Psychosis Only Skin Deep

TO THE EDITOR: This case report discusses a rare complication of Darier's disease and emphasizes the importance of obtaining a thorough medical history, including a family medical history, and a physical examination to rule out medical causes of patient complaints.

Mr. A was a 22-year-old man in basic training with the military. On the 12th day of training, he was found waking other soldiers in their bunks while on guard duty. He was unresponsive to commands, talking only in riddles and puns. The results of a mental status examination were significant for a blunted affect and poverty of thought. There was no evidence of a sleep disturbance or a flight of ideas. Mr. A was admitted to the hospital to rule out a psychotic disorder.

Mr. A's medical history revealed that he had sought medical care 3 days before for a rash. There was no personal or family psychiatric history. He was outgoing and socially involved, displayed no occupational difficulties, and maintained close friendships until his admission.

The results of Mr. A's physical examination were notable for a maculopapular, erythematous, crusting rash over his upper body and feet. There were no vesicles, pustules, or target lesions. His nails were thickened and had V-shaped scalloping. His drill sergeant revealed that the marines had recently exercised without shirts and rested in the sun with their boots off. Mr. A's father told us of his own history of Darier's disease, which is exacerbated by exposure to the sun. A skin biopsy of Mr. A's lesions revealed abnormal keratinization and loss of epidermal adhesion with acantholysis, which was consistent with keratosis follicularis, or Darier's disease.

Mr. A was removed from exposure to the sun and treated with topical isotretinoin. On his fourth day in the hospital, 4 mg/day of risperidone was added to help his disorganized thought process. His symptoms faded by the 12th day of admission, and he displayed no further psychotic symptoms. He was discharged with a diagnosis of psychotic disorder secondary to Darier's disease.

Darier's disease is an autosomal dominant disorder characterized by altered keratinization of the epidermis, nails, and mucous membranes. It was first discovered in an American patient who developed the lesions under a knapsack while training for the U.S. Army in 1862. It usually begins in the first or second decade of life and is found in equivalent numbers among men and women. It is a rare condition, affecting one person in 100,000. Darier's disease is frequently worse in the summer, when it is exacerbated by heat, humidity, ultraviolet B light, and mechanical trauma. Affective disorders, mainly bipolar disorders, that appeared as a result of Darier's disease have been reported recently, but they are considered rare complications. The association between the two diseases has been postulated to result from a defect in cell adhesion expressed in both the skin and the brain, which share a common ectodermal origin (1). Treatment is supportive, with removal from and education about sun exposure. Topical retinoids are used to treat the rash; oral retinoids are reserved to treat more severe forms of the disorder.

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Sildenafil and Erectile Dysfunction

TO THE EDITOR: Sildenafil is an oral agent that improves erectile functioning by inhibiting phosphodiesterase in the penis's vasculature, thereby prolonging the effects of cyclic GMP on smooth muscle tissue (1). Sildenafil is generally well tolerated, although possible side effects include headache, flushing, visual changes, and potentiation of the hypotensive effects of nitrates. Clinical investigators suggest that erectile dysfunction induced by selective serotonin reuptake inhibitors responds to treatment with sildenafil (2, 3). Although they are less well studied, neuroleptics are also associated with impaired erectile functioning (4). We report a case of haloperidol-associated erectile dysfunction remedied by sildenafil therapy.

Mr. A was a 52-year-old male veteran with a long history of schizoaffective disorder and intermittent cocaine abuse who reported erectile dysfunction over the past 2 decades while he was taking neuroleptics, including perphenazine, trifluoperazine, fluphenazine, and haloperidol. Because of erectile dysfunction, he frequently discontinued the neuroleptics. Sexual functioning invariably improved after he stopped taking them. Mr. A had no other systemic diseases, including diabetes, hypertension, peripheral vascular disease, or alcoholism, that affected erectile functioning. His medications for the last 4 months included haloperidol decanoate, 150 mg i.m. every 4 weeks, and benztropine, 1 mg b.i.d. Mr. A reported difficulty attaining and maintaining erections. He could achieve only partial erections that lasted less than a minute. He was interested in having sex, although he felt frustrated by his inability to maintain erections. For his erectile difficulties, we prescribed sildenafil, 50 mg. With sildenafil therapy, he was able to attain a complete erection and experience intercourse without difficulty. In fact, the first time he took sildenafil, he experienced three erections in a 5-hour period. He has successfully used the same dose of sildenafil approximately 20 times with satisfactory results. He reported no side effects, such as headaches, gastrointestinal disturbance, priapism, or visual disturbances.

In this patient, haloperidol-associated erectile dysfunction was alleviated by sildenafil therapy. The mechanism through which haloperidol induces erectile dysfunction is uncertain, although dopamine antagonism and a higher than normal prolactin level are implicated. Sildenafil appears to counteract haloperidol-associated erectile dysfunction, even though the mechanism may be unrelated. It is unknown if cocaine use contributed to any of the patient's erectile difficulties, although this possible pathology also responded to treatment with sildenafil. The improved treatment of haloperidol-associated sexual side effects may lead to improved compliance with neuroleptics and a more successful treatment of psychosis. Further clinical investigation, using sildenafil to treat sex-

ual dysfunction associated with the use of haloperidol or other antipsychotics, is warranted.

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Panic Disorder Associated With Clozapine

TO THE EDITOR: We present a case of treatment-resistant schizophrenia in which clozapine therapy resulted in both a marked improvement in positive psychotic symptoms and the onset of disabling panic. Substitution of olanzapine for clozapine treatment alleviated the panic symptoms without worsening the psychotic symptoms.

Ms. A, a 34-year-old woman, was first seen for psychiatric treatment at age 30 after experiencing 2 months of psychotic symptoms. She described hearing threatening voices saying that they wanted to cut her fingers. She suspected that her mother's doctors had formed an organization to harm her and that these doctors could hear her thoughts by means of a "neurotransmitter" installed inside her head. Treatment with two typical antipsychotics (haloperidol, 30 mg/day, and trifluoperazine, 40 mg/day) and one atypical antipsychotic (risperidone, 8 mg/day) resulted in no significant improvement in her symptoms. After 8 months of unsuccessful treatment, including two hospital admissions, the diagnosis of treatment-resistant paranoid schizophrenia (per DSM-IV) was confirmed, and Ms. A was treated with clozapine. Clozapine monotherapy (400 mg/day) led to a marked improvement in positive symptoms, but Ms. A remained a bit withdrawn. In the 20th week of clozapine treatment, Ms. A developed clozapine-induced sinus tachycardia and the fear of dying of a heart attack. She was effectively medicated with a β blocker (atenolol, 100 mg/day). Despite a normal ECG and the exclusion of other organic causes, Ms. A experienced recurrent attacks of sudden chest compression, dizziness, fear of dying, and intense anxiety. She often went to emergency clinics, where her symptoms were treated with benzodiazepines. Her panic symptoms occurred daily, and she developed agoraphobic symptoms that confined her to the house and compromised her rehabilitation.

When assessed by a blind rater with the Structured Clinical Interview for DSM-IV, Ms. A fulfilled the DSM-IV criteria for paranoid schizophrenia and panic disorder with agoraphobia. The temporal relationship between clozapine treatment and the development of panic attacks suggested that clozapine could have been inducing the panic symptoms. Reduction of clozapine therapy to 250 mg/day led to a modest improvement in Ms. A's anxiety symptoms but some worsening of her psychotic symptoms. Olanzapine (10 mg/day) was then substituted for clozapine without recurrence of the psychotic symptoms. Her panic symptoms progressively improved, and 2 months after switching antipsychotics, Ms. A patient was stable, with some negative symptoms but no panic or agoraphobic symptoms.

Clozapine treatment can induce obsessive-compulsive symptoms (1), but this is, to our knowledge, the first report associating it with panic disorder. Doctors should pay special attention to panic and agoraphobic symptoms when prescribing clozapine because its effect is easily confounded with negative symptoms, which can therefore be misdiagnosed. Panic and agoraphobia may greatly affect psychosocial rehabilitation and the quality of life of patients. Although clozapine remains the gold standard of atypical antipsychotic drugs, it has many and sometimes severe side effects; newer atypical antipsychotics can be a good alternative in this situation (2).

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Hallucinations in Guillain-Barré Syndrome

TO THE EDITOR: Guillain-Barré syndrome, or acute inflammatory demyelinating polyneuropathy, is generally regarded as predominantly a motor neuropathy. However, sensory disturbances such as paresthesias occur frequently, and outright pain occurs in up to 72% of the cases. Less widely appreciated is the occurrence of more pronounced perceptual disturbances and even outright hallucinatory experiences in this disorder. A review of the more recent medical literature uncovered only two descriptions of hallucinatory phenomena in Guillain-Barré syndrome (i.e., reference 1), and none in the English-language literature. We report a case of bizarre hallucinatory experiences in a man with severe Guillain-Barré syndrome.

Mr. A, a 76-year-old man, was admitted to the hospital with rapidly decreasing motor strength and was subsequently diagnosed with Guillain-Barré syndrome. During the first few days of hospitalization, he reported seeing cats in a large cage and people coming into his room to give lumber to his doctor. His weakness rapidly progressed, necessitating intubation and a 6-week stay in the intensive care unit. At extubation, he reported having been raped by a staff member. His description of the act of sodomy was highly implausible and did not stand up to investigation.

Over the next 6 months, the lack of return of his motor strength was disappointing. He regained only slight movement in his proximal upper and lower extremities. He continued to describe unusual experiences. These included

seeing pictures floating in his room and the recurrent sensation that "plastic worms" were writhing in his hands. A particularly disturbing and recurrent sensation that occurred on awakening was that of being suspended over an open chasm. This would abruptly disappear when nursing staff spoke to him. The sensation bore a striking resemblance to sleep paralysis, differing primarily in its length (lasting many minutes). Mr. A, in retrospect, admitted that these unusual experiences must have been "fantasies." He displayed no evidence of ongoing delusions, delirium, or any psychotic symptoms other than the experiences described. The addition of a low dose of trazodone (50 mg/day) and haloperidol (0.5 mg at bedtime) had no significant effect on his symptoms. Over time his physical sensations lessened only slightly, but the fantasies associated with them faded to a greater extent.

The perceptions described by this otherwise lucid man are strikingly similar to those seen in normal dreaming and hypnagogic or hypnopompic hallucinations. It has been postulated (2) that dreamlike and other hallucinatory experiences may occur when there is a disruption in the "corollary discharge" system that allows us to discriminate between self-generated and externally generated neural activity. Sleep, particularly REM sleep, is a state of greatly reduced responsiveness to external stimuli and partial flaccid paralysis largely caused by the postsynaptic inhibition of motor neurons. The sensory and motor denervation that occurs in Guillain-Barré syndrome might allow the same confusion between internally and externally generated thoughts and sensations that occur in sleep, resulting in thoughts having a dreamlike or hallucinatory quality.

Increased awareness of hallucinatory experiences in denervation syndromes will allow us to better allay the anxiety generated in patients by these profoundly disturbing experiences. Exploration of this phenomenon might also help increase our understanding of the pathophysiology of hallucinations in the "functional" psychoses.

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Twin Concordance for Bipolar Disorder and Migraines

TO THE EDITOR: Concordance rates of up to 80% have been reported in monozygotic twins with bipolar disorder (1); significantly elevated concordance rates among monozygotic twins with migraine headaches have also been reported (2). There is evidence that the prevalence of migraines is higher in patients with bipolar disorder (3). We report on a pair of monozygotic twins concordant for bipolar disorder and migraines who were successfully treated with carbamazepine.

Ms. A and Ms. B were 29-year-old twins who were born 6 weeks premature. Their mother and a younger sister suffered from migraines, a maternal aunt from bipolar disorder, and a paternal aunt from unipolar depression. Ms. A was left-handed, and Ms. B was right-handed.

Ms. A had suffered from weekly migraines since she was 13, and Ms. B had had them every 2 weeks since she was 14. The headaches were unilateral, were pulsating, lasted more than 4 hours, and were accompanied by loss of appetite, nausea, vomiting, photophobia, and phonophobia. Flashing lights, visual scotomata, and occasional fortification spectra preceded the headaches by half an hour.

Ms. B had major depression with marked feelings of guilt when she was 14 and required hospitalization. A second depressive episode occurred when she was 19, and at age 24 she had her first manic episode, which included flights of ideas and grandiose delusions with religious content. Three years later, a florid manic episode cut short a vacation in Europe. Since then she has been maintained with carbamazepine, 400 mg b.i.d., has remained symptom free, and has worked full-time as a nurse.

When she was 15, Ms. A apparently had a week-long, mild manic episode, which went unrecognized. At age 19 she had major depression; she had a manic episode when she was 21. Lithium therapy was begun, but it had to be discontinued because of severe side effects. Ms. A had a manic episode followed by depression when she was 25. This illness lasted for 6 months; it was during this episode that carbamazepine treatment was initiated. A year later Ms. A had another major depressive episode in which she took an overdose of carbamazepine; however, since then she has remained well on a regimen of carbamazepine, 400 mg b.i.d. After the introduction of carbamazepine as a mood stabilizer, both sisters experienced a marked reduction in the frequency of their migraines.

To our knowledge, this is the first report of monozygotic twins concordant for bipolar disorder and migraine. It is of interest that both conditions appear to have responded to treatment with carbamazepine. This supports a possible common pathogenesis for the illnesses.

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Sibutramine-Associated Psychotic Episode

TO THE EDITOR: Sibutramine, a new drug for the pharmacological treatment of obesity, has not been associated with the occurrence of psychosis, to our knowledge. We report the case of a young woman who received sibutramine for the treatment of obesity and, after 3 months of therapy, developed an acute paranoid episode.

Ms. A, a 19-year-old woman, was admitted to a psychiatric hospital because of acute paranoid symptoms. She had no history of psychiatric treatment, neurologic disturbances, or substance abuse. She had been given sibutramine (10 mg/day) to treat obesity. At first the drug was not well tolerated; side effects of sleeplessness, mild anxiety, and tachycardia emerged. After 8 weeks of therapy and a dose increase (to 15 mg/day), Ms. A began to be anxious

and complained of sleep disturbances, lack of appetite, constipation, and severe abdominal pain. Sibutramine therapy was withdrawn, and the side effects slowly faded, but in the next 7 days her mental state progressively deteriorated.

At admission to the psychiatric ward, Ms. A was preoccupied with internal stimuli and withdrawn and experiencing delusions of reference and auditory hallucinations. Clear signs of severe formal thought disorder were also present. Her heart rate was 100 bpm, and her blood pressure was elevated, at 130/100 mm Hg. The results of laboratory tests, a computerized tomography scan of her brain, ECG, and EEG did not reveal any significant abnormalities. She was given perazine, 500 mg/day, and within 20 days her mental state had improved, and her vital signs were normal. The 4-week follow-up revealed no psychotic symptoms, although Ms. A's antipsychotic treatment continued.

Sibutramine is a serotonin-norepinephrine reuptake inhibitor (1). It is widely used because it is not associated with a potential for abuse, which is a serious disadvantage for some groups of patients treated with methamphetamine derivatives. The frequently reported adverse effects of sibutramine include dry mouth, anorexia, headache, insomnia, and, in some patients, an increase in blood pressure and tachycardia due to anticholinergic activity (1).

Although we know of no reports of the psychotomimetic effects of the drug, such adverse events have been described in relation to other antiobesity agents (2, 3). In individuals vulnerable to psychosis, sibutramine may induce psychotic symptoms. It is also possible that some patients might develop psychosis without sibutramine, even though before the initiation of therapy there might be no clear history of prodromal symptoms. Nevertheless, this case report demonstrates the potential risks associated with the pharmacological treatment of obesity and suggests careful assessment of the patient's mental state before beginning treatment with a new drug.

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Maintenance ECT Replaced With Lamotrigine

TO THE EDITOR: Although the safety of lamotrigine for the epileptic population is known (1), clinical experience in elderly patients with bipolar disorder is limited.

Ms. A was a 76-year-old woman with a 50-year history of bipolar disorder. She had been successfully treated with lamotrigine, 75 mg/day, for 34 months without a recurrence of mood episodes. Before treatment with lamotrigine, while receiving ECT, she experienced major depressive symptoms of sadness, worthlessness, diminished interest, poor concentration and energy, and sleep disturbance. Her functioning while taking lamotrigine was superior to that experienced while she was receiving ECT. Minor adverse effects, some agitation and sleep disturbance, were treated with a dose reduction, from 100 mg/day to 75 mg/day.

Ms. A had taken lithium for 21 years for bipolar disorder. She functioned well, with no manic or major depressive episodes. She developed renal insufficiency, and her lithium therapy was discontinued. Her creatinine level had remained stable, in the 2.0–2.4 mg/dl range. When lithium therapy was discontinued in 1989, she began to cycle. Her recurrent major depressive episodes became quite severe. Over the next 6 years, she maintained a carbamazepine level of 8.6 μg/ml, with the addition of bupropion, nortriptyline, sertraline, and fluoxetine, but she experienced no improvement in her depressive symptoms. She continued to have mild depression and agoraphobia-like anxiety. She had routine CBC counts and thyroid and renal function laboratory monitoring. Because of her increasing problems with depression, ECT was considered. Ms. A had two brief courses of ECT in the 1950s with excellent results, but she has negative memories of those treatments.

Ms. A received a course of 12 ECT treatments in 1996, followed by maintenance treatments every 4–6 weeks, which she dreaded. She tolerated the treatments well and had no mania, but she never returned to the mood state she had achieved with lithium therapy. Ms. A and her husband sought alternative therapies; lamotrigine was discussed as a possible alternative therapy (2, 3).

Ms. A's local psychiatrist initiated treatment with lamotrigine, 12.5 mg every other day for 1 week, followed by 12.5 mg/day for 1 week, 25 mg/day for 1 week, then up to 50 mg/day, and ultimately to 100 mg/day. Ms. A returned to a euthymic state, with functioning superior to that experienced while she was receiving ECT and rivaling that experienced while she was taking lithium. Ms. A has maintained a high level of functioning and has actively participated in her community for 34 months.

This case report suggests that lamotrigine may be well tolerated and effective in the treatment of bipolar disorder in the geriatric population.

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Gabapentin Therapy for Cocaine Cravings

TO THE EDITOR: A difficult aspect of treatment for cocaine addiction is the recurrent nature of cravings, even long after active use has ceased. Cravings can be controlled in the early stages of withdrawal, but pharmacological agents that can abate cocaine cravings beyond the withdrawal phase are still wanting. I report on two patients with a long history of cocaine addiction in whom cravings were greatly reduced by daily use of gabapentin.

Mr. A was a 42-year-old man with a history of cocaine addiction since the age of 17 and heroin addiction since age 28. After repeated attempts at detoxification and rehabilitation, he was able to forgo the use of cocaine, then heroin, and later methadone. During his 15 years of substance abuse treatment, he had received imipramine for depression at doses of 75–300 mg/day. During the year after his last use of methadone, Mr. A became increasingly engaged in restoring his relationship with his children and in computer training through a vocational program. The many difficulties and setbacks he faced often discouraged him; it was at these times that his cravings for cocaine returned. After a discussion about the experimental nature of gabapentin treatment, he agreed to a trial of gabapentin while continuing treatment with imipramine, 200 mg/day. His dose of gabapentin was increased to 400 mg b.i.d. over 1 week. His blood level of gabapentin at that dose was 12.4 mg/liter (>2 mg/liter is needed for seizure control). He reported that his cravings had completely disappeared within a month of reaching a dose of 800 mg/day.

Ms. B was a 31-year-old woman with a diagnosis of schizoaffective disorder and cocaine abuse. Her psychotic symptoms were well controlled with a bimonthly injection of 50 mg of fluphenazine decanoate. She required supplements of oral fluphenazine, up to 20 mg/day, to control auditory hallucinations immediately after she used crack cocaine, which she typically consumed night and day during binges lasting up to 10 days. Afterward she could be abstinent for several months. Her relapses usually coincided with returning to live with her mother in a crack-infested neighborhood, which would prompt strong cravings and vivid dreams about smoking crack. She began a course of oral gabapentin therapy, reaching a dose of 1200 mg b.i.d. At that dose, her blood level of the drug was 15.6 mg/liter. She reported a marked reduction in cravings, at times being able to live in the crack-infested neighborhood without relapsing. In the 9 months since she began gabapentin treatment, she has experienced one relapse, which consisted of smoking two crack cigarettes.

Frustration with the difficulty of treating cocaine cravings led me to an extensive review of the neuroanatomy of the ventral tegmental area, including the nucleus accumbens, which is thought to drive many aspects of addictive behaviors (1). Within the nucleus accumbens, a large number of γ-aminobutyric acid (GABA) neurons and axon fibers have been noted (2). Repeated cocaine use inhibits GABA release from nucleus accumbens axon terminals in the ventral tegmental area, where the mesolimbic dopaminergic neurons are located (3). This effect attenuates the GABA-mediated feedback inhibitory action of nucleus accumbens neurons onto ascending mesolimbic dopaminergic neurons, leading to increased activation of dopamine neurons projecting to the nucleus accumbens. Gabapentin increases brain GABA levels proportionally with dose, typically in the 800–2400-mg range (4). It was thus hypothesized that gabapentin restores the altered feedback inhibition from the nucleus accumbens. These neurobiological data, the excellent pharmacological profile of gabapentin, and a report about an addicted woman who noticed a decrease in her cravings for cocaine after she began taking 600–1500 mg/day of her husband's gabapentin (5) prompted the trials described previously. Neither patient experienced significant side effects, such as sedation or ataxia, which are common with gabapentin therapy.

Should these findings be corroborated by further clinical observations and studies, gabapentin could become a safe, effective, and well-tolerated pharmacological agent to target this most vexing problem of recurrent cravings for cocaine.

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The Neuropsychiatric Symptoms of AIDS

TO THE EDITOR: As the director of a medical psychiatry unit, I have faced a common clinical problem in patients who have been diagnosed with AIDS that is complicated by neuropsychiatric symptoms. Patients with AIDS have been shown to benefit from the use of antiviral agents. Unfortunately, if they have variable compliance, they may develop resistant strains of the HIV virus, which complicate their treatment and have the potential to be introduced into the population. Therefore, it is common practice to discontinue treatment with antiviral agents for patients who are noncompliant (1–4).

Patients with AIDS suffer from a wide array of neuropsychiatric symptoms that can include depression, psychosis, anxiety, and cognitive impairment. Over the course of the illness, these develop in a majority of patients to varying degrees. They can contribute to noncompliance unless they are diagnosed and treated aggressively. I have treated a significant number of patients who trace their noncompliance to psychiatric symptoms as opposed to the typical side effects of antiviral agents.

Our institution's infectious disease service is often hesitant to initiate antiviral therapy in patients with current or past psychiatric symptoms for fear of noncompliance. This is clearly a circular argument, because if the disease is allowed to progress, patients are more likely to have cognitive impairment or psychiatric symptoms that will impair their compliance. We are often aware that psychiatric patients are given less than optimal care because of stereotypes and the discomfort they elicit in health care providers. Our institution has tried to educate our medical colleagues about this conundrum; yet, this has yielded no significant changes in standard practice (5–7).

We are making clear advances in treating psychiatric syndromes in patients with chronic medical and neurological illnesses. The situation is similar to the one I experienced over the last 15 years in regard to basal ganglia disease, stroke, dementia, and demyelinating illness. We did not recognize or treat the psychiatric comorbidity in these conditions. Cur-

rently, there is a wide appreciation for depression, psychosis, and anxiety in these conditions, and they are aggressively treated. It is incumbent on individual psychiatrists and the psychiatric community to educate our colleagues in this area. It is a sad commentary that patients who already have so much going against them may be deprived of life-prolonging treatment because of a lack of awareness of the psychiatric complications of their illness. It is hoped that in 10 years or less we will be able to see the same appreciation of the psychiatric comorbidity of AIDS. With this may come the effective treatment of psychiatric comorbidity and improved compliance with antiviral therapy, with prolonged life expectancy.

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Anorexia Nervosa and Body Mass Index

TO THE EDITOR: We noted with interest the findings of William T. Howard, M.D., M.S., et al. (1) and the discussion by Katherine A. Halmi, M.D. (2). They reported that inpatients who had not attained a body mass index of 19 in the hospital did less well in a day program setting. In our longitudinal study (3), we found that 50 such patients were still doing less well 6–10 years later (mean=8 years). There was a significant difference in total bone mineral density ($p<0.05$) between former inpatients with a body mass index of ≥19 after refeeding (osteoporosis in the femoral head=7%, osteoporosis in the lumbar spine=0%) and those who had a body mass index of <19 after refeeding (24% and 12%, respectively). Scores on the Eating Attitudes Test and the Drive for Thinness subscale of the Eating Disorders Inventory were significantly higher when body mass index was <19, and severe depression was reported only in this group. Outcome on the Morgan Russell criteria was more often in the poor category (22% versus 11%), and reproductive function was more compromised. Thus, failure to reach treatment goals early had long-lasting effects. When one considers the public health costs of osteoporosis and the private health costs (and the dangers) of assisted fertility—not to mention the costs of depression, chronic ill health, ongoing eating disorders, and the effect on the next generation—it can only be hoped that health funding bodies can recognize the false economy of shortening the period of nutritional rehabilitation in anorexia nervosa.

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Dr. Halmi Replies

TO THE EDITOR: It is of special interest that the inpatients in the study by Dr. Russell et al. who had not reached a body mass index of 19 (the lower end of the normal weight range) at the time of discharge were doing less well 6–10 years later than those who had reached or exceeded a body mass index of 19. There are now two databases from two continents supporting the fact that patients with anorexia nervosa will have a significantly better outcome if they can stay in a structured setting until they reach a normal weight range. In the inpatient unit for specialized eating disorders at Cornell Medical Center's Westchester Division, the characteristics of patients with anorexia nervosa who were hospitalized were examined during the years 1984 through 1998. During the 1980s the mean body mass index at discharge was 19.5; by 1998 it had fallen to 17.7. During this time, readmissions of patients with anorexia nervosa increased from 0% in the 1980s to 40% of those hospitalized on this specialized unit. The length of stay decreased significantly, from 149.5 days (1984) to 127.3 days (1989) to 57.4 days (1994) to 23.7 days (1998). These data indicate further that if patients are discharged at a body mass index below a normal range, they are more likely to relapse.

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Impairment in Generalized Anxiety Disorder

TO THE EDITOR: Ronald C. Kessler, Ph.D., and colleagues recently reported that among community respondents, generalized anxiety disorder (per the Composite International Diagnostic Interview and DSM-III-R) has a statistically significant independent association with impairment (1). On the strength of this finding, the authors called into question an earlier primary care study in which my colleagues and I used the Structured Clinical Interview for DSM-III-R (SCID); that study indicated that generalized anxiety disorder has only a

modest and statistically nonsignificant independent association with impairment (2).

The credibility of the findings reported by Dr. Kessler and co-workers turns on the validity of the Composite International Diagnostic Interview diagnosis of generalized anxiety disorder. In their Method section, they state, "A National Comorbidity Survey clinical reappraisal study found good test-retest reliability and procedural validity of all of the diagnoses compared to clinical reassessments." However, that study found that among sampled respondents to the National Comorbidity Survey, the Composite International Diagnostic Interview diagnosis of generalized anxiety disorder had a kappa of 0.35 with the SCID as the criterion standard (3). In general, kappa values below 0.40 suggest poor agreement beyond chance (4). Moreover, the positive predictive value of a Composite International Diagnostic Interview diagnosis of generalized anxiety disorder was 0.21 (3), meaning that nearly four out of five diagnoses of generalized anxiety disorder were not confirmed with the SCID.

A broader point that is easily overlooked in evaluating findings from large epidemiologic studies is the difference between statistical and clinical significance. Although the differences reported by Dr. Kessler and colleagues are statistically significant, their clinical significance is less clear. More than three-quarters (78.2%) of the group with generalized anxiety disorder reported that they had no days in the last month in which they had to cut back or did not get as much done as usual because of their mental health, and nearly as many (70.7%) reported that their mental health was good to excellent.

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Dr. Kessler and Colleagues Reply

TO THE EDITOR: Dr. Olfson cites the global kappa value from our overview article on the validity of the National Comorbidity Survey diagnoses (Kessler et al., 1998). He apparently did not read our more detailed report on the validity of the National Comorbidity Survey assessment of generalized anxiety disorder (1), in which we showed that the low concordance between a modified version (UM-CIDI) of the Composite International Diagnostic Interview and the SCID was due to a controversial component of DSM-III-R criterion A, that the worries must be excessive or unrealistic. This requirement was revised in DSM-IV. As reported in our 1995 article (1), kappa increases to 0.66 (with a positive predictive value of 0.63) when the excessive/unrealistic requirement is taken out of consideration. This kappa value is as high as the test-retest consistency of the SCID (2).

On the basis of this observation, I find it difficult to accept Dr. Olfson's conclusion that the failure of his small primary care study to replicate the National Comorbidity Survey's finding of significant impairment in pure generalized anxiety disorder was due to the imprecision of the National Comorbidity Survey's generalized anxiety disorder assessment. A more plausible explanation, in my view, is the one proposed in our article, but not mentioned in Dr. Olfson's letter: that Dr. Olfson's small study contained only four respondents with pure generalized anxiety disorder, making it impossible to assess the impairment of pure generalized anxiety disorder with any precision. Consistent with this interpretation, a much larger primary care study cited in our article, but not mentioned in Dr. Olfson's letter (3), yielded results consistent with those of the National Comorbidity Survey and inconsistent with Dr. Olfson's data.

Dr. Olfson also commented on the difference between statistical and substantive significance. He is, of course, correct in noting that this is an important difference. However, he is incorrect in saying that the clinical significance of our finding regarding the impairment of pure generalized anxiety disorder is unclear. The fact that 78.2% of community respondents with generalized anxiety disorder reported no work impairment means that 21.8% *did* report work impairment. This percentage is not meaningfully different from the 24.7% rate of work impairment found among respondents with pure major depression. Both these percentages were dramatically higher than the 5.3% rate of work impairment found among respondents with neither generalized anxiety disorder nor major depression. These effects on work impairment are much larger than those found for the vast majority of other chronic conditions (4) and account for literally millions of dollars in lost productivity in the United States each year.

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Hallucinations in Alzheimer's Disease and Charles Bonnet Syndrome

TO THE EDITOR: I read with interest the article by Fiona M. Chapman, F.R.C.Ophth., et al. (1) in which an association between visual hallucinations and impaired visual acuity was demonstrated in patients with probable Alzheimer's disease. It seems reasonable and useful for them to have concluded that glasses and cataract surgery need evaluation as prophylactic or adjunctive treatments for visual hallucinations in patients with probable Alzheimer's disease.

The association between visual hallucinations and impaired visual acuity in psychologically normal people is known as Charles Bonnet syndrome. For example, Teunisse et al. (2) found that 60 of 505 (12%) of visually handicapped patients suffered from Charles Bonnet syndrome. This suggests that visual hallucinations may occur in visually handicapped patients even if they do not suffer from Alzheimer's disease. Thus, there is a possibility that Dr. Chapman and colleagues' patients with visual hallucinations included those suffering from visual hallucinations due not to Alzheimer's disease but to impaired visual acuity. This possibility is supported by the fact that only impaired visual acuity was entered into the equation when logistic regression analysis examined cognition, visual acuity, and gender as associates of visual hallucinations. As the authors pointed out, however, it is necessary to do controlled trials to compare the prevalence of visual hallucinations in psychologically normal people with visual impairment and Alzheimer's patients with visual impairment under age- and gender-matched conditions.

If that possibility is the case, pharmacotherapy for Charles Bonnet syndrome can be applied to some patients with probable Alzheimer's disease when glasses and cataract surgery turn out to be useless, because some patients with Charles Bonnet syndrome do not respond to glasses and cataract surgery and need pharmacotherapy. At present there are several candidate treatments for Charles Bonnet syndrome, such as carbamazepine (3, 4), carbamazepine plus clonazepam (5), and valproate (unpublished data). These drugs are anticonvulsants, but they may be effective for the treatment of Charles Bonnet syndrome. These may be more effective and be associated with fewer side effects than neuroleptics for visual hallucinations in Alzheimer's disease patients. Since these treatments are not established, it is necessary to perform randomized placebo- or neuroleptic-controlled, double-blind studies to investigate the side effects of these drugs and their effects on visual hallucinations in Alzheimer's disease as well as in Charles Bonnet syndrome.

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Drs. Ballard and McKeith Reply

TO THE EDITOR: We thank Dr. Terao for his interest in our work. We certainly agree that our data indicated that impaired visual acuity may be attributable to visual hallucinations in elderly people with dementia, although further studies are needed to test this hypothesis. There is, however, also evidence that impairments at other levels of visual processing, including visual attention (1) and the visual association cortex (2), may be important. Certainly, a controlled trial of cataract treatment or impaired visual acuity would make an important contribution to this field.

We agree that there are clear parallels between the association of visual hallucinations and visual impairment in both Alzheimer's disease and Charles Bonnet syndrome. It has not, however, been established that Charles Bonnet syndrome is a discrete disease entity, and we would have considerable reservations about using extrapolated anecdotal treatment information as the basis for a pharmacological intervention strategy for visual hallucinations in Alzheimer's disease. There are, for example, no placebo-controlled treatment studies with antipsychotic agents or cholinesterase inhibitors specifically examining their efficacy in patients with Alzheimer's disease with visual hallucinations. Trials of this kind would seem to be a more urgent priority for pharmacological clinical intervention than more speculative approaches.

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