Elevated Plasma Ghrelin Levels in Night-Eating Syndrome

TO THE EDITOR: Night-eating syndrome is characterized by repetitive awakening because of hunger and excessive eating. In humans, food intake appears to be regulated reciprocally by the anorexigenic leptin and the orexigenic ghrelin. The physiological nocturnal leptin surge is blunted in night-eating syndrome . Ghrelin levels are changed in eating disorders, with elevation in anorexia and Prader-Willi syndrome and blunting in obesity (2). In night-eating syndrome, ghrelin levels are unknown so far. We report the course of ghrelin plasma levels during the treatment of night-eating syndrome.

Ms. A, a 27-year-old woman, reported that the first symptoms of night-eating syndrome appeared 1 year before she underwent our psychiatric examination. As in previous reports, administration of a selective serotonin reuptake inhibitor (citalopram, 100 mg/day) was started (3). A complete remission was obtained within 8 weeks. Medication was continued for another 8 weeks before withdrawal. About 8 weeks later, Ms. A described a relapse of night-eating syndrome.

Her plasma ghrelin concentrations were measured by radioimmunoassay (Phoenix Pharmaceuticals, Belmont, Calif.) at three times (before treatment, 8 weeks later [during drug treatment and full remission], and finally, after relapse). Specimens were collected on all three occasions: every 20 minutes between 10 p.m. and 7:00 a.m. by a long catheter.

Mean nocturnal ghrelin concentrations (10 p.m. to 7 a.m.) were 1051 pg/ml before treatment, 977 pg/ml 8 weeks later (during drug treatment and full remission), and 1013 pg/ml after relapse. The body mass index (kg/m^2) of Ms. A was about 23.5 at all examinations.

As control subjects we investigated three healthy women, 22, 23, and 32 years old, with body mass indexes of 21.9, 22.4, and 20.8 kg/m^2. Their mean ghrelin concentrations were 372, 402, and 338 pg/ml, respectively.

This preliminary observation suggests that nocturnal ghrelin levels are enhanced in night-eating syndrome. Despite the known sleep-promoting capacity of ghrelin, its elevated levels might disrupt sleep because of hunger at night. Similarly, a higher dose of exogenous ghrelin caused nocturnal eating in a normal subject, whereas a lower dose promoted sleep (4). It appears that elevated ghrelin concentration is not state-dependent and may reflect a marker of vulnerability for developing night-eating syndrome.

For this study, written informed consent and human subjects research committee approval were obtained.

References

1. Birketvedt GS, Florholmen J, Sundsfjord J, Osterud B, Dinges D, Warren B, Stunkard AJ: Behavioral and neuroendocrine characteristics of the night-eating syndrome. JAMA 1999; 282:657–663
2. Van Der Lely AJ, Tschöp M, Heiman ML, Ghigo E: Biological, physiological, and pharmacological aspects of ghrelin. Endocr Rev 2004; 25:426–457
3. O'Reardon JP, Stunkard AJ, Allison KC: Clinical trial of sertraline in the treatment of night eating syndrome. Int J Eat Disord 2003; 35:16–26
4. Weikel JC, Wichniak A, Ising M, Brunner H, Friess E, Held K, Mathias S, Schmid DA, Uhr M, Steiger A: Ghrelin promotes slow-wave sleep in humans. Am J Physiol Endocrinol Metab 2003; 284:E407–E415

MARCUS C. ROSENHAGEN, M.D.
MANFRED UHR, M.D.
PETRA SCHÜSSLER, M.D.
AXEL STEIGER, M.D.
Munich, Germany

Mania in a Boy Treated With Modafinil for Narcolepsy

TO THE EDITOR: Modafinil is the first-line treatment for narcolepsy. It may also improve mood in narcoleptic patients (1). However, psychostimulants may exacerbate psychotic symptoms in psychotic patients (2). Cases of psychosis have also been reported during psychostimulant abuse (3) and during abuse of prescribed drug in narcoleptic patients (4) but not following medical use. Here we report the case of a boy with narcolepsy.

Albert was a 17-year-old boy who was diagnosed with narcolepsy at age 14. He was first prescribed modafinil, 400 mg/day for 1 year, switched to methylphenidate, 40 mg/day for 2 years, then returned to modafinil, 400 mg/day. The switching was because of complaints of irritability and of a lack of efficacy for sleep attacks. Albert then experienced flight of ideas, sexual excitation, and increased irritability. These manic symptoms resulted in friction with family members and a fight for which he could have been put on trial. Then, free of psychostimulant treatment, Albert was described as sad, anhedonic, and withdrawn. Following reintroduction of modafinil, the same manic symptoms reoccurred. After a meeting with a judge, Albert experienced self-referential thinking and suspiciousness. Later, a full manic episode developed within 3 days, including insomnia, tachypsychia, logorrhea, psychomotor agitation, and mood-incongruent psychosis. There was no grandiosity but delusion of persecution, based on auditory hallucinations (his uncle reproaching him for his past sexual behavior), complex visual hallucinations (a vampire hiding in his bedroom and trying to bite him), and a feeling of being talked to through the television. Albert was hospitalized, and the modafinil was stopped. The mania required pharmacological treatment that started after written consent was obtained from both Albert and his parents.

These mood symptoms seem time-related to psychostimulant administration and interruption. Exposure lasted for only 3 years, but discontinuation and reintroduction might have lowered the manic threshold. Contrary to previous reports of psychosis induced by psychostimulant abuse (3), the patient showed no trend toward dose escalation. This could be the first report of mania under a therapeutic dose of modafinil. The symptoms were compatible with psychostimulant-induced psychosis. Although an independent psychiatric disorder cannot be ruled out, we suggest a careful psychiatric monitoring of patients receiving modafinil and other psychostimulants for the treatment of narcolepsy.

References

1. Becker PM, Schwartz JR, Feldman NT, Hughes RJ: Effect of modafinil on fatigue, mood, and health-related quality of life in patients with narcolepsy. Psychopharmacology (Berl) 2004; 171:133–139

2. Narendran R, Young CM, Valenti AM, Nickolova MK, Pristach CA: Is psychosis exacerbated by modafinil? (letter). Arch Gen Psychiatry 2002; 59:292–293
3. Spensley J, Rockwell DA: Psychosis during methylphenidate abuse. N Engl J Med 1972; 286:880–881
4. Leong GB, Shaner AL, Silva JA: Narcolepsy, paranoid psychosis, and analeptic abuse. Psychiatr J Univ Ott 1989; 14:481–483

FLORENCE VORSPAN, M.D.
DOMINIQUE WAROT, M.D., PH.D.
ANGÈLE CONSOLI, M.D.
DAVID COHEN, M.D., PH.D.
PHILIPPE MAZET, M.D.
Paris, France

Clozapine-Induced Agranulocytosis After 11 Years of Treatment

TO THE EDITOR: Clozapine can cause life-threatening agranulocytosis in up to 0.8% of patients treated with this medication (1). This limits the use of clozapine and mandates regular hematological monitoring. The risk of blood dyscrasia is highest in the initial 6–18 weeks but has been reported after years of treatment (2). We present the case of a patient with schizophrenia who developed clozapine-induced agranulocytosis after 11 years of pharmacotherapy.

Mr. A, a 46-year-old Hispanic man, was diagnosed with chronic schizophrenia in the 1970s and had only partial response to various antipsychotic medications until clozapine was initiated 11 years ago. He improved significantly while taking clozapine, 675 mg/day. Recently, his psychosis worsened. At one of his routine biweekly hematological screenings, his WBC count was 1,300/mm^3, his neutrophil count was 12%, and his bands were 2% (bands are immature neutrophils that increase when infection is present; normal ranges: WBC count=4,800–10,800/mm^3, neutrophil count=42%–75%, and bands=0%–5%). That prompted a referral to the hospital. During the workup, a urinary tract infection was documented, despite an absence of clinical symptoms or signs of infection. In the previous 4 months, his WBC count had fluctuated between 2,800/mm^3 to 5,000/mm^3, with granulocyte counts in the normal range, and he had three periods documented when his WBC counts were below 4,000/mm^3 (normal WBC count range=4,000–12,000/mm^3). These leukopenias lasted 26, 22, and 5 days each and spontaneously resolved without changes in clozapine dosing.

Mr. A was hospitalized with neutropenic precautions, and clozapine was discontinued. Because of his mental status deterioration, aripiprazole, 15 mg/day, was started orally on day 4. Although his WBC count had risen to 1,600/mm^3, one 480-mg dose of recombinant granulocyte colony stimulating factor was administered on the same day. On day 6, upper gastrointestinal bleeding occurred. An endoscopy revealed gastric ulcers that were cauterized. On day 10, a urinary tract infection was treated with trimethoprim-sulfamethoxazole. Mr. A's WBC count gradually normalized to 5,300/mm^3 (neutrophil count of 45.7%) on day 14 and remained normal throughout his hospitalization. He became more organized after 3 weeks of aripiprazole, 40 mg/day, but he did not regain his previous level of functioning. The risk for bone marrow suppression precluded restarting clozapine.

Clozapine can cause life-threatening agranulocytosis, which mandates weekly monitoring of the CBC during the first 6 months of treatment and biweekly monitoring thereafter. Neutropenia has been documented after 2.5 years of pharmacotherapy (2), and agranulocytosis has been reported after 17 months of treatment (3). In our patient, bone marrow suppression developed after 11 years of otherwise uncomplicated successful treatment with clozapine. Early detection of agranulocytosis reduces mortality (4). Although it involved a single case, this report suggests the importance of continued monitoring of CBC in clozapine-treated patients, even after many years of uncomplicated use.

References

1. Alvir JMJ, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA: Clozapine-induced agranulocytosis. N Engl J Med 1993; 329: 162–167
2. Bourin M, Guitton B, Dailly E, Hery P, Jolliet P: A follow-up study of a population of schizophrenic patients treated with clozapine. Prog Neuropsychopharmacol Biol Psychiatry 2001; 25: 1481–1495
3. Bhanji NH, Margolese HC, Chouinard G, Turnier L: Late-onset agranulocytosis in a patient with schizophrenia after 17 months of clozapine treatment. J Clin Psychopharmacol 2003; 23:522–523
4. Atkin K, Kendall F, Gould D, Freeman H, Lieberman J, O'Sullivan D: The incidence of neutropenia and agranulocytosis in patients treated with clozapine in the UK and Ireland. Br J Psychiatry 1996; 169:483–488

KARIM SEDKY, M.D.
RITA SHAUGHNESSY, M.D., PH.D.
TIFFANY HUGHES, M.D.
Philadelphia, Pa.
STEVEN LIPPMANN, M.D.
Louisville, Ky.

Pramipexole, Ropinirole, and Mania in Parkinson's Disease

TO THE EDITOR: Dopamine receptor agonists, such as pramipexole and ropinirole, are a safe and effective initial therapy for mild to moderate Parkinson's disease. There are at least three lines of evidence to suggest that this class of drugs may also be related to mood symptoms. First, at the clinical level, besides ameliorating motor symptoms, pramipexole has shown antidepressant effects in Parkinson's disease, in major depression, and in treatment-resistant unipolar and bipolar depression. Next, at the basic science level, pramipexole and ropinirole are novel dopamine receptor agonists with a high affinity for all dopamine D_2 subfamily receptors and show highest affinity for the D_3 receptor subtype (1). The antidepressant effect of pramipexole and ropinirole may be related to a resensitization or potentiation of the D_2/D_3 receptors in the mesolimbic system, a region relevant to mood regulation (2). Finally, in a recent clinical trial by Goldberg and colleagues (3), one case of mania was reported in a patient with a personal history of bipolar depression while being treated with pramipexole. Here, we describe a case of mania in a patient with Parkinson's disease given pramipexole and ropinirole who had no personal or family history of bipolar disorder.

Ms. A was a 37-year-old white woman with a 4-year history of Parkinson's disease. Her family history revealed a paternal grandmother with a single major depressive episode and a sibling with anorexia nervosa. Her Parkinson's disease symptoms had been treated with levodopa and