Sweet's Syndrome and Polyserositis With Clozapine

TO THE EDITOR: The occurrence of irreversible agranulocytosis has limited the use of clozapine as a first-line medication in the treatment of schizophrenia. Additional severe side effects, such as myocarditis, pancreatitis, and sudden death, have been described. We report a case of neutrophilic dermatosis, or Sweet's syndrome, and polyserositis induced by clozapine treatment.

Ms. A, a 44-year-old Caucasian with a 26-year history of schizophrenia, was admitted to our facility because of neuroleptic-induced dyskinesia. She was suffering from auditory hallucinations and delusions of persecution. At admission, her treatment consisted of 12 mg/day of risperidone. The results of a physical examination were normal except for rhythmic choreoathetotic trunk movements. Laboratory tests showed normocytic anemia (3,700,000/μl) without acanthocytosis but otherwise normal results. Findings of cranial magnetic resonance imaging (MRI), chest radiography, ECG, and EEG were normal. There was no family history of movement disorders.

Risperidone was discontinued, and clozapine was started at an initial dose of 25 mg/day and increased by 25 mg/day every other day to 150 mg/day. On day 8 of treatment, Ms. A complained of respiratory difficulty. Results of laboratory examinations revealed a WBC count of 13,000/μl, an erythrocyte sedimentation rate of 110 mm/hour, a C-reactive protein level of 116 mg/liter, a fibrinogen level of 11.8 g/liter, and a creatine kinase level of 121 U/liter. Results of cardiac enzyme measurements, an ECG, and echocardiography were normal. Ms. A's body temperature rose to 103.1°F (rectal); watery diarrhea appeared, and she became delirious. The EEG indicated generalized slowing without focal abnormalities. A cranial MRI and measurement of cerebrospinal fluid level produced normal findings. Results of repeated blood and stool cultures were negative. Levofloxacin, 500 mg/day over 5 days, was ineffective. Extensive microbiological and immunological investigations produced inconclusive results. The results of a colonoscopy and a gastroscopy were normal.

On day 16, ankle edema developed. Results of a gynecological examination and abdominal computerized tomography scan remained normal. Increasing dyspnea prompted a repeat chest radiography, revealing pleural and pericardial effusions and mediastinal lymphadenopathy. The ECG remained unchanged, and echocardiography indicated no compromise of cardiac function. Ms. A's urine was positive for Bence Jones protein. On day 17, a generalized exanthema became apparent, consisting of well-demarcated, tender, erythematous papules and plaques. A skin biopsy yielded dense perivascular and periappendageal infiltrates of neutrophils and edema of the papillary dermis. Clozapine was discontinued.

Within 2 weeks, Ms. A's pericardial and pleural effusions resolved. All laboratory parameters returned to normal. Risperidone, 6 mg/day, was reintroduced. Over the next year, Ms. A exhibited some suspiciousness but no delusions or hallucinations. Her laboratory parameters remained within normal limits.

With clozapine treatment, this patient suffered from a life-threatening disorder characterized by pleural and pericardial effusions and neutrophilic dermatosis. Light-chain proteinuria and radiographic evidence of mediastinal lymphadenopathy led to a presumptive diagnosis of Sweet's syndrome associated with lymphoma. However, in view of an earlier report of polyserositis with clozapine treatment (1), an idiosyncratic reaction could not be ruled out. Upon discontinuation of clozapine, the patient improved rapidly and remained well over the next year. While, for ethical reasons, a rechallenge was not possible, a causative role of clozapine appears probable regarding the time course and the lack of other possible etiologies. This new adverse event has been formally reported to the Food and Drug Administration and to the manufacturer of the drug.

Reference

1. Daly JM, Goldberg RJ, Braman SS: Polyserositis associated with clozapine treatment (letter). Am J Psychiatry 1992; 149:1274–1275

CARLOS SCHÖNFELDT-LECUONA, M.D.
BERNHARD J. CONNEMANN, M.D.
Ulm, Germany

Modafinil for Social Phobia and Amphetamine Dependence

TO THE EDITOR: The treatment of psychiatric disorders in individuals with an active substance use problem is a challenge for the practicing clinician (1).

Ms. A was a 45-year-old Caucasian woman who came to our outpatient clinic for treatment of social phobia and comorbid amphetamine dependence. Her symptoms started during her early 20s. She described episodes of overwhelming anxiety, especially when she needed to present projects to her teachers. She had a partial response to fluoxetine. A friend introduced her to amphetamines; she started using them on a regular basis at age 27. She reported some relief of her anxiety, but 1 year later she met criteria for amphetamine dependence. She dropped out of school, became homeless, and was incarcerated several times for drug possession.

Her health care providers recommended that she enroll in drug rehabilitation before any further pharmacological treatment could be pursued. At one point, Ms. A was given a trial of methylphenidate and dextroamphetamine. She misused these prescription drugs. She had difficulties working with health care providers because of her explosiveness, overwhelming anxiety, agitation, and depression. She refused to take any medication that caused her to gain weight. She achieved no benefit from trials of lithium, anticonvulsants, venlafaxine, bupropion, selective serotonin reuptake inhibitors, and atypical antipsychotics. We started modafinil treatment, up to 200 mg b.i.d. At this point, she was also taking fluoxetine, 40 mg/day. She reported that her craving for amphetamines diminished, and her anxiety and depression improved. She did not spend most of her time looking for the amphetamines in the street and was able to apply for a regular job. She did not report the same "high" with modafinil that she experienced with amphetamines. Ms. A now works part-time and recently returned to school.

Modafinil is a new stimulant approved for the treatment of narcolepsy. Its mechanism of action is unknown (2). Studies (3) have indicated that it does not have the anxiogenic prop-

erties of dextroamphetamines. Recent studies (4) have raised the hypothesis of a possible link between dopamine dysfunction and social phobia.

In 1997, San Diego reported the highest mortality rate associated with methamphetamine overdose; it continues to be the most common primary drug of abuse (5). This case illustrates the increasing need for double-blind placebo-controlled clinical trials in the dually diagnosed population, specifically in individuals actively using stimulants.

References

1. Marlatt GA, Tucker JA, Donovan DM, Vuchinich RE: Help-seeking by substance abusers: the role of harm reduction and behavioral-economic approaches to facilitate treatment entry and retention. NIDA Res Monogr 1997; 165:44–84
2. Engber TM, Dennis SA, Jones BE, Miller MS, Contreras PC: Brain regional substrates for the actions of the novel wake-promoting agent modafinil in the rat: comparison with amphetamine. Neuroscience 1998; 87:905–911
3. Simon P, Panissaud C, Costentin J: The stimulant effect of modafinil on wakefulness is not associated with an increase in anxiety in mice: a comparison with dexamphetamine. Psychopharmacology (Berl) 1994; 114:597–600
4. Schneier FR, Liebowitz MR, Abi-Dargham A, Zea-Ponce Y, Lin S-H, Laruelle M: Low dopamine D_2 receptor binding potential in social phobia. Am J Psychiatry 2000; 157:457–459
5. Community Epidemiology Work Group: Epidemiologic Trends in Drug Abuse, Highlights and Executive Summary, vol 1. Bethesda, Md, National Institute on Drug Abuse, 1998, pp 59–66

ALVARO CAMACHO, M.D.
MURRAY B. STEIN, M.D.
San Diego, Calif.

Tardive Dyskinesia With Risperidone and Anticholinergics

TO THE EDITOR: The following are reports on three Japanese women who developed early-onset tardive dyskinesia during short-term risperidone treatment while taking an anticholinergic agent. All three met DSM-IV criteria for schizophrenia but not for mood disorders.

Ms. A, a 40-year-old woman who had never taken psychotropics, developed dysarthria and salivation 2 months into risperidone treatment (3–6 mg/day). Although this was resolved within 2 weeks by the addition of biperiden (3 mg/day), Ms. A's lips and jaw showed signs of moderate dyskinesia. Risperidone administration was then gradually terminated over 2 weeks and replaced with olanzapine (7.5 mg/day), which was increased to 10 mg/day 2 weeks later. The symptoms of dyskinesia disappeared 23 days after the discontinuation of risperidone and have not reappeared since (5 months to date).

Ms. B was a 28-year-old woman who also had no prior experience with psychotropics. Initially treated with amoxapine (an average of 125 mg/day), she was given risperidone (2 mg/day), which was titrated to 9 mg/day over 7 days. Three weeks later, she developed dysarthria and salivation, requiring either biperiden (6 mg/day) or trihexyphenidyl (4 mg/day). She developed dyskinesia in her lips and jaw 2 months into treatment. This was cured within 6 weeks by gradual termination of risperidone administration and replacement with quetiapine (100–200 mg/day). Ms. B has not had dyskinesia since (8 months to date).

Ms. C, a 24-year-old woman, had taken chlorpromazine (an average of 75 mg/day) and haloperidol (an average of 6 mg/day) for less than 6 weeks. Four months before the treatment, she had also experienced ECT five times. Initially, she had started with haloperidol (an average of 18 mg/day) but was then given risperidone (2 mg/day) and biperiden (2–4 mg/day) because of dysarthria and salivation. Two months later, she developed lip and tongue dyskinesia, requiring replacement of risperidone with quetiapine (150 mg/day) over 6 weeks, as in the case of Ms. B. She has not had dyskinesia since (6.5 months to date).

All patients took anticholinergic agents for extrapyramidal symptoms that were relatively limited to the perioral area. Of interest, delayed tardive dyskinesia was also observed in the same area. It is thought that anticholinergic agents diminish the atypicality of risperidone or they increase the risk of tardive dyskinesia. In the case of tardive dyskinesia induced by conventional antipsychotics, the existence of preceding extrapyramidal symptoms and the coadministration of anticholinergic agents have been recognized as risk factors (1). Patients taking conventional antipsychotics who develop severe extrapyramidal symptoms could be at particular risk of developing tardive dyskinesia, even with the use of atypical antipsychotics. Moreover, these cases suggest that early recovery can be achieved by switching to another atypical psychotic. Thus, atypical antipsychotics, reported to be useful in the treatment of tardive dyskinesia caused by conventional antipsychotics (2), may also be useful in treating tardive dyskinesia induced by atypical antipsychotics.

References

1. Kane JM, Smith JM: Tardive dyskinesia: prevalence and risk factors, 1959–1979. Arch Gen Psychiatry 1982; 39:473–481
2. Gupta S, Mosnik, Black DW, Berry S, Masand PS: Tardive dyskinesia: review of treatments past, present, and future. Ann Clin Psychiatry 1999; 11:257–266

EIJI SUZUKI, M.D., PH.D.
MICHIYUKI OBATA, M.D.
YOSHIKO YOSHIDA, M.D., PH.D.
HITOSHI MIYAOKA, M.D., PH.D.
Kanagawa, Japan

Mirtazapine for PTSD Nightmares

TO THE EDITOR: I would like to report on the use of the antidepressant mirtazapine for the treatment of nightmares characteristic of severe posttraumatic stress disorder (PTSD) and of the insomnia that accompanies these nightmares. The group under consideration consists of more than 300 patients treated at several community clinics serving refugees in the Chicago metropolitan area. While these refugees come from many different parts of the world, including Southeast Asia, Bosnia, Kosovo, several African nations, and Latin America, they are united in having experienced catastrophic stress levels. These patients have experienced one or more of the following: wartime violence and witnessing death as combatants or civilians, detainment in prison camps or concentration camps, physical and psychological torture, including the persistent threat of death, and for women, repeated sexual assault, usually by representatives of governmental and paramilitary forces.

Often the exposure to trauma and terror has extended over a period of years. The patients are frequently retraumatized during the exodus from their native countries. While these patients usually exhibit the entire range of symptoms characteristic of PTSD, it is the pervasive disturbance of sleep by nightmares that so often stands in the way of healing. We have found mirtazapine especially helpful in mitigating these symptoms by suppressing nightmare activity or in blocking the memory of the dream state upon awakening. Consequently, sleep becomes restorative and patients have more psychic energy for combating the daytime symptoms of PTSD. While exact figures are not yet available, I estimate that of more than 300 patients treated, approximately 75% have reported improvement due to reduction of the frequency and intensity of nightmares. A substantial minority of these patients have reported a total absence of dreams related to the traumatic events.

Although such patients are often treated with multiple medications, typically a selective serotonin reuptake inhibitor and an anxiolytic, it was not until mirtazapine was introduced as part of the treatment regimen that the dramatic reduction in nightmares occurred. Reports of side effects are extremely rare. The excessive drowsiness and weight gain sometimes reported by patients taking mirtazapine for depression almost never occur when this drug is used to treat severe PTSD. Certainly, carefully planned research to test these findings is necessary. However, it was felt important to report the positive result of this use of mirtazapine for this disorder, given the devastating effects of the nightmares and sleeplessness caused by catastrophic stress.

JONATHAN D. LEWIS, M.D.
Chicago, Ill.

"Rehospitalization" Versus "Recidivism"

TO THE EDITOR: The term "recidivism" is often used in the psychiatric and mental health literature to mean "rehospitalization." This is puzzling, since the concept of recidivism generally refers to criminal reoffense. For example, the *Oxford English Dictionary* defines recidivism as "the habit of relapsing into crime" (http://dictionary.oed.com/cgi/entry/00199164). *Merriam-Webster's Collegiate Dictionary* defines recidivism as "a tendency to relapse into a previous condition or mode of behavior; especially: relapse into criminal behavior" (http://www.m-w.com). Similarly, a well-known web site uses the following definition: "a tendency to lapse into a previous condition or pattern of behavior; especially, a falling back or relapse into prior criminal habits.... A recidivist is one who relapses or who is an incorrigible criminal" (http://www.dictionary.com/wordoftheday/archive/2001/03/08.html). While some dictionaries recognize the use of the term in the psychiatric literature (in one instance, citing the phrase "a study of recidivism in mental patients") (http://collections.chadwyck.com/mwd/htxview?template=basic.htx&content=frameset.htx), clearly, the primary meaning of recidivism refers to criminal reoffense.

This is supported by a review of the medical literature. PUBMED was accessed to identify articles with the words "recidivism," "readmission," "rehospitalization," "rehospitalizations," or "rehospitalized" in the title. Of the 291 articles with "recidivism" in the title, 162 (55.7%) dealt with criminal behavior or reoffense by mentally disordered individuals, 47 (16.2%) were about psychiatric readmission, 34 (11.7%) were about medical readmission, and 23 (7.9%) were about substance abuse treatment. (Thirteen [4.5%] were in a foreign language and thus were not further analyzed, and 12 [4.1%] were on other topics. These were combined for statistical analysis.)

Of the 535 articles with "readmission," "rehospitalization," "rehospitalizations," "or "rehospitalized" in the title, 282 (52.7%) were about medical readmission, 169 (31.6%) were about psychiatric readmission, and 16 (3.0%) were about substance abuse treatment. None dealt with criminal behavior or reoffense by mentally disordered individuals. (Fifty-nine [11.0%] were in a foreign language, and nine [1.7%] were on other topics.) The difference in distribution between "recidivism" and this group of words was significant (χ^2=410.41, df=4, p<0.001).

Thus, in this group of articles, 21.8% (N=47) of the 216 articles on psychiatry used the word "recidivism" in the title, compared to 10.8% (N=34) of the 316 articles dealing with the rest of medicine. An article on psychiatry was twice as likely to use the word "recidivism," with its connotations of criminality, in the title. Given the association between the word "recidivism" and criminality, I suggest that as a means of decreasing stigmatization of psychiatric patients, we should avoid the word "recidivism" when what we mean is "rehospitalization."

HAROLD A. CARMEL, M.D.
Durham, N.C.