. Issues such as the ones in this case can overlap, and it takes time to tease them apart. Unfortunately, even when talking to a therapist about prior counseling, it is often difficult to get a firm idea on what has been happening. For one thing, the therapist may be a little defensive.

DR MUZINA: All of these points are valid. The therapy, as best I could tell, focused chiefly on the patient's soured relationship with the former girlfriend. His mother was involved with 1 or 2 of those sessions at the outset. One of the therapist's principal concerns was that the patient was depressed and anxious—and perhaps even bipolar—because he had taken a couple of antidepressant medications without benefit.

Also, there was some concern that he might have a predilection for stalking. There was no evidence that he was stalking the ex-girlfriend, except perhaps the frequency of going online to visit her MySpace page.

DR BLACK: Because the patient did not tolerate the antidepressants and stopped taking them on his own, it is hard to know whether he is truly treatment-refractory or if something else is going on. He has never been adequately medicated. It also sounds like sertraline was administered at a dose too low to have an impact.

I wonder, too, if he may have some kind of body dysmorphic disorder—a feeling that his muscles are too small. I believe Pope, Hudson, and colleagues called it *bigorexia*.[2] Or does the patient have some other kind of personality disturbance? He was preoccupied with the young woman, checking her out online. I have certainly seen that sort of thing in individuals with personality disorders.

DR MUZINA: Yes, I had the same thoughts about personality disorder. From what I was able to gather in the first 90-minute visit, nothing he or his mother said strongly suggested a primary personality disorder diagnosis.

DR BLACK: I have one other comment. He was taking power drinks to help with exercise and muscle building. These products contain stimulants. I wonder if he might be a stimulant abuser, even though he may not see it that way.

DR MUZINA: I agree. There is a reason why locker rooms for competitive athletes have tubs of these energy drinks available before and during games. It is not just to boost energy but to increase the desire to go out and play hard. The drinks claim to improve performance,

TABLE Distinguishing bipolar from unipolar depression

SYMPTOM	BIPOLAR	UNIPOLAR
Substance abuse	Very high	Moderate
Family history	Almost uniform	Sometimes
Seasonality	Common	Occasional
First episode <25 years	Very common	Sometimes
Psychotic features <35 years	Highly predictive	Uncommon
Rapid on/off pattern	Typical	Unusual
>3 recurrent major depressive episodes	Common	Unusual
Antidepressant-induced mania/hypomania	Predictive	Uncommon
Mixed depressions (presence of hypomanic features within the depressive episode)	Predictive	Rare

Kaye NS. Is your depressed patient bipolar? *J Am Board Fam Pract.* 2005;18(4):271-281. Reproduced by permission of the American Board of Family Practice. © 2005 American Board of Family Practice.

especially during times of increased stress or strain, to increase concentration and improve reaction speed, and to stimulate the metabolism. The ingredients almost always include caffeine; they will throw in amino acids and things like taurine and pyridoxine, ostensibly to help with performance and concentration.

DR NASRALLAH: Could he have been taking the anabolic and herbal preparations before he broke up with his girlfriend? Is it possible that his depression, irritability, and volatility could have been instigated by anabolic steroid use?

DR MUZINA: Yes. The timeline, as I was able to put it together, was that midway through his senior year of high school he was working out heavily and using these supplements along with friends. And he was dating the young woman. All of this continued the first 6 months after graduation. So the complaint of having felt sad over 14 months before I saw him certainly suggests that the substances could have been affecting him before any relationship problems developed with the girlfriend.

DR NASRALLAH: Then it is possible this patient could have a bipolar spectrum disorder exacerbated by steroid use (**TABLE**).[3]

DR BLACK: A toxicology screen would be appropriate, and not only for steroids. In a patient like this, you wonder what else he was putting into his body.

DR PARISER: And what about duty to warn? He was getting into e-mail, is that correct? Cocaine could even be an issue, in addition to steroids—that would be worrisome.

DR MUZINA: He was blocked from the e-mailing functionality on the social network. But that does not stop one from posing as someone else and being assigned a friend in one of these social networks. So, he could still be finding a way to track what another person is doing and still be looking at the pictures and blogs.

DR PARISER: Dr Muzina, does the patient recognize anything strange in what he was doing, or is it egosyntonic? Has he admitted this is something he should not be doing, or does he see nothing wrong with looking the ex-girlfriend up on My Space and violating boundaries?

DR MUZINA: I do not know if he recognizes his behavior as strange. His own words were, "I know I shouldn't be doing this because she is no longer my girlfriend. She told me she doesn't want to talk with me or communicate with me anymore, and I was told by my mom, my family doctor, and a psychologist that I should just let this all go." There was still a sort of an irresistible urge to go online to check out those photos and see what she had been doing recently. Even though he knew he should not be doing it because he had been told it was not a good thing to do.

DR NASRALLAH: A bipolar patient of mine was jilted by a boyfriend. For several weeks, she would drive her car around his block as many as 50 times in a few hours, just hoping to see him come out of his apartment. I have seen this kind of behavior in many bipolar patients who simply will not let go. Their manic energy and grief combine to cause this kind of behavior. That is why it seemed to me that this patient, in exhibiting what I call "mini-stalking," may not know how to let go of the object of his affection.[4,5]

DR BLACK: When you said that his father gave him sleeping pills, do we know if he was not sleeping because he was psychometrically active at night, or whether he was tired the next day?

DR MUZINA: No, he was not particularly tired the next day. He described what I thought was anxiety: lots of tension and being wound up. In some ways, it was almost an obsessive urge to log on and look at his ex-girlfriend's Web page. He knew he should not be doing that. These thoughts were coming to him in the evening and that prevented him from sleeping. One of the first things I discussed with his mother was limiting his Internet access or turning the wireless network off when everyone went to bed.

DR PARISER: He would meet most of the research diagnostic criteria for agitated depression, which does not exist in the DSM. The tension, the psychomotor agitation, the questions are what are called "crowded thoughts."[6] Whether it is a variant of psychosis or of bipolar disorder, it is certainly not a simple unipolar presentation, and it is likely aggravated to some extent by substances. From a management standpoint, agitated depression warrants greater concern about the patient acting on impulses and calls for prescribing an antipsychotic.

DR NASRALLAH: I am wary of the term agitated depression. Any time a patient with presumed unipolar disorder is said to have agitated depression I want to rule out bipolar II disorder that has irritability, anger, and hostility as features. Using the MDQ and differentiating between agitated depression and bipolarity is useful for diagnostic accuracy. But in a sense, it is less useful for management because we have a treatment that addresses both situations.

A quandary for many practitioners is whether to use or avoid an antidepressant in bipolar disease. But the quetiapine-lamotrigine combination Dr Muzina is using with this patient would work in either case.

DR BLACK: Another aspect to this patient's case is the possibility of paranoia. I worry about the kind of intrusive behavior he has exhibited, and using an atypical antipsychotic may be appropriate.

DR PARISER: The psychological testing you have requested should yield answers about his potential for psychotic thinking, especially under stress, and as to whether any Cluster A personality disorder exists.

DR NASRALLAH: Dr Muzina, did you feel that this patient exhibited some psychotic or prepsychotic features?

DR MUZINA: Yes. He made me more uncomfortable than most patients do, and I supposed he was not giving me the whole story. He alluded to what could be psychotic or developing psychotic symptoms.

DR PARISER: What about traumatic brain injury? Any number of organic issues, including frontal lobe involvement, might be considered. You said there was no history of closed head trauma or anything like that?

DR MUZINA: None that he told me and none that his mother reported.

DR BLACK: Dr Nasrallah, I think you may have taught me that agitated depression in the late teens can often herald the onset of bipolar disorder. Nothing in this case absolutely indicates bipolar disorder, but there are clues suggesting it could evolve that way.

DR PARISER: That would be good news in terms of diminishing the possibility of Cluster A disturbance.

Conclusion

DR NASRALLAH: Yet, do not underestimate the potential for destructive behavior in this young man who had low self-esteem and was so worried about his dysmorphic features. He was obsessed about his lost girlfriend and was tracking her in what amounts to a mini-form of stalking. But I do not think that predicts psychosis as much as it does bipolar-related stress. I expect that medication and psychotherapy will get him out of it. So, unless anyone has further comment, I think we're all agreed on the therapeutic approach Dr Muzina has chosen for this patient. ■

REFERENCES

1. Kim B, Wang HR, Son JI, et al. Bipolarity in depressive patients without histories of diagnosis of bipolar disorder and the use of the Mood Disorder Questionnaire for detecting bipolarity. *Compr Psychiatry* 2008;49:469-75.
2. Pope HG Jr, Katz DL, Hudson JI. Anorexia nervosa and "reverse anorexia" among 108 male bodybuilders. *Comp Psychiatry* 1993;34:406-9.
3. Talih F, Fattal O, Malone D Jr. Anabolic steroid abuse: Psychiatric and physical costs. *Cleve Clin J Med* 2007;74:341-52.
4. Whyte S, Petch E, Penny C, et al. Who stalks? A description of patients at a high security hospital with a history of stalking behavior. *Crim Behav Ment Health* 2008;18:27-38.
5. Southworth C, Dawson S, Fraser C, et al. A high tech twist on abuse: Technology, intimate partner stalking, and advocacy. Safety Net Project at the National Network to End Domestic Violence Fund. 2005. www.mincava.umn.edu/documents/commissioned/stalkingandtech/stalkingandtech.pdf. Accessed September 29, 2008.
6. Maj M, Pirozzi R, Magliano L, et al. Agitated depression in bipolar I disorder: prevalence, phenomenology, and outcome. *Am J Psychiatry* 2003;160:2134-40.

Issues associated with the use of atypical antipsychotic medications

HENRY A. NASRALLAH, MD
DONALD W. BLACK, MD
JOSEPH F. GOLDBERG, MD
DAVID J. MUZINA, MD
STEPHEN F. PARISER, MD

First-generation ("conventional") antipsychotic agents are often associated with troubling extrapyramidal symptoms (EPS), including pseudoparkinsonism, erectile dysfunction, and tardive dyskinesia.[1,2] Newer atypical antipsychotic medications are generally regarded as offering improved efficacy and fewer EPS relative to conventional agents, as well as having broad application for the treatment of both schizophrenia and bipolar disorders. However, concern has grown in recent years about the metabolic effects of these agents, particularly with respect to weight gain, hyperglycemia, dyslipidemia, and development of diabetes.[3,4] This article will review current evidence pertaining to the metabolic effects of atypical antipsychotics with an emphasis on weight gain, which psychiatrists are highly likely to encounter in their practices. Other metabolic and pharmacokinetic aspects of atypical antipsychotics will be briefly discussed as they pertain to dosage, drug interactions, and mechanism of action.

Atypical antipsychotics have been defined as agents that produce minimal catalepsy in animal models and minimal EPS or movement disorders at therapeutic doses, and which significantly reduce positive and negative symptoms of schizophrenia.[5,6] The major atypical antipsychotic agents currently available in the United States are listed in **TABLE 1**.

While the incidence of both obesity and diabetes is soaring among the general population, these conditions are more prevalent in patients with schizophrenia, even those who have no history of antipsychotic drug use.[7] Prevalence rates for both diabetes and obesity are approximately 1.5 to 2 times higher in people with schizophrenia and other affective disorders than in the general population.[4] This suggests that people with psychiatric illness may be somehow predisposed toward metabolic disorders, although the precise mechanisms are not well understood. Many confounding factors inevitably enter the picture, including baseline weight, family history, diet and exercise habits, concomitant medications, and comorbid diseases.[8] Importantly, the propensity toward weight gain and development of hyperlipidemia or diabetes during atypical antipsychotic treatment appears to vary widely among individuals.[9] Thus, it is difficult to predict which patients will be affected and the precise role drug treatment might play in this process.

Potential mechanisms of metabolic dysfunction in psychiatric patients

Various hypotheses have been discussed to explain the metabolic changes observed in patients using antipsychotic drugs.[8] Some proposed mechanisms pertain to the direct impact of these drugs on glucose homeostasis, such as an interaction between glucose and 5-HT serotonin receptor antagonism, damage to pancreatic islet cells, or sympathetic nervous system dysregulation.[10] There are numerous case reports of patients who rapidly develop hyperglycemia after initiation of drug therapy, primarily when using olanzapine or clozapine.[11-14] This effect often abates after the drug is discontinued. However, it is important to remember that development of diabetes is most likely to occur secondary to obesity.[4,9] Smoking, a common behavior among those with affective disorders, confers an additional risk for diabetes and cardiovascular disease.[15]

What causes medication-related weight gain? People with psychiatric disease are prone to the same mismatch of caloric intake and energy expenditure that is causing obesity in the general population. Additional causal factors proposed include regaining of weight lost during psychiatric illness; food cravings; alterations in resting metabolic rate; and reduced physical activity.[9,16] The last could be exacerbated by

TABLE 1 Atypical antipsychotics and FDA-approved indications

DRUG	COMMON TRADE NAMES	APPROVED INDICATIONS
Aripiprazole	Abilify	Schizophrenia (acute and maintenance treatment in adults); bipolar I disorder (acute and maintenance treatment of manic and mixed episodes with or without psychotic features—adult and pediatric); major depressive disorder (adjunct to antidepressants); agitation in schizophrenia or bipolar mania
Clozapine	Clozaril	Treatment-resistant schizophrenia (second-line agent); reducing risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder
Olanzapine	Zyprexa	Schizophrenia; bipolar disorder (acute and maintenance); combination therapy with valproate or lithium in bipolar disorder; agitation associated with schizophrenia and bipolar I mania
Quetiapine	Seroquel	Bipolar depression; bipolar mania (bipolar I, as either monotherapy or adjunct therapy to lithium or divalproex); maintenance treatment of bipolar I disorder (as adjunct to lithium or divalproex); acute and maintenance treatment of schizophrenia (Seroquel XR)
Risperidone	Risperdal	Schizophrenia; manic symptoms of acute manic or mixed episodes associated with bipolar I disorder. (Available as solution for depot injection.)
Ziprasidone	Geodon	Schizophrenia; bipolar mania; acute agitation in schizophrenia

Source: Manufacturers' prescribing information.

medication side effects such as somnolence. In addition, the binding affinities of atypical antipsychotics with specific neurotransmitters may alter the sensations of hunger and satiety (eg, alpha-adrenergic stimulation is thought to stimulate the appetite).[16] Finally, many drugs used in combination with atypical antipsychotics, including lithium and divalproex, are known to cause significant weight gain.[17]

Review of data on weight gain among atypical antipsychotics

To address growing concerns and put the mounting case-based and clinical trial evidence into perspective, the American Diabetes Association (ADA) and the American Psychiatric Association (APA) convened with 2 other national organizations to develop a consensus statement on the metabolic impact of atypical antipsychotic agents.[4]

The ADA/APA statement ranked clozapine and olanzapine as being associated with the greatest risk of weight gain, diabetes, and dyslipidemia.[4] Risperidone and quetiapine were put into an intermediate risk category for weight gain, while aripiprazole and ziprasidone were, at the time, too new to categorize. More recent data have shown ziprasidone and aripiprazole to be relatively weight-neutral.[8]

However, the consensus statement must be interpreted with caution. Criticism has been leveled at the report from many corners, including the Division of Neuropharmacological Drug Products of the FDA, which argued that insufficient data were available to appropriately "rank" obesity/diabetes risks for the atypical antipsychotic agents.[18] Other authors pointed out that efficacy considerations of these drugs are a critical and overlooked component of the discussion and that the data used to compare the agents did not adequately control for key lifestyle factors such as overreliance on "junk food."[19,20]

Data from CATIE study

The large-scale Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study enrolled nearly 1500 patients with schizophrenia at 57 US centers between 2001 and 2004.[3] The study compared efficacy variables and weight gain in the course of treatment with olanzapine, perphenazine, quetiapine, and risperidone. Ziprasidone was added later in the study. Weight change (defined as kg/month of treatment) in phase 1 of the CATIE trial is shown in **TABLE 2**.

The CATIE investigators found that among the patients randomized to olanzapine, 30% experienced weight gain in excess of 7% of baseline, compared with 16%, 14%, 12%, and 7% of those randomized to quetiapine, risperidone, perphenazine, and ziprasidone, respectively. Exposure-adjusted changes in cholesterol or triglyceride blood levels were highest for olanzapine, followed by quetiapine and perphenazine, with decreases noted for ziprasidone and risperidone. With

TABLE 2 Weight change from baseline to last observation in phase I of the CATIE trial

ANTIPSYCHOTIC	MEAN LB PER MONTH OF TREATMENT	MEAN WEIGHT CHANGE (LB)	RANGE (LB)
Olanzapine	2.0	9.4 ± 0.9	–14 to 42
Quetiapine	0.5	1.1 ± 0.9	–25 to 25
Risperidone	0.4	0.8 ± 0.9	–24 to 24
Perphenazine	–0.2	–2.0 ± 1.1	–29 to 22
Ziprasidone	–0.3	–1.6 ± 1.1	–24 to 18

CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

Source: Lieberman JA, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1:09-1223.

TABLE 3 Atypical antipsychotics and metabolic abnormalities

DRUG	WEIGHT GAIN	RISK FOR DIABETES	WORSENING LIPID PROFILE
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/–	–	–
Ziprasidone*	+/–	–	–

+ = Increased effect; – = No effect; D = Discrepant results. *Newer drugs with limited long-term data.

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. © 2004 American Diabetes Association. *Diabetes Care*®, Vol 27, 2004; 596-601. Reprinted with permission from The American Diabetes Association.

any of the agents, these effects must be balanced against the benefits of the drug in individual patients.

Results from other controlled studies

As Glick states in his analysis of the CATIE trial, long-term tolerability and efficacy of antipsychotic therapy is the goal of schizophrenia management to ensure treatment adherence and garner maximum benefit.[21] In most clinical trials of antipsychotics, the effects on core symptoms of schizophrenia are balanced against drug side effects. However, symptoms of schizophrenia vary significantly from person to person, and antipsychotic medications can adversely affect functioning.

Of concern is that much of the data on weight gain from antipsychotic agents comes not from controlled trials like CATIE but from uncontrolled trials. A meta-analysis conducted by Allison and colleagues compared data on weight change after 10 weeks of treatment among patients receiving conventional and atypical antipsychotics and placebo.[22] These authors observed that many of the studies "report their weight gain in an incomplete, idiosyncratic, and poorly defined manner," noting that this area of research would benefit from standardization. Again, clozapine (12 studies) and olanzapine (7 studies) resulted in the highest weight gain and risperidone resulted in moderate weight gain (26 studies). Ziprasidone was weight-neutral (22 studies) and available data were insufficient to evaluate quetiapine (3 studies).[22]

Monitoring patients for weight gain, dyslipidemia, and diabetes

Should patients be switched to another agent if weight gain is observed? If so, how much is too much? The ADA/APA consensus report recommended considering a switch if a patient gains weight ≥5% above baseline at any point during therapy (**TABLE 3**).[4] However, this view might be somewhat simplistic given the challenges involved in identifying a drug regimen that controls symptoms optimally for that individual.[1,20,23] Switching agents can potentially introduce new problems, with the possible loss of therapeutic benefit, need for additional dosage monitoring, and potential to introduce adherence problems and/or other adverse effects.

The ADA/APA report does provide some prudent monitoring steps that serve as a useful guideline for practitioners while maintaining patients on atypical antipsychotics (**TABLE 4**).

Other metabolic issues related to atypical antipsychotics

While weight gain and glucose metabolism have received much recent attention, several other issues pertaining to atypical antipsychotic metabolism bear mentioning, a few of which are highlighted below.

Role of cytochrome P450 enzymes in antipsychotic metabolism

Cytochrome P450 (CYP) enzymes have significant involvement in the metabolism of atypical antipsychotics. Clozapine is primarily metabolized by CYP1A2; risperidone mainly by 2D6; quetiapine and ziprasidone mainly by 3A4; and aripiprazole by 2D6 and 3A4.[24] This hepatic metabolism increases the potential for drug–drug interactions with other agents that inhibit or induce CYP enzymes. These interactions could alter antipsychotic plasma levels and result in reduced effectiveness of the antipsychotic agent or increased risk of adverse events.[25] Since many drugs used concomitantly with antipsychotics work along these pathways (for example, ketoconazole and fluconazole are highly potent inhibitors of P450 3A), the prescriber should exercise caution and be aware of potential interactions.

Effect of smoking on plasma levels of antipsychotics

Cigarette smoking is a highly prevalent habit in patients with schizophrenia, with rates estimated as high as 88%.[26] These patients tend to smoke heavily and many also use excessive caffeine or other addictive substances.[27] The role of these habits in dosage adjustment and therapeutic response may be overlooked.[28] Smoking is known to increase metabolism of drugs that act primarily via CYP1A2, notably clozapine and olanzapine.[29] Modification of clozapine or olanzapine dosages may be necessary in smokers.[30] In addition, it is important to consider that patients who are forced to stop smoking while hospitalized are likely to return to the habit after discharge, potentially altering the metabolism of these drugs.

Drug metabolites and new mechanisms

In some cases, a better understanding of the metabolic pathways of antipsychotic agents has contributed to new knowledge about their mechanisms of action and has yielded new pharmacologic agents. For example, the recently approved antipsychotic paliperidone is the active metabolite of risperidone. According to the authors of a recent Cochrane Review on this agent, it remains unknown whether this metabolite confers any benefit over the "parent compound," risperidone.[31]

An active metabolite of quetiapine (N-desalkylquetiapine) has recently been found to exert an inhibitory effect on the norepinephrine transporter (NET), which is an important site of therapeutic action for several antidepressants. Goldstein and colleagues reported that inhibiting NET leads to elevation of noradrenaline levels in specific brain areas.[32] This effect is likely to account for the antidepressant activity of quetiapine and helps explain its efficacy in unipolar depression.[33,34]

TABLE 4 Monitoring metabolic profiles in patients receiving atypical antipsychotic drugs

Recommendations from the American Psychiatric Association/American Diabetes Association Consensus Report

- Baseline monitoring of body mass index, personal/family history, waist circumference
- Baseline monitoring for symptoms of hyperglycemia (advise patients of hyperglycemia symptoms)
- Reassess weight change at 4, 8, and 12 weeks after initiation or change of antipsychotic therapy and quarterly thereafter
- Reassess fasting plasma glucose, lipids, and blood pressure at 3 months and annually thereafter

Adapted from 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.

Conclusion

Although the effects of atypical antipsychotic medications are often lumped together, it is important to consider this a heterogeneous group of medications. They can produce highly differing results, depending on individual patient variables and a number of external factors. Clozapine and olanzapine are the most commonly associated with weight gain, risperidone and quetiapine with moderate effects, and aripiprazole and ziprasidone the least, but other factors that lead to weight gain should be taken into account. In addition, efficacy, dosage, and adherence are critical components that must be weighed as part of the

decision to switch a patient to a different therapy. Dosage of atypical antipsychotics is a complex matter, and metabolic interactions with other drugs and agents such as cigarette smoke must be taken into account as well. With more research into the metabolism of these drugs, new pathways have been identified that add to our understanding of their specific mechanisms of action. ■

REFERENCES

1. Citrome L, Volavka J. The promise of atypical antipsychotics: fewer side effects mean enhanced compliance and improved functioning. *Postgrad Med* 2004;116:49-63.
2. Davis JM, Chen N. Old versus new: weighing the evidence between the first- and second-generation antipsychotics. *Eur Psychiatry* 2005;20:7-14.
3. Lieberman JA, Stroup TS, McEvoy JP, et al, for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353:1209-23.
4. 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.
5. Markowitz JS, Brown CS, Moore TR. Atypical antipsychotics. Part I: Pharmacology, pharmacokinetics, and efficacy. *Ann Pharmacother* 1999;33:73-85.
6. Kinon BJ, Lieberman JA. Mechanisms of action of atypical antipsychotic drugs: a critical analysis. *Psychopharmacology (Berl)* 1996;124:2-33.
7. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naïve patients with schizophrenia. *Am J Psychiatry* 2003;160:284-9.
8. Baptista T, DeMendoza S, Beaulieu S, et al. The metabolic syndrome during atypical antipsychotic drug treatment: mechanisms and management. *Metab Syndr Relat Disord* 2004;2:290-307.
9. Citrome L, Vreeland B. Schizophrenia, obesity, and antipsychotic medications: what can we do? *Postgrad Med* 2008;120:18-32.
10. Goldstein LE, Sporn J, Brown S, et al. New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. *Psychosomatics* 1999;40:438-43.
11. Kohen I, Gampel M, Reddy L, et al. Rapidly developing hyperglycemia during treatment with olanzapine. *Ann Pharmacother* 2008;42:588-91.
12. Duiverman ML, Cohen D, van Oven W, et al. A patient treated with olanzapine developing diabetes de novo: proposal for hyperglycaemia screening. *Neth J Med* 2007;65:346-8.
13. Cohen D. Atypical antipsychotics and new onset diabetes mellitus. *Pharmacopsychiatry* 2004;37:1-11.
14. Clark C, Burge MR. Diabetes mellitus associated with atypical antipsychotic medications. *Diabetes Technol Ther* 2003;5:669-83.
15. McCreadie RG. Use of drugs, alcohol, and tobacco by people with schizophrenia: case-control study. *Br J Psychiatry* 2002;191:321-5.
16. Zimmerman U, Kraus T, Himmerich H, et al. Epidemiology, implications, and mechanisms underlying drug-induced weight gain in psychiatric patients. *J Psychiatr Res* 2003;37:193-220.
17. Isojarvi JIT, Laatikainen TJ, Knip M, et al. Obesity and endocrine disorders in women taking valproate for epilepsy. *Ann Neurol* 1996;39:579-584.
18. Boehm G, Racoosin JA, Laughren TP, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes: response to consensus statement. *Diabetes Care* 2004;27:2088-9.
19. Citrome L, Volavka J. Consensus development conference on antipsychotic drugs and obesity and diabetes: response to consensus statement. *Diabetes Care* 2004;27:2087-8.
20. Isaac MT, Isaac MB. Consensus development conference on antipsychotic drugs and obesity and diabetes: response to consensus statement. *Diabetes Care* 2004;27:2088-90.
21. Glick ID. Understanding the results of CATIE in the context of the field. *CNS Spectr* 2006;11(suppl 7):40-7.
22. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999;156:1686-96.
23. Citrome L. Efficacy should drive atypical antipsychotic treatment. *BMJ* 2003;326:283.
24. Urichuk L, Prior TI, Dursun S, et al. Metabolism of atypical antipsychotics: involvement of cytochrome p450 enzymes and relevance for drug-drug interactions. *Curr Drug Metab* 2008;9:410-8.
25. Conley RR, Kelly DL. Drug-drug interactions associated with second-generation antipsychotics: considerations for clinicians and patients. *Psychopharmacol Bull* 2007;40:77-97.
26. Hughes JR, Hatsukami DK, Mitchell JE, et al. Prevalence of smoking among psychiatric outpatients. *Am J Psychiatry* 1986;143:993-7.
27. Williams JM, Foulds J. Successful tobacco dependence treatment in schizophrenia. *Am J Psychiatry* 2007;164:222-7.
28. Dratcu L, Grandison A, McKay G, et al. Clozapine-resistant psychosis, smoking, and caffeine: managing the neglected effects of substances that our patients consume every day. *Am J Ther* 2007;14:314-8.
29. Derenne JL, Baldessarini RJ. Clozapine toxicity associated with smoking cessation: case report. *Am J Ther* 2005;12:469-71.
30. Dalack GW, Becks L, Hill E, et al. Nicotine withdrawal and psychiatric symptoms in cigarette smokers with schizophrenia. *Neuropsychopharmacology* 1999;21:195-202.
31. Nussbaum A, Stroup TS. Paliperidone for schizophrenia. *Cochrane Database Syst Rev* 2008;April 16:CD006369.
32. Goldstein JM, Christoph G, Grimm S, et al. Unique mechanism of action for the antidepressant properties of the atypical antipsychotic quetiapine. Poster presented at: American Psychiatric Association, 160th Annual Meeting; May 19-24, 2007; San Diego, CA. Poster NR336.
33. Jensen NH, Rodriguiz RM, Caron MG, et al. N-desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-HT1A agonist, as a putative mediator of quetiapine's antidepressant activity. *Neuropsychopharmacology* 2008;33:2303-12.
34. Pira L, Mongeau R, Pani L. The atypical antipsychotic quetiapine increases both noradrenaline and dopamine release in the rat prefrontal cortex. *Eur J Pharmacol* 2004;504:61-4.

POSTTEST QUESTIONS

SELECT THE SINGLE LETTER RESPONSE THAT BEST ANSWERS THE QUESTION OR COMPLETES THE SENTENCE.

1. In Dr Black's patient, who was diagnosed with chronic schizophrenia and was not responding well to therapy, what diagnostic studies were suggested?
   a. Metabolic profiles and syphilis screening
   b. Neuroimaging studies
   c. Testosterone and vitamin levels
   d. All of the above

2. The only agent shown to be effective in treating refractory bipolar patients with mania or depression is:
   a. Olanzapine
   b. Clozapine
   c. Quetiapine
   d. Risperidone

3. Among the side effects of atypical antipsychotics associated with metabolic changes such as weight gain, in the CATIE trial which drug was found to result in the greatest weight gain?
   a. Clozapine
   b. Risperidone
   c. Olanzapine
   d. Ziprasidone

4. The National Depressive and Manic Depressive Association Survey in 2002 showed approximately what misdiagnosis rate for bipolar disorder?
   a. 25%
   b. 40%
   c. 50%
   d. 70%

5. In the Rotterdam study, a deficiency of what vitamins were shown to be related to depression?
   a. Vitamin B_{12} and folate
   b. Vitamins B_{12} and C
   c. Vitamins C and D
   d. Vitamins B_6 and B_{12}

6. Symptoms of SSRI discontinuation syndrome include all of the following EXCEPT:
   a. Vertigo and ataxia
   b. Nausea and vomiting
   c. Paresthesia
   d. Excessive sleepiness

7. Pope, Hudson, et al labeled a type of body dysmorphic disorder in which the patient believes his muscles are too small as:
   a. Bromosis
   b. Bigorexia
   c. Somatoform disorder
   d. Narisexia

8. A feature of bipolar depression that would not commonly occur with unipolar depression is:
   a. Substance abuse
   b. Family history of the disorder
   c. Seasonality
   d. Psychotic features at <35 years of age

9. Causal factors for medication-related weight gain in patients taking antipsychotic drugs include all except:
   a. Food allergies
   b. Alterations in metabolic rate
   c. Altered sensations of hunger/satiety
   d. Reduced physical activity/somnolence

10. A consensus statement from the American Diabetes Association and the American Psychiatric Association associate what drugs with the greatest risk of weight gain, diabetes, and dyslipidemia?
    a. Aripiprazole and ziprasidone
    b. Risperidone and quetiapine
    c. Clozapine and olanzapine
    d. Perphenazine and quetiapine

CME REGISTRATION FORM

▸ PLEASE PRINT CLEARLY

NAME (FIRST) LAST DEGREE

STREET ADDRESS

CITY STATE ZIP

TELEPHONE FAX

E-MAIL

AFFILIATION SPECIALTY

SIGNATURE (I CERTIFY THAT I HAVE COMPLETED THIS CME ACTIVITY.)

ACTUAL TIME SPENT ON THIS ACTIVITY HOURS / MINUTES

This activity is designated for a maximum of *4.0 AMA PRA Category 1 Credits*™.

Activity release date:
December 1, 2008

Activity expiration date:
December 1, 2009

To receive CME credit, return this page with your completed posttest and evaluation to:

Office of CME
University of Cincinnati
PO Box 670556
Cincinnati, OH 45267

Or complete the CME posttest and evaluation online at:
http://webcentral.uc.edu/cpd_online2/ce/category.cfm?id=2
or **www.dowdencme.com**

CME EVALUATION FORM

▸ PLEASE CIRCLE THE LETTER THAT BEST REFLECTS YOUR AGREEMENT WITH THE STATEMENTS BELOW, USING THE FOLLOWING SCALE: **A. STRONGLY AGREE B. AGREE C. DISAGREE D. STRONGLY DISAGREE E. DOES NOT APPLY**

1. The activity objectives were fully met.	A	B	C	D	E
2. The quality of the educational process (method of presentation and information) was satisfactory and appropriate.	A	B	C	D	E
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	E
5. The program level was appropriate for the intended audience.	A	B	C	D	E
6. I intend to change my clinical practice as a result of the information presented in this CME program.	A	B	C	D	E

7. Suggestions regarding this material or recommendations for future educational activities:

FDA-APPROVED DRUGS MENTIONED IN THIS ACTIVITY

GENERIC NAME	BRAND NAME
amphetamine/dextroamphetamine	Adderall
androstenedione	"Andro"
aripiprazole	Abilify
bupropion	Wellbutrin
carbamazepine	Tegretol
chlorpromazine	Thorazine
clonazepam	Klonopin
clozapine	Clozaril
desvenlafaxine	Pristiq
divalproex	Depakote
duloxetine	Cymbalta
escitalopram	Lexapro
fluconazole	Diflucan
fluoxetine	Prozac
fluphenazine	Prolixin
haloperidol	Haldol
ketoconazole	Nizoral
lamotrigine	Lamictal
lithium	Eskalith, Lithobid
metformin	Glucophage
molindone	Moban
olanzapine	Zyprexa
paliperidone	Invega
perphenazine	Trilafon
quetiapine	Seroquel
risperidone	Risperdal
risperidone, long-acting	Risperdal Consta
sertraline	Zoloft
sertindole	Serdolect
sibutramine	Meridia
thioridazine	Mellaril
topiramate	Topamax
trihexyphenidyl	Artane, Trihexane
valproate	Depacon
venlafaxine	Effexor
ziprasidone	Geodon

ANNALS OF
CLINICAL PSYCHIATRY
Available at www.aacp.com
Vol 20 No 4S • December 2008

Diagnosing and managing psychotic and mood disorders