Topiramate-Induced Psychosis

TO THE EDITOR: With the use of topiramate as a strategy for treatment-resistant bipolar disorder (1)—not to mention other off-label uses for conditions such as borderline personality disorder (2) and eating disorders (3)—clinicians need to be aware of the possibility of topiramate-induced psychosis in patients who have not previously had a psychotic episode. Although there is a small amount of literature in neurology journals regarding psychiatric adverse events in seizure patients (4), the psychiatric literature is largely silent on the subject (5). We report on a patient without a previous history of psychosis who developed psychosis after an increase in his dose of topiramate.

Mr. A was a 32-year-old man with obsessive-compulsive disorder who was initially administered 25 mg/day of topiramate for mood stabilization and weight loss. Eight months later, his dose was increased from 150 mg b.i.d. to 200 mg b.i.d. Within 1 week of the increase, he became paranoid, believed he was "the messiah," and intended to sacrifice himself as directed by God. He also developed disorganized and illogical thought processes and a flattened affect. He appeared to be responding to internal stimuli. Mr. A was transferred to our care 2 months later, after having no improvement with a reduction in his dose of topiramate and the use of risperidone, 6 mg b.i.d. After discontinuation of topiramate, he became less paranoid and more organized, and his affect brightened. He improved continuously throughout the day, and within 24 hours, his psychosis had resolved.

The anticonvulsant topiramate is known to cause cognitive adverse events. Psychiatric adverse events reported in the neurology literature include paranoid delusions, visual and auditory hallucinations, depression, aggressive behavior, and irritability (4). In some case reports of patients with seizure disorder, a decrease in the dose of topiramate resulted in resolution of the psychosis (6). Although no controlled trials have shown topiramate to be adequate for mood stabilization, clinicians need be aware of adverse psychiatric events in patients taking topiramate and consider decreasing the dose or discontinuing the medication altogether.

References

1. Lykouras L, Hatzimanolis J: Adjunctive topiramate in the maintenance of treatment of bipolar disorders: an open-label study. Med Res Opin 2004; 20:843–847
2. Cassano P, Lattanzi L, Pini S, Dell'Osso L, Battistini G, Cassano GB: Topiramate for self-mutilation in a patient with borderline personality disorder (letter). Bipolar Disord 2001; 3:161
3. Hedges DW, Reimherr FW, Hoopes SP, Rosenthal NR, Kamin M, Karim R, Capece JA: Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, part 2: improvement in psychiatric measures. J Clin Psychiatry 2003; 64:1449–1454
4. Mula M, Trimble MR: Topiramate and psychiatric adverse events in patients with epilepsy. Epilepsia 2003; 44:659–663
5. Andrade C: Confusion and dysphoria with low-dose topiramate in a patient with bipolar disorder. Bipolar Disord 2001; 3:211–212
6. Khan A, Faught E, Gilliam F, Kuzniecky R: Acute psychotic symptoms induced by topiramate. Seizure 1999; 8:235–237

DANA KOBER, M.D.
GLEN O. GABBARD, M.D.
Houston, Tex.

Reversal of Symptomatic Hyperprolactinemia by Aripiprazole

TO THE EDITOR: Hyperprolactinemia is a well-recognized complication of treatment with antipsychotics, causing multiple endocrine and sexual side effects, including the risk for osteoporosis and possibly breast cancer (1). We report a case of successful treatment of risperidone-induced hyperprolactinemia by the partial dopamine agonist aripiprazole.

Anne was a 17-year-old adolescent diagnosed with schizophrenia complicated by medication noncompliance. She was admitted to the inpatient service while acutely psychotic. She had mild asthma but no other medical problems. Her periods had been normal since menarche. Her maternal grandfather also has schizophrenia but had been asymptomatic for many years while taking haloperidol.

Risperidone was started because of the option for a long-acting formulation. Anne accepted the idea of an intramuscular injection because of her grandfather's history. Her oral dose was titrated up to 4 mg/day over 2 weeks, after which she received her first injection of 25 mg. She reported a decrease in psychotic symptoms but began to complain of bilateral breast pain, swelling, and galactorrhea. Serum prolactin was drawn and found to be elevated, at 119 μg/ml (normal range 0–25 μg/ml). Aripiprazole (15 mg/day) was added to her drug regimen because of its partial agonism at the dopamine receptor (2), making it a theoretically useful tool in lowering prolactin. Anne remained taking oral risperidone, 4 mg/day, and had a gradual resolution of her breast pain and galactorrhea. Another prolactin level taken 12 days later was 18 μg/ml. Anne was discharged from the hospital much improved while taking a combination of a long-acting intramuscular injection of risperidone, 25 mg every 2 weeks, and aripiprazole, 15 mg/day.

Aripiprazole lowers serum prolactin below placebo when it is used as a single agent (3). To our knowledge, this is the first case report of aripiprazole used in combination with another antipsychotic expressly to treat symptomatic hyperprolactinemia. Risperidone causes more marked elevations in prolactin than other atypical antipsychotics because it does not fully cross the blood-brain barrier (4). Dopamine D_2 receptor occupancy is therefore higher at the level of the pituitary than in the striatum. Aripiprazole has a greater affinity for the D_2 receptor than risperidone, with central D_2 receptor occupancy around 90% at a dose of 15 mg/day (5). The partial agonist property of this compound means that in the presence of dopamine hypoactivity, as induced by risperidone, aripiprazole will function as a dopamine agonist with roughly 30% intrinsic activity at postsynaptic receptors (5), restoring tonic inhibition to anterior pituitary lactotrophs. Spontaneous prolactin decline in this case would be unlikely because the time since risperidone exposure was short. However, nor-

malization after longer-term treatment (1 year) has been reported (6).

It may be advantageous to avoid the use of directly acting dopaminergic agents in psychotic patients because of the risk for worsening psychosis. Whether this risk is really any lower for aripiprazole when combined with a direct D_2 receptor antagonist is not clear and would need to be answered in a controlled trial.

References

1. Wang PS, Walker AM, Tsuang MT, Orav EJ, Glynn RJ, Levin R, Avorn J: Dopamine antagonists and the development of breast cancer. Arch Gen Psychiatry 2002; 59:1147–1154
2. Kane JM, Carson WH, Saha A, McQuade RD, Ingenito G, Zimbroff DL, Ali MW: Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2002; 63:763–771
3. Keck PE Jr, Marcus R, Tourkodimitris S, Ali M, Liebeskind A, Saha A, Ingenito G (Aripiprazole Study Group): A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. Am J Psychiatry 2003; 160:1651–1658
4. Kapur S, Langlois X, Vinken P, Megens AA, De Coster R, Andrews JS: The differential effects of atypical antipsychotics on prolactin elevation are explained by their differential blood-brain barrier disposition: a pharmacological analysis in rats. J Pharmacol Exp Ther 2002; 302:1129–1134
5. Grunder G, Carlsson A, Wong DF: Mechanism of new antipsychotic medications: occupancy is not just antagonism. Arch Gen Psychiatry 2003; 60:974–977
6. Findling RL, Kusumakar V, Daneman D, Moshang T, De Smedt G, Binder C: Prolactin levels during long-term risperidone treatment in children and adolescents. J Clin Psychiatry 2003; 64: 1362–1369

REBECCA WAHL, M.D.
ROBERT OSTROFF, M.D.
New Haven, Conn.

Clozapine-Induced Allergic Vasculitis

TO THE EDITOR: Recently, a patient in our institution developed palpable purpura shortly after initiation of the antipsychotic clozapine. Palpable purpura is an indication of inflammatory hemorrhage and is highly suggestive of allergic vasculitis. A literature search revealed no prior reported cases. We are reporting this case of clozapine-induced allergic vasculitis to promote a swifter diagnosis and treatment of this rare complication.

Mr. A was a 59-year-old man with a history of paranoid schizophrenia, deafness, hypothyroidism, and tardive dyskinesia. Haloperidol was being discontinued and clozapine initiated because of persistent extrapyramidal symptoms, tardive dyskinesia, and treatment-resistant psychotic symptoms. Clozapine had been introduced 17 days earlier and was being slowly titrated upward. Besides haloperidol, his other medications included benztropine, divalproex sodium, lorazepam, trazodone, and levothyroxine. When the total dose of clozapine was 137.5 mg/day, a rash developed on his legs. The rash was a confluent, nonblanching, erythematous, elevated patch consistent with a palpable purpura. It continued to spread up his lower extremities but never involved his palms or soles. He was afebrile with stable vital signs and had a benign examination otherwise. Aside from the clozapine, treatment with all other medications was longer than 2 months, with haloperidol, benztropine, and divalproex sodium having been administered for more than 10 years.

The initial differential diagnosis included Rocky Mountain spotted fever, Churg-Strauss syndrome, Wegener's granulomatosis, microscopic polyarteritis, mixed cryoglobulinemia, and Henoch-Schönlein purpura. Mr. A was empirically administered doxycycline in case of Rocky Mountain spotted fever, and his divalproex sodium and clozapine doses were held steady. Rocky Mountain spotted fever was ruled out by serology and by the fact that Mr. A had been indoors (hospitalized) for the last 2 months. Churg-Strauss syndrome was unlikely because he did not have a history of asthma or eosinophilia. The results of urine and blood cultures and serologies (CBC, liver function tests, creatine kinase, erythrocyte sedimentation rate) were all unremarkable. He was transferred to a tertiary care center for further evaluation. Mr. A was managed conservatively without steroids and had further serologies (serum cryoglobulins, complement C3, complement C4, hepatitis C, and antineutrophil cytoplasmic antibodies studies) whose results were negative. A punch biopsy of his skin revealed perivascular neutrophilic infiltrate with extravasation of red blood cells, suggestive of early leukocytoclastic vasculitis.

The diagnosis of allergic vasculitis was made because of Mr. A's age, recent medication adjustments, and the isolated skin involvement (1). A closer review of his medications revealed that clozapine was the only new medication in the last 2 months. He improved with conservative management, and it was decided not to rechallenge him with clozapine.

Clozapine is the drug of choice for schizophrenia patients with persistent residual symptoms. Clozapine-induced allergic vasculitis is a rare but serious complication that should be added to the adverse reactions to clozapine therapy. We hope that this case will promote awareness and expedite diagnosis and treatment of this adverse reaction.

Reference

1. Michel BA, Hunder GG, Bloch DA, Calabrese LH: Hypersensitivity vasculitis and Henoch-Schönlein purpura: a comparison between the 2 disorders. J Rheumatol 1992; 19:721–728

KENAN M. PENASKOVIC, M.D.
Chapel Hill, N.C.
SIDDHARTHA ANNAMRAJU, M.D.
JOHN E. KRAUS, M.D., PH.D.
Raleigh, N.C.

Smokeless Tobacco for a Nicotine-Dependent Schizoaffective Patient

TO THE EDITOR: Approximately 83% of the patients with schizophrenia and 65% with mood disorders are nicotine dependent (1). The following case demonstrates the benefit of switching from smoking to oral tobacco in a severely nicotine-dependent psychiatric patient.

Ms. A, a 52-year-old woman with schizoaffective disorder, bipolar type, started smoking shortly after her first psychotic episode at age 19 and, on average, smoked about 1½ packs per day for 33 years. She had attempted to quit using pharmacotherapy, nicotine gum, or patches in combination with cessation classes. Both gum and patch treatments were ineffective since they did not control her craving for cigarettes. Her motivation to quit was strong because of the sequelae of smoking: bronchitis,