Schizophrenia and Binge-Eating Disorders

Sir: There are many reasons why people with schizophrenia may have problems with food and weight. However, few empirical studies have examined the potential comorbidity between eating disorders and schizophrenia. Recent advances in the pharmacotherapy of schizophrenia have altered the side effect profiles of patients taking the newer generation of atypical antipsychotic drugs compared with older, conventional drugs. The older concerns with motor side effects have been replaced by problems even more relevant than before with overeating, obesity, and type 2 diabetes mellitus and its associated complications. Considering that overeating and obesity can be the features of eating disorders, knowledge of an association between schizophrenia and these disorders can lead to earlier identification of the comorbid conditions and prevention of other likely complications.

Method. We evaluated a sample of 31 outpatients (25 men with a mean ± SD age of 34.8 ± 9.2 years and 6 women with a mean ± SD age of 41.1 ± 10.1 years) after obtaining informed consent and institutional review board approval. All were diagnosed as having schizophrenia by experienced clinicians using the Structured Clinical Interview for DSM-IV. Each of these subjects was administered the semistructured Binge Eating Clinical Interview (BEDCI) to determine the presence or absence of binge-eating disorder. The diagnosis of bulimia nervosa was made by clinicians experienced in treating these conditions, again using the BEDCI. While we have suggested that the differentiation between binge-eating disorder and bulimia nervosa, nonpurging type (BN-NP), may be artificial, for the purposes of this communication, we have relied on the existing classification system (DSM-IV). Additional assessment was performed with the Eating Disorders Inventory (EDI). Data were gathered from September through December 2001.

Results. Most patients (71%; N = 22) were overweight as defined by a body mass index (BMI) of > 25. Sixty-two percent (N = 19) were obese as defined by a BMI of > 27. Five of the obese subjects (all males), representing 16% of the sample, were diagnosed with binge-eating disorder or BN-NP. Three of these patients developed binge eating after the onset of treatment with atypical antipsychotics. Specific items on the BEDCI and the EDI reflected the subjects’ attitudes toward eating and weight. All 5 patients with binge-eating disorder/BN-NP and 5 other patients (32% of the entire sample) had scores indicating that weight and shape affected their self-esteem. The patients with binge-eating disorder displayed low drive for thinness and body dissatisfaction scores on the EDI, reflecting either an attitude of giving up on dieting and concerns with the body or never having been concerned with these issues; this attitude is not unusual for males.

The present study suggests an association between schizophrenia and bulimia nervosa or binge-eating disorder, but not anorexia nervosa. However, this study is limited by the small patient group size, and the specificity of the patient environment limits the ability to generalize these results to other settings.

Brewerton and Shannon reported on the potential exacerbation of bulimia nervosa when patients were given clozapine, and clozapine therapy has been found to generate binge-eating episodes in some patients. The potential association between schizophrenia and bulimia nervosa or binge-eating disorder has not been widely investigated, a result, perhaps, of the complicated relationship that has been described for these disorders. From the few published case studies that are available on women with schizophrenia and reported bulimic disturbances, a reciprocal relationship appears to exist between these syndromes. Specifically, binge and purge cycles have been found to emerge during periods of decreased psychotic symptoms, and, as the negative symptoms of schizophrenia have progressed, the drive to restrict or binge and purge has diminished as goal-directed behavior has become deficient. In accordance with this evidence, Hugo and Lacey hypothesized that bulimia nervosa may in fact protect against a psychotic state and help to alleviate a psychotic process.

The majority of evidence focused on understanding the comorbidity between schizophrenia and bulimia nervosa and binge-eating disorder points to the use of antipsychotic medication as the main reason for this association. In our sample, 60% of the binge-eating disorder/bulimia nervosa group developed their eating symptoms after use of the new generation of neuroleptic drugs. The newer, atypical antipsychotics olanzapine and clozapine have been implicated in causing significant weight gain in 40% to 80% of patients who use these medications, and treatment with the medications can result in weight gain of 20% or more beyond ideal body weight. This phenomenon seems to be due to an increase in body fat, caused by enhanced caloric intake without a subsequent increase in physical activity. Theories concerning possible involvement with serotoninergic, dopaminergic, and histaminic receptors have been suggested.

Other hypotheses for the link between eating disorders and schizophrenia target the lifestyle of schizophrenic patients. For example, level of physical activity has been deemed low in this group. One study found that patients spent less than 10 continuous minutes in moderate activity during the day despite encouragement from staff, which is much less activity than that reported for healthy individuals. In addition, there is a high level of unemployment in this population, leading to little exercise from work-related activities. It may also be helpful to view the onset of eating disorders in schizophrenic patients within the context of lack of achievement in other life areas (e.g., academic or social). Dymek and le Grange described the development of an eating disorder as a response to a feeling of success in weight loss. In addition, Ferguson and Damluji suggested that an eating disorder appears in many ways to provide some semblance of value and organize the life of schizophrenic patients.

Probably the most important issue highlighted by this work is the need to develop weight control programs for patients with
schizophrenia. These should include lifestyle intervention programs that focus on diet, emphasize physical activity, and teach problem-solving skills specified for patients with schizophrenia. Current evidence suggests that short-term weight loss is achievable in this population, but other strategies must be generated to target long-term weight loss or the prevention of weight gain.

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The Effects of Newer Antidepressants on Low-Density Lipoprotein Cholesterol Levels

Sir: Nicholas et al.1 must be commended for investigating a topic of major clinical importance, i.e., the effects of the newer antidepressants, such as mirtazapine, on serum levels of low-density lipoprotein cholesterol (LDL-C). Indeed, LDL-C levels are considered as an important predictor of cardiovascular events.2 The authors showed a statistically nonsignificant increase of 3% in LDL-C in healthy controls after 4 weeks of mirtazapine treatment compared with placebo treatment and concluded that mirtazapine did not increase LDL-C levels. We believe that there may be methodological explanations for their neutral findings.

Lara et al.1 have shown that 20 mg q.d. of paroxetine significantly increased LDL-C by 9 mg/dL (11.5%) after an 8-week treatment period in 18 male healthy controls, with LDL-C levels returning to baseline after discontinuation of paroxetine. Another study4 showed that 12 and 28 weeks of treatment with venlafaxine in patients with generalized social phobia induced dose-related mean increases of LDL-C of 7.7 and 10.4 mg/dL, respectively, suggesting a dose- and duration-dependent increase in LDL-C. In a less-controlled and naturalistic, but long-term study5 in which most patients were treated with sertraline, we found a mean increase of 39.9 mg/dL in LDL-C concentrations. Together, these data suggest that the 4-week study by Nicholas and colleagues was too short to assess whether mirtazapine induces an increase in LDL-C levels.

Nicholas et al.3 included 10 men and 18 women in the mirtazapine group. In a recent study from our group that included 42 men and women, paroxetine-induced increase in LDL-C was limited to men and did not take place in women (M.C.A.; J.-M.L.; N. Lara, M.D.; et al.; unpublished data, October 2003). A dilution effect due to the absence of an impact of mirtazapine on LDL-C in women (18 of 28 subjects in the mirtazapine group) may therefore have also contributed to the neutral findings. In this regard, a separate analysis by gender would be informative. A study with a longer duration of treatment and a greater male representation might be necessary to fully assess the effect of mirtazapine on lipids.

The mechanism of the effects of paroxetine, venlafaxine, sertraline, and possibly mirtazapine on LDL-C level remains to be determined, but these agents all cause an increase in firing of serotonergic neurons. The increase in LDL-C appears to be independent of the antidepressant/anxiolytic activity of these compounds since such an effect was also observed in healthy controls.

We do not believe that the increase in LDL-C observed after acute treatment with several antidepressants is a major concern for most medically healthy psychiatric patients, although monitoring of lipid levels during long-term administration of those antidepressants would appear prudent. The antidepressant-induced increase in LDL-C is a greater concern in the numerous patients with major depressive disorder who suffer from comorbid coronary heart disease, for whom even a small increase in LDL-C carries a significant cardiovascular risk. However, antidepressants with a positive impact on endothelium function and platelet activity are likely to induce beneficial cardiovascular effects that could offset the deleterious effect of the LDL-C increase.

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Letters to the Editor

Dr. Le Mellédo has performed clinical trials as a site investigator for GlaxoSmithKline, Lundbeck, Roche, Merck, Janssen, Eli Lilly, Wyeth, Pfizer, and Aventis and has served as a speaker for Wyeth, Lundbeck, and Pfizer. Dr. Tsuyuki has received grant/research support from Merck Frosst and Pfizer and has served on the speakers/advisory board for Merck Frosst.

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Dr. Nicholas and Colleagues Reply

We appreciate Le Mellédo and colleagues’ interest in our work. Their point is well taken: our 4-week study may not have detected changes in levels of low-density lipoprotein cholesterol (LDL-C) and other lipids that could have reached statistical significance only after 8 or more weeks of mirtazapine exposure. However, we deliberately chose to study healthy control subjects in order to avoid potential confounding effects of a psychiatric disease state per se in our investigation of the effects of mirtazapine. For practical and ethical considerations, we limited the exposure of these healthy subjects to 1 month. We believe that while it is possible that longer-term exposure might uncover a statistically significant effect, it is unlikely that the effect would be clinically meaningful, except possibly in patients who already have problematic elevations in LDL-C levels. It should be noted that there was a trend toward increases in high-density lipoprotein cholesterol levels following mirtazapine exposure as well, and this favorable effect may balance any negative consequences of elevated LDL-C.

We controlled for sex in our analyses, and the effect of the sex factor did not approach significance. However, since our groups were not balanced, it is still possible that there were confounding factors and that the absence of an LDL-C increase in our 18 women diluted the overall effect of a noteworthy LDL-C increase in our 10 men.

To further clarify the sex effect on LDL-C, we reanalyzed the study data by sex. Within the mirtazapine treatment group at week 4, the men showed a small mean LDL-C increase from baseline of 1.2 mg/dL, which was an increase of 0.8%, while the women showed a larger increase of 5.3 mg/dL, which was an increase of 6.2%. Since about the same proportion of men (6/10) and women (10/18) showed some increase, it is clear that the difference was due to larger increases among the women.

Closer inspection of the data reveals that only 6 of 18 women accounted for most of this effect. Among the 8 of 28 subjects with the largest increases in LDL-C (increase of more than 10%); 6 were women (only 2 were men); 4 of these women (no men) had increases of more than 25%, and 3 had increases in LDL-C of 30% from baseline. These results were not statistically misleading “outliers,” since individual subjects’ levels were generally quite variable, demonstrating moderate decreases, as well as some large increases, within both sexes; this large individual variability (pooled SD = 14%) works against finding statistical significance and may suggest the influence of some other unknown factor (e.g., diet, exercise).

We conclude that there could possibly be a noteworthy sex effect even though it was not significant in our sample. However, in contrast to the findings of Le Mellédo et al., our results show the most robust LDL-C increases in women rather than men. We thank Le Mellédo and colleagues for bringing these interesting and clinically important issues to our attention.

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Duloxetine’s Role in the Treatment of Depression and Associated Painful Physical Symptoms

Sir: The recent letter by Leo¹ raises a number of questions concerning the role of antidepressants in the treatment of painful physical symptoms associated with depression and pain in nondepressed patients. The author focuses on published data for the antidepressant duloxetine and attempts to determine whether there is a role for duloxetine in chronic pain management. We wish to reply to points raised in the letter and add data that were not in the public domain at the time of the letter’s submission.

These new results support the following conclusions: (1) duloxetine is an effective antidepressant that successfully treats painful physical symptoms in depressed patients; (2) alleviation of painful physical symptoms in depressed patients significantly increases their probability of achieving remission; (3) approximately 50% of duloxetine’s effect on pain in depressed patients occurs independently of changes in core emotional depression symptoms; and (4) duloxetine effectively treats pain associated with diabetic neuropathy in nondepressed patients.

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First and foremost, duloxetine is an effective antidepressant. While some studies have investigated the efficacy of duloxetine in pain states, the primary focus of our clinical development program has been the treatment of major depressive disorder (MDD). Results from double-blind, placebo-controlled studies 8–5 and a long-term, open-label study 6 have established duloxetine as a safe and effective treatment for MDD.

Duloxetine is a balanced and potent reuptake inhibitor of both serotonin and norepinephrine. In addition to their role in the neurobiology of depression, these neurotransmitters act as pain modulators in the descending inhibitory pain pathways of the spinal cord. 7 In placebo-controlled studies, 8,9 duloxetine has demonstrated efficacy in the treatment of painful physical symptoms in depressed patients, as assessed using visual analog scales for pain.

Dr. Leo relates that reductions in pain severity ratings are often regarded as artifacts of improvements in mood observed when depressed patients are effectively treated. In contrast, results obtained during duloxetine clinical trials 8,9 support its direct effect on pain in both depressed and nondepressed patients and demonstrate the importance of effective treatment of painful physical symptoms associated with depression.

Statistical analyses, e.g., path analysis, can help demonstrate the independence of the effects of antidepressants on mood versus pain. We performed a path analysis on pooled data from 2 MDD clinical trials of duloxetine (60 mg q.d.) and demonstrated that approximately 50% of the decrease in pain severity in depressed patients is directly attributable to duloxetine treatment and occurs independently of improvement in depressive symptoms.8

If painful physical symptoms truly represent an important component of MDD, it may be expected that the alleviation of these symptoms should contribute to a patient’s recovery from depressive illness and thereby influence the probability that a patient will achieve remission. 10 To further investigate this concept, we analyzed pooled data from 2 clinical studies of duloxetine (60 mg q.d.) and demonstrated that approximately 50% of the decrease in pain severity in depressed patients is directly attributable to duloxetine treatment and occurs independently of improvement in depressive symptoms. 8

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Dr. Leo also states, “Given the experimental paradigms employed to date, it would be erroneous to assume that duloxetine has a direct pain-relieving effect.” 11 To address this, we propose the need for “compelling data . . . from studies demonstrating efficacy in pain patients with clear, identifiable disorders who are not depressed.” 11 To further investigate this concept, we analyzed pooled data from 2 clinical studies of duloxetine (60 mg q.d.) and demonstrated that improvement in pain severity was associated with an increased probability of achieving remission even after accounting for improvement in core emotional symptoms of depression. 11 These data are clearly inconsistent with Dr. Leo’s statement that “as depression is alleviated, so too is the amplification of somatic symptoms reduced.” 11

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Metyrapone for Delirium Due to Cushing’s Syndrome Induced by Occult Ectopic Adrenocorticotropic Hormone Secretion

Sir: Cushing’s syndrome secondary to ectopic adrenocorticotropic hormone (ACTH) syndrome is rare. Ectopic ACTH-dependent Cushing’s syndrome is encountered in 2 forms, the classic overt ectopic ACTH syndrome and “occult” ectopic ACTH-secreting tumors. 1 Occult ectopic ACTH-secreting tumors are often small, and their detection requires meticulous examination. Despite recent technological advances, including inferior petrosal sinus sampling and the corticotropin-releasing hormone (CRH) stimulation test, localization of the tumor remains difficult. 2,3 We report a case of psychiatric manifestations that were caused by Cushing’s syndrome induced by occult ectopic ACTH secretion and that have been controlled by metyrapone, an 11β-hydroxylase inhibitor.

Case report. Ms. A, a 53-year-old woman, was admitted to the hospital for evaluation of general fatigue and headache. She also presented with hirsutism and a recent weight gain of 7 kg (16 lb), and 3 months before her admission in April 2001, she had developed truncal obesity, “moon face,” and general fatigue. Biochemical testing showed hypokalemia and hypercorti-
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Beneficial Effects of Gonadotropin-Releasing Hormone Analogue Treatment on Positive and Negative Symptoms of Schizophrenia: A Case Report

Sir: This letter reports a patient with chronic treatment-resistant schizophrenia and deviant sexual behavior who showed clinical improvement after treatment with the depot gonadotropin-releasing hormone (GnRH) analogue buserelin acetate. The patient’s clinical improvement included decrease in positive (hallucinations, disorganization) as well as negative (social withdrawal, academic interest) symptoms. The possible therapeutic and theoretical implications of the putative role of hormones in schizophrenia are briefly discussed.

Case report. Mr. A, a 24-year-old married Orthodox Jew from a low socioeconomic status, presented in June 1999 with a history suggestive of a diagnosis of DSM-IV schizophrenia. At 20 years of age, Mr. A experienced his first psychotic episode, which lasted for more than a year. During this period, he had...
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