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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.

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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

selegiline with moderate response. Because of episodic rigidity and dyskinesia, pramipexole was added to her treatment regimen and increased to 1.5 mg b.i.d., with improvement of motor symptoms. However, in the first week after its addition, she developed symptoms of elevated mood, increased sex drive, energy, psychomotor activity, and decreased need for sleep. After 6 months on this regimen, she developed irritability, paranoia, and delusions of jealousy. Selegiline and pramipexole were discontinued, and she began taking quetiapine, titrated to 50 mg, at bedtime. Her psychotic symptoms resolved in 1 month. Quetiapine was discontinued without symptom recurrence. Two months later, her levodopa dose was decreased because of tremors and dyskinesias, and ropinirole was added and titrated to 0.75 mg t.i.d. She rapidly developed insomnia, increased energy, and agitation. Consequently, ropinirole was discontinued, which led to symptom resolution. She remained stable taking levodopa alone for several months. Ropinirole was reinstituted but led to reemergence of manic symptoms, necessitating discontinuation, which resulted in amelioration of mania.

The long-term studies of dopamine receptor agonists support their use instead of levodopa earlier in the treatment of Parkinson's disease in order to delay levodopa-related motor complications. We provide evidence here that dopamine receptor agonists may induce mood symptoms and that there is potential for the novel agents of this class, pramipexole and ropinirole, to induce manic symptoms necessitating close monitoring and further study.

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5-Methoxy-N,N-Diisopropyltryptamine-Induced Flashbacks

TO THE EDITOR: The drug 5-methoxy-N,N-diisopropyltryptamine (5-MeO-DIPT) has hallucinogenic and mild euphoric properties, similar to those of other tryptamine compounds (1). Hallucinogen-persisting perception disorder is characterized by the transient recurrence of perceptual symptoms experienced while intoxicated with the hallucinogen, often called "flashbacks." LSD-induced flashbacks are well known. It is also reported that hallucinogen-persisting perception disorder is induced by cannabis and methamphetamine. However, to our knowledge, there are no published reports of 5-MeO-DIPT-induced hallucinogen-persisting perception disorder.

Mr. A, a 35-year-old Japanese man without a previous psychiatric history, was seen with perceptual disturbances. One month before his evaluation, he had stopped using 5-MeO-DIPT because of a so-called bad trip—anxiety, palpitations, auditory oversensitiveness, and visual distortion—after six or seven times using between 15 mg and 30 mg of 5-MeO-DIPT over 5 months. He was bisexual and had used the drug to enhance intercourse with a male partner. A few days before his evaluation, after the announcement of his father's diagnosis of a brain tumor, his 5-MeO-DIPT-induced phenomena of a "bad trip" returned, although he had not taken 5-MeO-DIPT.

There was no evidence of CNS infection or organic brain disease. Amphetamine was not detected in Mr. A's urine. He was not clinically depressed. Schizophrenia-like symptoms, such as delusions or auditory hallucinations, were not present. He was given oral risperidone, 1 mg/day. Within 3 days, his perceptual disturbances remarkably decreased, and 7 days later, they had almost completely disappeared. Given his clinical features and history of drug ingestion, we made a diagnosis of hallucinogen-persisting perception disorder induced by 5-MeO-DIPT. Mr. A was discharged 1 month later. Although this medication was maintained for 4 months and then terminated, he has had no relapse.

The disturbances of serotonergic function may be a factor in hallucinogen-persisting perception disorder, although the pathophysiology remains unclear. Regarding the treatment of LSD-induced flashbacks, the choice of medication is still controversial. The use of various agents, including neuroleptics, serotonin reuptake inhibitors (SSRIs), anticonvulsants, and benzodiazepines, has met with limited success (2). Some researchers report that risperidone, which is a serotonin-dopamine antagonist, exacerbates symptoms of hallucinogen-persisting perception disorder (3). Others note that SSRIs exacerbate flashbacks (4). In this case, his perceptual disturbance symptoms responded to risperidone treatment.

For public safety, 5-MeO-DIPT is a controlled substance in several countries. However, it is available in many areas, and the patient obtained it through the Internet quite easily. We are concerned that the abuse of 5-MeO-DIPT may be more widespread than previously thought. We believe that studies are needed to verify the relationship between 5-MeO-DIPT and hallucinogen-persisting perception disorder and to call public attention to the toxicity of 5-MeO-DIPT.

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