Letters to the Editor

Risperidone Treatment for Psychosis in End-Stage Friedreich's Ataxia

TO THE EDITOR: Friedreich's ataxia is an inherited autosomal-recessive condition with childhood onset of progressive ataxia of gait and limbs and absent deep tendon reflexes and extensor plantar responses (1). Despite reports of cognitive decline and psychotic symptoms in end-stage Friedreich's ataxia (2–5), MEDLINE and PsychINFO searches revealed no reports on the treatment or incidence of the psychosis that occasionally complicates the final stages of this illness. We describe a patient with Friedreich's ataxia who developed psychosis in the end stage of his illness and responded to risperidone treatment.

Mr. A was a 36-year-old Caucasian man who had had Friedreich's ataxia since age 5. Dysphoria, decreased energy, poor concentration, and anhedonia had evolved over several months. A previous 2-month trial of fluoxetine, 20 mg/day, resulted in no improvement. Mr. A was in a wheelchair and had recently lost the ability to perform daily functions, such as maintaining hygiene and caring for his daughter. His most recent decrease in function made him entirely dependent on care provided by his mother. Mr. A's family history was notable for an older brother who also had Friedreich's ataxia and died at the age of 34 from the illness.

His mother reported a gradual onset of unusual behaviors that Mr. A minimized and rationalized as part of his sensory deterioration. At home, he kept the radio on to drown out frightening sounds that he (but no one else) heard. He developed paranoia and multiple conspiracy theories, e.g., believing his ex-wife had thrown a puppy out of the window, even when presented with evidence to the contrary. He developed visual hallucinations that included seeing an aide walk into the room and then vanish.

We diagnosed Mr. A with psychotic disorder not otherwise specified and started him on a regimen of 1 mg of risperidone at night, increased to 1 mg b.i.d. after 1 week. His dysphoria improved, the delusions about his caregivers and his ex-wife resolved, and his visual hallucinations diminished. He experienced no extrapyramidal symptoms or other side effects. He became more observant and more insightful into his health status and was able to address many end-of-life issues as his thought organization improved. He died from progressive cardiac complications of Friedreich's ataxia 6 weeks after starting risperidone treatment.

Risperidone was an effective and well-tolerated treatment for psychosis in our patient with end-stage Friedreich's ataxia.

REFERENCES

1. Adams RD, Victor M, Roper AH: Principles of Neurology, 6th ed. New York, McGraw Hill, 1997, pp 1081–1084
2. Barbeau A: Friedreich's ataxia 1976: an overview. Can J Neurol Sci 1976; 3:389–397
3. Durr A, Cossee M, Agid Y, Campuzano V, Mignard C, Penet C, Mandel JL, Brice A, Koenig M: Clinical and genetic abnormalities in patients with Friedreich's ataxia. N Engl J Med 1996; 335:1169–1175
4. Hart RP, Kwentus JA, Leshner RT, Frazier R: Information processing speed in Friedreich's ataxia. Ann Neurol 1985; 17: 612–614
5. Johnson WG: Friedreich's ataxia. Clin Neurosci 1995; 3:33–38

MATT J. SALBENBLATT, M.D.
RANDALL D. BUZAN, M.D.
STEVEN L. DUBOVSKY, M.D.
Denver, Colo.

Bright Light Therapy's Effect on Postpartum Depression

TO THE EDITOR: Postpartum depression is a mood disorder affecting approximately 10%–15% of women after childbirth. Prompt diagnosis and treatment are crucial for maternal and infant well-being (1). Many women reject treatment with pharmacotherapy, especially while breast-feeding, because they are concerned about the possible deleterious effects of medication on the developing infant. Bright light therapy is an effective treatment for seasonal affective disorder and for nonseasonal depression. We report the cases of two women, both suffering from a major depressive episode with postpartum onset, who were treated with bright light therapy.

Ms. A, a 33-year old woman, developed abrupt changes in her mood within 2 weeks of the birth of her first child. Her symptoms included fatigue, irritability, anxiety, social withdrawal, guilt, and increased appetite with carbohydrate craving. Even after her baby began sleeping through the night, she experienced initial insomnia and unrestorative sleep. The pregnancy had been planned and was uneventful. Labor had had to be induced because of oligohydramnios. A healthy baby was born at term. She had no previous history of depressive episodes or mood disorders. She was otherwise healthy. Ms. A delayed seeking treatment, hoping her condition would improve. Her mood, management of household responsibilities, and competence in taking care of her baby continued to deteriorate; thus she sought treatment at 5 months postpartum. She refused the option of antidepressant medication, consenting instead to a trial of phototherapy by means of a 10,000-lux light box for 30 minutes between 7:00 a.m. and 9:00 a.m. daily. Her baseline Hamilton Rating Scale for Depression score (29 items) was 29; it decreased to 18 after 2 weeks of treatment with light therapy. After 4 weeks of treatment, her score decreased to 11.

Ms. B, a 27-year old woman, experienced an abrupt worsening of her anxious and depressed mood, initial and middle insomnia, anergia, fatigue, and an overwhelmed feeling 1 week after the birth of her second child. The strained relationship with her husband was felt to be the

precipitant for her dysphoric feelings during pregnancy, but her mood change had not progressed sufficiently to warrant a diagnosis of major depression. Delivery of a healthy baby was at term after a 28-hour labor. Ms. B was otherwise medically healthy. She refused treatment with antidepressant medication. Conjoint therapy did not reduce her symptoms and hence was discontinued after 1 month. At that time, she accepted a trial of bright light therapy by means of a 10,000-lux light box for 30 minutes between 7:00 a.m. and 9:30 a.m. daily. Her Hamilton depression scale score (29 items) was 28 at baseline; it decreased to 16 after 10 days of treatment, and after 4 weeks, her score was 12.

These two patients showed a good clinical response (i.e., a 75% reduction in Hamilton depression scale scores) to treatment with light therapy. Both patients subjectively reported sufficient improvement in mood and other depressive symptoms, tolerated the treatment well, and reported no adverse effects during the course of treatment.

The use of bright light therapy may represent a viable, nonpharmacologic treatment for postpartum depression, especially for women who choose to breast-feed their babies.

REFERENCE

1. Weinberg MK, Tronick EZ: The impact of maternal psychiatric illness on infant development. J Clin Psychiatry 1998; 59(suppl 2):53–61

MARIA CORRAL, M.D., F.R.C.P.C.
ANNIE KUAN, B.A.
DEMETRA KOSTARAS, B.SC., M.A.
Vancouver, B.C., Canada

Dextromethorphan-Induced Psychosis

TO THE EDITOR: Recent formulations of a hypoglutamatergic hypothesis for the development of schizophrenia have begun to rival the explanatory power of the long-dominant dopamine hypothesis (1). A major impetus to this work was the observation of complex psychotic states after the ingestion of phencyclidine (PCP, often referred to as "angel dust"), which is an antagonist of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. Recreational PCP use has now waned, but we recently encountered a case of deliberate abuse of dextromethorphan appearing with similar symptoms.

Mr. A, an 18-year-old high school student, came to the psychiatric emergency room after several days of consuming cough syrup (one to two 8-oz bottles per day containing dextromethorphan, 711 mg per bottle). He described experiencing dissociative phenomena involving the belief that he had died and had "become just [his] thoughts," coupled with the experience of observing himself from outside his body. He reported vivid visual hallucinations, including the ability to "see 360° in all four quadrants" and to literally "see into people." He also recounted delusions of telepathy (he could ascertain the thoughts of other students at school if he sat near them and could communicate with them without speaking) and paranoia (his employer was trying to kill him and strangers might hurt him). Mr. A had previous diagnoses of attention deficit hyperactivity disorder and social phobia. His past medical history was unremarkable. He recounted occasional marijuana use (one to two joints per week). His father had bipolar disorder.

Mr. A's symptoms showed complete remission without neuroleptic treatment within 4 days after discontinuing the abuse of dextromethorphan, and he was discharged from the hospital with no evidence of psychosis. He was rehospitalized twice more over the next 2 months with similar symptoms. Each time, he reported consuming large doses of dextromethorphan and showed complete resolution of his psychotic symptoms with abstinence from the ingestion of cough syrup. During a subsequent sustained abstinence from dextromethorphan while participating in outpatient substance abuse treatment, Mr. A had no recurrent psychosis. He acknowledged that his previous episodes of cough syrup abuse were routinely followed by states of hallucinosis, paranoia, and dissociation.

Earlier reports of psychosis following excessive cough syrup ingestion were generally attributed to the sympathomimetic amines contained in many preparations (2, 3). However, Schadel and Sellers (4) first suggested that dextromethorphan could be the causative agent because of its metabolism to dextrorphan, a noncompetitive NMDA receptor antagonist. Individuals with the rapid metabolizer phenotype cytochrome P4502D6 can be particularly vulnerable to these psychotogenic effects (5). Since dextromethorphan is not routinely assayed in urine toxicology screenings, clinicians should be vigilant in treating cases that suggest dextromethorphan abuse.

REFERENCES

1. Jentsch JD, Roth RH: The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 1999; 20:201–225
2. Mendez MF: Mania self-induced with cough syrup. J Clin Psychiatry 1992; 53:173–174
3. Craig DF: Psychosis with Vicks Formula 44-D abuse. CMAJ 1992; 146:1199–1200
4. Schadel M, Sellers EM: Psychosis with Vicks Formula 44-D abuse. CMAJ 1992; 147:843–844
5. Schadel M, Wu D, Otton SV, Kalow W, Sellers EM: Pharmacokinetics of dextromethorphan and metabolites in humans: influence of the CYP2D6 phenotype and quinine inhibition. J Clin Psychopharmacol 1995; 15:263–269

LAWRENCE H. PRICE, M.D.
JACQUELINE LEBEL, J.D., M.D.
Providence, R.I.

Intoxication With Olanzapine

TO THE EDITOR: Olanzapine is a new antipsychotic drug that is thought to have fewer side effects than other neuroleptics (1–4). There is one autopsy report (5) about a lethal overdose of olanzapine to date; however, there appear to be no reports about the clinical course and therapy of acute intoxication with olanzapine. We report the case of a 22-year-old man who was admitted to the hospital after he tried to commit suicide by tablet ingestion.

Mr. A suffered from schizophrenia and was currently being treated with olanzapine, 10 mg/day. He was not taking any other medications. Upon arrival in the emergency room, Mr. A was alert and oriented; he reported having ingested about 800 mg of olanzapine approximately 2.5

hours before his arrival. His vital signs at admission were stable; results of a physical examination and all routine laboratory tests were normal. Mr. A was admitted to the intensive care unit, and his condition was tracked with a Holter monitor. His olanzapine serum levels reached a maximum of 200 ng/ml, which is about 20 times higher than therapeutic levels of the drug (at a dose of 10 mg/day, normal serum levels are about 10 ng/ml). About 30 minutes later, he started to become progressively somnolent, a status that was interrupted by short periods of aggressive agitation. Because olanzapine has anticholinergic effects with a slowing of gastrointestinal passage, we performed a gastric lavage under protective intubation. In the gastric contents, multiple tablets could be seen. Further gastrointestinal decontamination was performed with active charcoal (10 g every 4 hours), sodium bicarbonate, and sodium sulfate.

Mr. A's vital signs were stable at all times. His blood pressure ranged from 110/75 to 130/80 mm Hg; his heart rate was 100–120 bpm upon arrival and gradually declined to 60 bpm at discharge from the intensive care unit. Physostigmine, 2 mg i.v., administered in the acute phase, did not affect his heart rate, blood pressure, or breathing. Mr. A was extubated after 8 hours and completely alert and oriented after 10 hours. The observation period of 24 hours on the Holter monitor was without incident; no cardiac arrhythmia, neurological disorders, anticholinergic syndrome, laboratory test abnormalities, fever, or rhabdomyolysis were observed. After 24 hours, Mr. A was transferred to a psychiatric service for further observation.

In conclusion, olanzapine, approximately 800 mg taken for suicidal purposes, produced mainly sedative effects with only mild anticholinergic symptoms.

REFERENCES

1. Gerlach J, Peacock L: New antipsychotics: the present status. Int Clin Pharmacol 1995; 10(suppl 3):39–48
2. Baldwin DS, Montgomery SA: First clinical experience with olanzapine (LY 170053): results of an open-label safety and dose-ranging study in patients with schizophrenia. Int Clin Pharmacol 1995; 10:239–244
3. Casey DE: Side effect profiles of new antipsychotic agents. J Clin Psychiatry 1996; 57(suppl 11):40–45
4. Martin J, Gomez JC, Garcia-Bernardo E, Cuesta M, Alvarez E, Gurpegui M: Olanzapine in treatment-refractory schizophrenia: results of an open-label study. The Spanish Group for the Study of Olanzapine in Treatment-Refractory Schizophrenia. J Clin Psychiatry 1997; 58:479–483
5. Elian AA: Fatal overdose of olanzapine. Forensic Sci Int 1998; 91:231–235

RALPH F. BOSCH, M.D.
ANDREAS BAUMBACH, M.D.
MICHAEL BITZER, M.D.
CHRISTIANE M. ERLEY, M.D.
Tûbingen, Germany

Conflicted Caregivers

TO THE EDITOR: The clinical case conference by Nada L. Stotland, M.D., M.P.H. (1), was truly heartrending. It occurred to me that the real difference between the determined believer, the patient, and all the frustrated caregivers was not so much that their value systems were contrary. The real difference was that the patient was willing not only to risk but to actually lay down her life for her sincere convictions. None of the caregivers was willing to go so far; not only did the caregivers not risk their lives, but they also escaped legal, financial, and career repercussions that would have followed had they proceeded in doing what was clinically necessary to save her life.

REFERENCE

1. Stotland NL: When religion collides with medicine (case conference). Am J Psychiatry 1999; 156:304–307

EDMUND F. KAL, M.D.
Fresno, Calif.

Dr. Stotland Replies

TO THE EDITOR: Dr. Kal raises a thought-provoking question: how far ought we to go in pursuing our duty to heal? The woman whose religious beliefs led her to choose to die rather than to accept a blood transfusion was willing to back her values with her very life. She knew that her children would grow up without a mother, but she expected that they all, after a relatively brief sojourn in this life, would be rejoined in heaven for eternity. Her decision directly affected no one else. But the "frustrated caregivers," in order to carry out their value of healing by administering a blood transfusion to this competent and unwilling woman, would have intruded on the autonomy and physical integrity of their patient. Would that not have violated their duty to do no harm?

NADA L. STOTLAND, M.D., M.P.H.
Chicago, Ill.

Cost-Effectiveness of Psychiatrists

TO THE EDITOR: The title of the article ("Are Psychiatrists Cost-Effective? An Analysis of Integrated Versus Split Treatment") by Mantosh Dewan, M.D. (1), is misleading. Dr. Dewan modeled one measure of the costs associated with different potential treatments for unspecified psychiatric disorders and showed that integrated treatment could be less costly than split treatment. However, his analytic model did not address the issue of treatment effectiveness; it implicitly assumed that all the treatment combinations in the model were equally effective for a broad range of clinical conditions. We are not aware of any data that support this assumption. Therefore, although the article does provide further support for the contention examined in the article by Goldman et al. (2) that integrated treatment may not be more expensive than split treatment, it does not in any way provide information about the cost-effectiveness of either form of treatment (3). Although the more narrow focus of the study on cost (and not cost-effectiveness) is clearly stated in the study's aims and methods, the title of the study and one of the primary conclusions of the study, that "When both medication and psychotherapy are indicated, a patient is best and most cost-effectively served by a psychiatrist providing both treatment modalities" (1, p. 325), misrepresent the study. This is an important area of research and clinical policy; however, in the field of psychiatry, we need to be careful not to overstate the case before relevant research has been conducted.

REFERENCES

1. Dewan M: Are psychiatrists cost-effective? an analysis of integrated versus split treatment. Am J Psychiatry 1999; 156: 324–326
2. Goldman W, McCulloch J, Cuffel B, Zarin DA, Suarez A, Burns BJ: Outpatient utilization patterns of integrated and split psychotherapy and pharmacotherapy for depression. Psychiatr Serv 1998; 49:477–482
3. Gold MR, Siegel JE, Russell LB, Weinstein MC (eds): Cost-Effectiveness in Health and Medicine. New York, Oxford University Press, 1996

DEBORAH A. ZARIN, M.D.
JOYCE C. WEST, PH.D., M.P.P.
Washington, D.C.

TO THE EDITOR: Dr. Dewan demonstrated by simple addition that one more than one equals two: that health plan fees for combined psychotherapy and pharmacotherapy by a psychiatrist cost less than split treatment by a pharmacologist and a nonpsychiatrist psychotherapist. This elegant and clever brief report deserves acclaim, given the paucity of research on this topic. Psychiatry must broaden its literature to ensure its economic survival (1). The American Psychiatric Association's Commission on Psychotherapy by Psychiatrists seconds Dr. Dewan's call for the clinical trials that are now desperately needed to supplement his accounting. This research should assess not simply cost (cf. Goldman et al., 1998) but also the quality and associated outcomes of treatment: remission of patient symptoms, restored or enhanced function, and better quality of life.

REFERENCE

1. Markowitz JC: Managed care and American psychotherapy, in Manage or Perish: The Challenges of Managed Mental Health Care in Europe. Edited by Guimon G, Sartorius N. New York, Plenum Publishing, 1999

JOHN C. MARKOWITZ, M.D.
NORMAN A. CLEMENS, M.D.
GLEN O. GABBARD, M.D.
New York, N.Y.

Dr. Dewan Replies

TO THE EDITOR: The comments by Drs. Zarin and West provide an opportunity for clarifying the background and assumptions of my article. It is clear that the mental health model practiced by managed care organizations has at least two major assumptions: compared to integrated treatment provided by a psychiatrist, split treatment is at least equally effective and less expensive for treating all conditions. This is obvious from managed care's preferential use of nonpsychiatric psychotherapists for evaluation and treatment at the initial diagnosis. As Drs. Zarin and West correctly point out, there are no data comparing outcomes under these different treatment conditions for any specific disorder. Given this lack of outcome data and assuming equivalent outcomes for split versus integrated treatment, I attempted to evaluate only the presumption that split treatment is less expensive. I first presented data in 1997 (1) showing that this is not necessarily correct and suggested that the "preference for split treatment should be reconsidered." Goldman et al. subsequently provided utilization data in 1998 from one specific managed care organization that showed that only 12.5% of the patients received integrated treatment. The other 87.5% who received split treatment needed more sessions than the patients who received integrated treatment (26 versus 15, respectively) and had total payments of $1,854 versus $1,336. The authors did not present data on treatment outcomes but concluded that "for all its limitations, this study contradicts the pervasively held belief that split treatment is more *cost-effective*" (Goldman et al., 1998, p. 482, italics added). It is therefore surprising that my use of the term "cost-effective" in the title under the same limitations is labeled as "misleading" by Drs. Zarin and West. Given the consistent and continuing assumption of treatment outcomes being equal, and the many caveats enumerated in my article, the article's title and the summary statement given are both justified.

The dangers of drawing firm conclusions regarding cost-effectiveness in the absence of outcome data, as emphasized by Drs. Zarin and West, should serve to temper the praise by Dr. Markowitz and colleagues. Although much appreciated, their praise should await the author-to-be of the more comprehensive study that all of us recognize is critically needed, one that objectively assesses a variety of treatment outcomes and cost measures.

REFERENCE

1. Dewan M: Cost of care by a psychiatrist versus split treatment, in New Research Program and Abstracts, American Psychiatric Association Annual Meeting, 1997, p 147

MANTOSH DEWAN, M.D.
Syracuse, N.Y.

Magnetic Resonance Imaging Abnormalities and Psychiatric Illness

TO THE EDITOR: We noted with interest the recent article by Eileen P. Ahearn, M.D., Ph.D., and colleagues (1). The authors found a high prevalence of white and gray matter abnormalities on cranial magnetic resonance imaging (MRI) studies in a family with a strong history of mood disorders. The ability of this pedigree to illuminate the genetics of bipolar disorder, however, is limited by several considerations.

1. The significance of the apparently high occurrence of radiological abnormalities in the pedigree is difficult to evaluate in the absence of a comparison group, particularly since over one-half of the abnormal scans showed only one or two MRI lesions of 3 mm or less. Six of the nine patients with bipolar disorder and MRI lesions were over the age of 50. Subtle MRI changes are common in older individuals, even in the absence of psychiatric symptoms (2).

2. The data presented in table 1 in the article by Dr. Ahearn and colleagues show a lack of association between MRI lesions and the diagnosis of mood disorder (χ^2=1.22, df=1, n.s.), suggesting that radiological abnormalities and psychiatric phenomena may be unrelated. It is not clear, therefore, how the MRI changes could serve as a biological marker for bipolar disorder.

3. Bipolar disorder, like other psychiatric illnesses, represents a syndrome that can be produced by many different underlying processes. A wide variety of inherited metabolic disorders can appear as primary psychiatric illnesses, including adrenoleukodystrophy, Tay-Sachs disease, Huntington's disease, Wilson's disease, metachromatic leukodystrophy, and mitochondrial diseases (3–6). The ability of many different pathobiological pathways to give rise to similar psychiatric syndromes underscores the difficulty of trying to relate bipolar disorder to a single gene abnormality, such as the chro-

mosome 19 mutation associated with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

We agree with the authors that patients with psychiatric illnesses and abnormal neuroimaging findings should be investigated for underlying etiologies, including those listed previously. This line of investigation is likely to yield crucial information for the understanding of the pathophysiology of psychiatric disorders.

REFERENCES

1. Ahearn EP, Steffens DC, Cassidy F, Van Meter SA, Provenzale JM, Seldin MF, Weisler RH, Krishnan KR: Familial leukoencephalopathy in bipolar disorder. Am J Psychiatry 1998; 155:1605–1607
2. Verny M, Duyckaerts C, Pierot L, Hauw JJ: Leuko-araiosis. Dev Neurosci 1991; 13:245–250
3. Garside S, Rosebush PI, Levinson AJ, Mazurek MF: Late-onset adrenoleukodystrophy presenting with long-standing psychiatric symptoms. J Clin Psychiatry 1999; 60:460–468
4. Rosebush PI, MacQueen GM, Clarke JT, Callahan JW, Strasberg PM, Mazurek MF: Late-onset Tay-Sachs disease presenting as catatonic schizophrenia: diagnostic and treatment issues. J Clin Psychiatry 1995; 56:347–353
5. Hyde TM, Ziegler JC, Weinberger DR: Psychiatric disturbances in metachromatic leukodystrophy: insights into the neurobiology of psychosis. Arch Neurol 1992; 49:401–406
6. Inagaki T, Ishino H, Seno H, Ohguni S, Tanaka J, Kato Y: Psychiatric symptoms in a patient with diabetes mellitus associated with point mutation in mitochondrial DNA. Biol Psychiatry 1997; 42:1067–1069

SARAH GARSIDE, PH.D., M.D.
PATRICIA I. ROSEBUSH, M.SC.N., M.D., F.R.C.P.(C.)
ANTHONY J. LEVINSON, M.D.
MICHAEL F. MAZUREK, M.D., F.R.C.P.(C.)
Hamilton, Ont., Canada

Dr. Ahearn and Colleagues Reply

TO THE EDITOR: We appreciate Dr. Garside and colleagues' letter regarding our report of MRI lesions in a family with bipolar disorder. The authors are correct in noting that white matter lesions are common in the elderly. Our study found no age effect when comparing family members with MRI lesions to those without.

While we did not have an active comparison group in this study, our research group did a previous study of comparison subjects (1), using the same spin-echo pulse sequences, the same classification system for reporting the data, and the same raters who were blind to information about the study subjects. These data were reported in the introduction and indicate a low incidence of MRI lesions (1%) in subjects under age 45 and a higher incidence of lesions in the elderly.

The purpose of this study was not to look for correlations between the clinical manifestations of bipolar disorder and MRI lesions. Other researchers have already documented such findings (2–5). Rather, we were specifically looking at the prevalence of MRI lesions in affected and unaffected family members in a family with a substantial history of bipolar disorder. As noted in the article, the prevalence of white matter and subcortical lesions was high in unaffected family members and those with bipolar disorder. In the absence of other diseases that could explain these findings (the family had few risk factors), we postulate that they may correlate with a genotypic risk factor for the disorder.

REFERENCES

1. Krishnan KR, McDonald WM, Escalona PR, Doraiswamy PM, Na C, Husain MM, Figiel GS, Boyko OB, Ellinwood EH, Nemeroff CB: Magnetic resonance imaging of the caudate nuclei in depression: preliminary observations. Arch Gen Psychiatry 1992; 49:553–557
2. Dupont RM, Jernigan TL, Butters N: Subcortical abnormalities detected in bipolar affective disorder using magnetic resonance imaging. Arch Gen Psychiatry 1990; 47:55–59
3. Swayze VW, Andreasen NC, Alliger RJ, Ehrhardt JC, Yuh WTC: Structural brain abnormalities in bipolar affective disorder: ventricular enlargement and focal signal hyperintensities. Arch Gen Psychiatry 1990; 47:1054–1059
4. Figiel GS, Krishnan KR, Rao VP, Doraiswamy M, Ellinwood EH Jr, Nemeroff CB, Evans D, Boyko O: Subcortical hyperintensities on brain magnetic resonance imaging: a comparison of normal and bipolar subjects. J Neuropsychiatry Clin Neurosci 1991; 3:18–22
5. Strakowski SM, Woods BT, Tohen M, Wilson DR, Douglass AW, Stoll AL: MRI subcortical hyperintensities in mania at first hospitalization. Biol Psychiatry 1993; 33:204–206

EILEEN P. AHEARN, M.D., PH.D.
DAVID C. STEFFENS, M.D.
FREDERICK CASSIDY, M.D.
SUSAN VAN METER, M.D.
JAMES M. PROVENZALE, M.D.
RICHARD H. WEISLER, M.D.
K. RANGA RAMA KRISHNAN, M.D.
Raleigh, N.C.

Cognitive Effects of Testosterone Supplementation

TO THE EDITOR: The literature review by Harvey Sternbach, M.D. (1), on testosterone supplementation and andropause is an important contribution to our knowledge concerning the identification and management of hormone-related somatic and psychological disorders in men. We believe, however, that one of the author's statements regarding the cognitive effects of testosterone supplementation in men may lead to an incorrect inference on the part of readers. Dr. Sternbach states that "low and high levels are associated with poorer performance" (p. 1314) on tests of spatial cognition. Indeed, this is a simple paraphrase of the conclusions of Moffat and Hampson (2), but it fails to mention that in their study, such a conclusion only applied to right-handers and reflected the combined data of the influence of testosterone level on each of the sexes, i.e., a negative correlation in men and a positive one in women (lower testosterone levels in men and higher levels in women were associated with better performance). Data from at least two studies in men (3, 4) have shown that performance on tests of spatial cognition is inversely correlated with testosterone levels—i.e., lower levels of endogenous or exogenous testosterone were associated with better performance on these tests. However, other studies with men (5–11) have either failed to show such an inverse correlation or have even described a positive correlation. While the data in the literature are far from consistent, it would be misleading to suggest that low and high testosterone levels are associated with poor spatial abilities in men.

REFERENCES

1. Sternbach H: Age-associated testosterone decline in men: clinical issues for psychiatry. Am J Psychiatry 1998; 155: 1310–1318
2. Moffat SD, Hampson E: A curvilinear relationship between testosterone and spatial cognition in humans: possible influ-

ence of hand preference. Psychoneuroendocrinology 1996; 21:323–337
3. Gouchie C, Kimura D: The relationship between testosterone levels and cognitive ability patterns. Psychoneuroendocrinology 1991; 16:323–334
4. Shute VJ, Pellegrino JW, Hubert L, Reynolds RW: The relationship between androgen levels and human spatial abilities. Bull Psychon Soc 1983; 21:465–468
5. Gordon HW, Lee PA: A relationship between gonadotropins and visuospatial function. Neuropsychologia 1986; 24:563–576
6. Christiansen K, Knussman P: Sex hormones and cognitive functioning in men. Neuropsychobiology 1987; 18:27–36
7. Hassler M, Gupta D, Wollmann H: Testosterone, estradiol, ACTH and musical, spatial and verbal performance. Int J Neurosci 1992; 65:45–60
8. Christiansen K: Sex hormone-related variations of cognitive performance in Kung San hunter-gatherers of Namibia. Neuropsychobiology 1993; 27:97–107
9. Janowsky JS, Oviatt SK, Orwoll ES: Testosterone influences spatial cognition in older men. Behav Neurosci 1994; 108: 325–332
10. Kampen DL, Sherwin BB: Estradiol is related to visual memory in healthy young men. Behav Neurosci 1996; 110:613–617
11. Alexander GM, Swerdloff RS, Wang C, Davidson T, McDonald V, Steiner B, Hines M: Androgen-behavior correlations in hypogonadal men and eugonadal men, II: cognitive abilities. Horm Behav 1998; 33:85–94

MARK J. SMITH, M.D., PH.D.
PETER J. SCHMIDT, M.D.
DAVID R. RUBINOW, M.D.
Bethesda, Md.

Dr. Sternbach Replies

TO THE EDITOR: Dr. Smith et al. write to clarify a point that they believe could be misconstrued regarding my statement on the relationship between cognitive—more specifically, visuospatial—function and testosterone levels, i.e., that a curvilinear relationship exists. Actually, we do not disagree on this point, because I indicate that the interpretation of, and comparisons between, results of the different studies on this subject is hampered by the multiple methodological differences that include variables such as handedness. Janowsky et al., 1994, have also noted that "it may be that testosterone has a curvilinear relationship to spatial cognitive performance" (p. 330). Recognizing, however, that this relationship is the subject of debate (1), I chose to write, "it appears that there exists a curvilinear relationship between testosterone level and performance on tests of spatial cognition" (Sternbach, 1998, p. 1314), rather than make a more definitive statement of such a relationship. Undoubtedly, the relationship between testosterone levels in both men and women and cognitive function is a complex one that is influenced by multiple other hormonal and nonhormonal variables.

REFERENCE

1. Hampson E, Moffat SD: Is testosterone related to spatial cognition and hand preference in humans? Brain Cogn 1994; 26: 255–266

HARVEY STERNBACH, M.D.
Santa Monica, Calif.

Theoretical-Clinical-Empirical Approach to Classifying Axis II Disorders

TO THE EDITOR: The recent articles by Drew Westen, Ph.D., and Jonathan Shedler, Ph.D. (1, 2), described an innovative and important clinical-empirical approach to classifying personality-disordered functioning. The authors suggested that their method could be used to "replace the current approach" (2, p. 284) to organizing axis II disorders. However, their results (2) lacked a theoretical discussion examining the similarities and differences between the six categories that are clinically near the axis II disorders and their appropriate DSM-IV counterparts. While a full discussion is beyond the scope of this letter, a few comments on some apparent contradictions seem necessary.

1. The statement "Has little psychological insight into own motives, behavior, etc.; is unable to consider alternative interpretations of his/her experiences" (2, p. 277) appears on the diagnostic categories for both schizoid and antisocial personality disorders (2). One explanation is that this statement is intrinsic to both categories. Another explanation is that this criterion reflects low self-directedness (3), a character dimension that has empirically/dimensionally discriminated disordered personality functioning from less disordered levels.

2. Three Shedler-Westen Assessment Procedure-200 (SWAP-200) descriptions (i.e., "Tends to feel he/she is not his/her true self with others; tends to feel false or fraudulent," "Tends to feel life has no meaning," and "Tends to feel empty and bored" [2, p. 279]) that appeared in the authors' narcissistic personality disorder diagnostic category do not appear among the DSM-IV criteria for narcissistic personality disorder. While it could be that the DSM-IV Personality Disorders Work Group overlooked or intentionally excluded important features of the disorder, it seems more likely that the discrepancies reflect a pretreatment (for the DSM-IV work group) versus an in-treatment (for the reporting clinicians) focus. Drs. Westen and Shedler stated that their study's "patients were well known to the reporting clinicians and had been seen in treatment an average of 33.95 sessions before the SWAP-200 assessment" (1, p. 266).

3. The SWAP-200 statements that describe individuals in the obsessional personality disorder diagnostic category include a preponderance of mature character traits rather than the pervasive pattern of "preoccupation with orderliness, perfectionism, and mental and interpersonal control, at the expense of flexibility, openness, and efficiency" (DSM-IV, p. 669) found in the DSM-IV obsessive-compulsive personality disorder criteria. For example, four of the first five SWAP-200 statements seem to better reflect maturity and self-directedness (3) than the functioning of disordered personality disorder (2, p. 278).

This brief discussion underscores the importance of including relevant theory in discussions of outcome data. In my opinion, a clinical-empirical derivation such as that of Drs. Westen and Shedler (1, 2) can inform theory but not de facto replace theory.

REFERENCES

1. Westen D, Shedler J: Revising and assessing axis II, part I: developing a clinically and empirically valid assessment method. Am J Psychiatry 1999; 156:258–272
2. Westen D, Shedler J: Revising and assessing axis II, part II: toward an empirically based and clinically useful classification of personality disorders. Am J Psychiatry 1999; 156:273–285

3. Cloninger CR, Svrakic DM, Przybeck TR: A psychobiological model of temperament and character. Arch Gen Psychiatry 1993; 50:975–990

KEVIN P. PROSNICK, PH.D.
Cleveland, Ohio

Drs. Westen and Shedler Reply

TO THE EDITOR: We appreciate Dr. Prosnick's comments; our response is primarily by way of clarification rather than disagreement. One minor point: our Q-factor analysis produced seven primary clusters or categories of personality disorders, of which one (dysphoric) had five subtypes that are more descriptive than the general cluster. Thus, the procedure indicated the existence of 11 distinct clusters of personality pathology, not far from the 10 listed under axis II disorders in DSM-IV. Several of these diagnostic groupings resemble current axis II categories, and in a multipart unpublished study, we describe some of the similarities and differences between our empirically generated prototypes and the categories and criteria selected by the DSM-IV Personality Disorders Work Group.

Aside from similarities and differences in content, perhaps the major difference between our empirically derived classification system and that found in DSM-IV, which we believe may suggest a revision for DSM-V, is a shift from a symptom-counting to a prototype-matching approach. Several features of a prototype-matching approach are advantageous. For example, in our article we noted the psychometric problems with diagnosing a disorder with eight items and counting them, such as the inherent comorbidity that would be built into such a system. A conceptual and practical advantage of having clinicians consider the gestalt and make a rating of the extent to which a patient matches the prototype of a disorder is that it is easier, is faster, probably is much more reliable (something we are now exploring empirically), and permits diagnoses that are both dimensional (degree of match to the prototype) and categorical (based on a cutoff above which a rating can be considered above the threshold for categorical diagnosis of the disorder, e.g., a rating of 5 on a scale of 1 to 7). A prototype-matching approach also does not require that clinicians try to dichotomize symptoms (present/absent) that are, by their nature, actually continuous (e.g., grandiosity, emotional lability, lack of empathy, lack of insight, fear of betrayal by others, and preoccupation with being criticized by others).

An equally important advantage of a prototype-matching system (particularly one in which the prototypes are empirically determined) is that a diagnostic criterion can, and should be, part of more than one diagnosis if it applies to more than one type of disorder. This would not lead to the inflated estimates of comorbidity that have plagued the list of axis II disorders in DSM-IV. When a prototype-matching approach is used with a larger number of criteria than eight per disorder, the meaning of any item reflects its embeddedness in a constellation of personality characteristics (the diagnostic criteria). Thus, one possible interpretation of the fact that the statement "Has little psychological insight into own motives, behavior, etc." appeared on both the schizoid and antisocial diagnostic categories is, as Dr. Prosnick suggests, that the item reflects an underlying construct shared by the two. Another possibility, and one that may be complementary, is that the clinical significance and meaning of an item depends in part on the broader construct of which it is a part. For the schizoid patient, a lack of self-insight is part of a character style characterized by divorce from the human world and an avoidance of feelings, including one's own. For the antisocial patient, a lack of self-insight may have more to do with an impulsive style that deters self-reflection or, if the patient has the functioning aspects of a conscience that gets overridden when impulses or affects are strong, promotes an effort to avoid reflecting on things that lead to guilt or shame.

With respect to Dr. Prosnick's comments on the diagnostic profiles of narcissistic and obsessional personality pathology that emerged empirically, we are in no particular disagreement. Regarding narcissistic personality disorder, we suspect that a diagnosis that takes into account what the patient actually looks like over time—in particular, the patient's phenomenology and not just overt self-reported symptoms—is likely to be more useful clinically, but that is an empirical question. The relatively healthy appearance of the obsessive patients in our study was an interesting and unexpected finding, as was the fact that the "sicker" obsessive patients, who appeared more like the DSM-IV axis II description of obsessive-compulsive personality disorder, all had an axis I diagnosis of obsessive-compulsive disorder, suggesting a confounding of the two disorders in DSM-IV (or at least in clinicians' use of the manual). We are completing a cluster-analytic study of 60% of the patients treated in clinical practice for personality pathology not severe enough to warrant an axis II diagnosis but severe enough to require clinical attention (1). The aim is to learn, empirically, about the categories or dimensions that define such patients with "neurotic" character pathology—that is, most patients who seek psychiatric help—for whom we currently have no diagnostic categories.

Finally, we agree with Dr. Prosnick's comments about the importance of replication and theory-guided empiricism. As we noted in our article, our findings clearly need to be replicated with a less constrained study group. With respect to theory, there is no substitute for using theory—and particularly theory informed by clinical observation—in determining which items to include in an instrument such as the SWAP-200 Q-sort (on which our study was based). We included items based on personality theory, as well as clinical observation and empirical research, covering the ways in which different kinds of patients experience affect, styles of affect regulation, thought patterns, interpersonal patterns, their intrapsychic components, and the like. There is also no substitute for theory in selecting factor- or cluster-analytic solutions. Empirical procedures of the sort we used in our article are, we believe, essential for developing a more accurate, useful, and clinically valid system for assessing and classifying personality pathology, but they are of little value if they do not draw on the last century's clinical and theoretical wisdom about personality and its pathology.

REFERENCE

1. Westen D, Arkowitz-Westen L: Limitations of axis II in diagnosing personality pathology in clinical practice. Am J Psychiatry 1998; 155:1767–1771

DREW WESTEN, PH.D.
JONATHAN SHEDLER, PH.D.
Cambridge, Mass.

Comparison of Clozapine and Risperidone

TO THE EDITOR: In their interesting comparison of clozapine and risperidone in partially responding schizophrenic patients, Alan F. Breier, M.D., and colleagues (1) made several statements for which interpretation may be problematic.

First, this extremely small group, with subgroups, clozapine or risperidone, and two measurement time points, pretreatment and 6 weeks into treatment, was correctly analyzed as a two-group analysis of covariance (ANCOVA) by using the baseline score for each subject as the covariate. However, the small group size (N=29, with 14 subjects assigned to risperidone and 15 assigned to clozapine treatment) makes interpretation of any nonsignificant results problematic.

For example, in their analysis of the response rates, the authors found no difference between the two treatments (χ^2= 0.9, df=1, p<0.34). With the small group size, a change in the response status of one subject in each group changes the p value from the 0.34 they found to 0.07, which is a lower value than that found in the results they called "a trend" later in the article. Failure to reject a null hypothesis should not be taken as tantamount to deciding the null hypothesis is true. In several places in the article, there were statements such as "We found no significant differences between the two agents for negative symptoms" (p. 296) and "Moreover, neither drug demonstrated significant reductions in negative symptoms" (pp. 296–297). Although the language was very carefully and correctly used to state that no significant differences were found, we believe a typical reader might infer from the language that the authors intended to communicate evidence that no difference exists. Had the authors placed a statement in the article noting the small group size, and had they done a post hoc power analysis, they might have helped readers understand that with the size of the group, they had little chance of finding any except a very large difference to be statistically significant.

Second, they made errors in the degrees of freedom in their chi-square tests in several places. On page 296, the chi-square tests in the first two paragraphs are stated to have 28 (N–1) degrees of freedom. Both tests used 2×2 analysis, and each test has only one degree of freedom. The value of the chi-squares calculated in both cases are correct, as are the p values. It was simply the degrees of freedom that were incorrect.

Third, in several places, the authors used a test of parallel slopes in the ANCOVA to decide whether to use a single-slope ANCOVA model. When they rejected the null hypothesis of single slopes, they moved to an analysis of change scores. This is illogical. Using an ANCOVA assuming equal slopes makes one assumption: that the slopes are equal. Using change or difference scores not only assumes that the slopes are equal, but it assumes they both equal 1. Thus, an analysis of variance (ANOVA) on change scores is simply an ANCOVA with the slopes not only constrained to be equal but to both equal 1. (The two-group, unequal-slope, ANOVA model may be stated as $Y_{ij}=\mu_i + \beta_i X_{ij} + s_{ij}$, where the Y_{ij}'s are the endpoint scores, the X_{ij}'s are the baseline scores, the μ_i's—with appropriate constraints—are the two group population means, and the β_i's are the two slopes. If the authors are unwilling to assume that the β_i's are equal, they should be even more unwilling to assume that they both equal 1. [If we substitute 1 into the model for β, we obtain $Y_{ij}=\mu_i + (1)X_{ij} + s_{ij}$, and if we use algebra to move that term to the left side of the equals sign, we have $Y_{ij} - X_{ij}=\mu_i + s_{ij}$, which is the analysis the authors chose—an ANOVA on change scores.])

Fourth, in table 2 in the article, change is reported as a percent. If the percent change is really of interest, then it should have been analyzed. It is not correct to analyze the data, without transformation, by t tests of differences or even by an ANCOVA. The outcome of interest should be what is used in the analysis. This could be done by using percent change or by possibly, more appropriately, using a log transformation with an ANCOVA. A partial attempt to look at percent change was made by the investigators when they looked at a 20% change in the Brief Psychiatric Rating Scale scores.

Fifth, no justification for the 20% cut point was given. Typically, a 50% change in scores indicates a response. Had the authors used 50% improvement as their cut point, fewer subjects than the already small number would have met the criteria for response, and it would have been more obvious that the study had failed to detect group differences.

Sixth, the analysis of neuroendocrine levels is problematic. Typically, these levels can fluctuate considerably during the day. Not only is there a diurnal variation with many neuroendocrine parameters, but they fluctuate widely within a relatively short period of time. The wide variance found for the groups indicates such a fluctuation. It also makes the use of a t test inapplicable with such a small group.

It is probable that the major conclusions of this article, particularly with respect to the differences found between clozapine and risperidone, will hold. It may be less plausible that the differences Dr. Breier and colleagues failed to find indicate more than a small group size and lack of power. Our criticisms revolve around about the analysis and the presentation of results.

REFERENCE

1. Breier AF, Malhotra AK, Su TP, Pinals DA, Elman I, Adlere CM, Lafargue RT, Clifton A, Pikar D: Clozapine and risperidone in chronic schizophrenia: effects on symptoms, parkinsonian side effects, and neuroendocrine response. Am J Psychiatry 1999; 156:294–298

ROBERT M. HAMER, PH.D.
PIPPA M. SIMPSON, PH.D.
Piscataway, N.J.

Sympathoadrenal Hyperactivity and Neuroleptic Malignant Syndrome

TO THE EDITOR: We read with great interest the article by Ronald J. Gurrera, M.D. (1), a distinguished researcher, regarding the etiology of neuroleptic malignant syndrome. He correctly stated that the current theories of origin—hypothalamic hypodopaminergia and direct myotoxicity—do not explain the entire pathophysiological changes found in neuroleptic malignant syndrome. He further added that the treatment options based on these mechanisms are not reliable and are reported to be insufficiently effective in overall management of the symptoms of neuroleptic malignant syndrome. Similarly, when we reviewed and updated the relevant literature (2) and presented nine cases (3) of neuroleptic malignant syndrome, one of our main conclusions was that all the manifestations of neuroleptic malignant syndrome are not explained exclusively by dopaminergic antagonism in the central nervous system. Therefore, we recommended that other putative neurotransmitters and also peripheral factors should be explored in studying its pathophysiology.

The author partially bridged this gap by presenting an alternative hypothesis to that of sympathoadrenal hyperactivity, which, in a person genetically vulnerable to the development of neuroleptic malignant syndrome, is the interplay of the dysregulated and/or overactivated sympathetic nervous system in response to emotional or psychological stress. Although Dr. Gurrera did not highlight them, we feel that there are several future research implications in his article.

1. Despite a recent study's negative results (4) regarding the genetic etiology of the features of neuroleptic malignant syndrome, further studies are needed to discover the phenotypes and genetic markers of this syndrome.

2. As the author claimed, this pathophysiological model explains most of the features of neuroleptic malignant syndrome; therefore, the unexplained manifestations should have been better elucidated. Their identification may in fact guide researchers to explore other possible alternative pathophysiological mechanisms underlying the development of neuroleptic malignant syndrome.

3. The author did not suggest any alternative treatments based on his hypothesis; hence, the hypothesis should be the avenue in future studies for developing suitable drugs for the treatment of both neuroleptic malignant syndrome and psychological disorders.

4. Finally, in the context of this new pathophysiological model, is it possible to prematurely rename neuroleptic malignant syndrome as "sympathoadrenal hyperactivity hyperpyrexia syndrome"?

REFERENCES

1. Gurrera RJ: Sympathoadrenal hyperactivity and the etiology of neuroleptic malignant syndrome. Am J Psychiatry 1999; 156:169–180
2. Qureshi NA, Al-Amri AH, Al-Beyari TH, Abdelgadir MH, Al-Habeeb TA: Neuroleptic malignant syndrome: a comprehensive review and update. Saudi Pharmaceutical J 1996; 4:138–148
3. Qureshi NA, Al-Beyari TH, Al-Amri AH, Abdelgadir MH, Al-Habeeb TA: Neuroleptic malignant syndrome: a report of 9 suspected cases. Saudi Pharmaceutical J 1996; 4:179–189
4. Kawanishi C, Hanihara T, Shimoda Y, Suzuki K, Sugiyama N, Onishi H, Miyakawa T, Yamada Y, Kosaka K: Lack of association between neuroleptic malignant syndrome and polymorphisms in the 5-HT_{1A} and 5-HT_{2A} receptor genes. Am J Psychiatry 1998; 155:1275–1277

NASEEM AKHTAR QURESHI, M.D.
Buraidah, Saudi Arabia
TARIQ ALI AL-HABEEB, K.S.U.F.
Riyadh, Saudi Arabia

Dr. Gurrera Replies

TO THE EDITOR: Drs. Qureshi and Al-Habeeb endorse my thesis that sympathoadrenal hyperactivity is responsible for the clinical manifestations of neuroleptic malignant syndrome. They even go so far as to propose a new name for this disorder, namely "sympathoadrenal hyperactivity hyperpyrexia syndrome"! Beyond their support for the article's central thesis, however, they express the view that it should have included some discussion of the potential implications for future research and treatment. Space limitations precluded consideration of these issues in my article, but I would like to comment briefly.

The handful of studies that have been done (1–3; Kawanishi et al., 1998) have not identified any genetic defects causally related to neuroleptic malignant syndrome, but there are many other, as yet untested, candidates. Most notable among these, in my opinion, are the regulatory proteins that maintain intracellular electrochemical homeostasis through their function as calcium buffers and channels. Multiple individual point mutations affecting genetic loci for several of these proteins are known to cause malignant hyperthermia. Considering the many clinical features shared by neuroleptic malignant syndrome and malignant hyperthermia, it seems reasonable to hypothesize that similar but distinct mutations affecting this heterogenous group of proteins could be the basis for vulnerability to developing neuroleptic malignant syndrome. In this model, the role of sympathoadrenal hyperactivity would be analogous to that of volatile anesthetics in malignant hyperthermia—i.e., hyperstimulated adrenoceptors interact with a genetically defective regulatory protein to produce excessive intracellular calcium levels.

This highly speculative model hints at possible alternative treatments for neuroleptic malignant syndrome. In particular, two general categories of pharmaceutical agents seem worthy of future investigation: calcium channel blockers and adrenoceptor antagonists. However, the existence of multiple types of calcium channels, the possible involvement of proteins other than as calcium channels, and the functional opposition of α- and β-adrenoceptors under normal physiological conditions (a consequence of which is that antagonizing one adrenoceptor type while leaving the other type unopposed can precipitate a medical crisis) are just some of the challenges that future studies need to surmount.

I thank Drs. Qureshi and Al-Habeeb for their interest in my article and for giving me an opportunity to elaborate further on some of the ideas contained therein.

REFERENCES

1. Iwahashi K: CYP2D6 genotype and possible susceptibility to the neuroleptic malignant syndrome. Biol Psychiatry 1994; 36:781–782
2. Iwahashi K, Nakamura K, Suwaki H, Tsuneoka Y, Ichikawa Y: CYP2D6 Hhal genotype and the neuroleptic malignant syndrome (letter). Clin Chim Acta 1997; 265:143–144
3. Ram A, Cao Q, Keck PE Jr, Pope HG Jr, Otani K, Addonizio G, McElroy SL, Kaneko S, Redlichova M, Gershon ES, Gejman PV: Structural change in dopamine D2 receptor gene in a patient with neuroleptic malignant syndrome. Am J Med Genet 1995; 60:228–230

RONALD J. GURERRA, M.D.
Brockton, Mass.