Clozapine-associated Pseudomembranous Colitis

A Case Report and Review of the Literature

To the Editors:

Clozapine is a tricyclic dibenzodiazepine derivative, atypical antipsychotic which exhibits relatively potent antiserotonergic (5-HT₂, 5-HT₃), anticholinergic, antihistaminic (H₁), antimuscarinic activity, and induces preferential blockade of dopamine D₁ and D₄ receptors in vivo. Various adverse gastrointestinal effects have been associated with its use including constipation, gastric outlet obstruction, prolonged postoperative ileus, gastric mucosal ischemia, and inflammatory debris. Stool specimens were negative for enteric pathogens and Clostridium difficile cytotoxin.

In 2003, she developed a tonic-clonic convulsion and, based on abnormal electroencephalography findings and consultation with her neurologist, sodium valproate was added. She was also maintained on benzhexol 6 mg/d and lorazepam 3 mg/d. During this time, she had no history of upper or lower gastrointestinal complaints.

In December 2004, she was noted to pass copious amounts of soft, brown stools. Physical examination revealed hypotension with 80/60 mm Hg of systolic/diastolic blood pressure. Two days later, she developed a distended abdomen and colonoscopy revealed colitis with plaque-like lesions in the sigmoid and descending colon. Histologic examination of colonic biopsy showed superficial erosion of the mucosa and adherent "pseudomembranes" of fibrin, mucus, and inflammatory debris. Stool specimens were negative for enteric pathogens and Clostridium difficile cytotoxin.

A full blood count of the patient revealed a white blood cell count of 8.3 x 10⁹/L (eosinophil count of 3.1%, within normal limits of 1–6%) and platelet count of 417 x 10⁹/L. As the patient remained ill and repeat colonoscopy subsequently revealed necrotic-looking areas, a surgical decision was made for colonic resection and ileorectal anastomosis. Postoperatively, the patient developed prolonged ileus which resolved 3 weeks later.

The clozapine in her psychotropic regimen was stopped in December 2004. Presently, she is receiving sulphiride 100 mg/d, sodium valproate 2400 mg/d, fluvoxamine 25 mg/d, and remains psychiatrically stable.

Pseudomembranous colitis often occurs in patients without a background of chronic enteric disease and has previously been associated with the use of antituberculous drugs, antibiotics, but not neuroleptics. This is the first reported case of pseudomembranous colitis in a patient after prolonged clozapine administration, which was further complicated by postoperative ileus. Although the pathogenesis of necrotizing colitis may be related to the anticholinergic properties of clozapine, it is less clear for pseudomembranous colitis, which warrants further investigation.

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Neuroleptic Malignant Syndrome and Aripiprazole in an Antipsychotic-naive Patient

To the Editors:

Neuroleptic malignant syndrome (NMS) is a rare side effect from antipsychotics that is potentially fatal if not recognized and treated early. The features essential to NMS are muscle rigidity and elevated temperature in a patient using an antipsychotic. These are accompanied by 2 or more of the following: diaphoresis, dysphagia, tremor, incontinence, altered level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, and evidence of muscle injury from laboratory findings (eg, elevated creatine phosphokinase, CPK) (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, DSM-IV-TR). As case reports accumulate for NMS with the atypical antipsychotics, it has been suggested that these agents may produce milder forms of NMS with less dramatic temperature elevations and less muscle rigidity.1

The incidence of NMS has been estimated between 0.02% and 3.43% for patients receiving antipsychotics, with a pooled estimate of 0.1–0.2%.2,3 Certain risk factors have been suggested to increase the risk of NMS, including dehydration, prior episodes of NMS, high doses of antipsychotics (especially if given intramuscularly), rapid loading of antipsychotics, concurrent use of lithium, prolonged use of physical restraints, withdrawal of antiparkinsonian medications, alcoholism, and previous brain injury.4

The mechanism of NMS is not completely understood. One accepted mechanism is the dopamine blockade theory. According to this theory, massive and sudden reduction in dopaminergic activity secondary to antipsychotic-induced dopamine blockade mediates the symptoms of NMS.5 Recently, other theories have emerged, such as sympathetic hyperactivity leading to a hyperadrenergic state caused by antipsychotics and an imbalance of dopaminergic activity with other neurotransmitters such as gamma amino butyric acid and acetylcholine.4,5

CASE REPORT

The patient was a 23-year-old white woman who was admitted to a psychiatric facility for a 2-week history of psychosis (delusional thoughts of “visiting the devil’s house,” auditory and visual hallucinations, and disorganized behaviors). She had no prior psychiatric treatment history and denied family history of psychiatric illness. She had been using methamphetamine and cannabis, but no urine toxicology was done. She was not a regular user of alcohol. The temporal relationship between stimulant use and onset of psychosis could not be definitively established. During her psychiatric admission, she was treated with aripiprazole 30 mg QD and lorazepam 1 mg PRN for agitation. She improved within 3 days and was discharged on aripiprazole 30 mg QD. Her psychiatric diagnoses at discharge were psychotic disorder NOS and methamphetamine dependence.

She presented 2 weeks later to the emergency room with complaints of “fever, sweats, and shakes” increasing over several days, and was admitted to the hospital. Her last dose of aripiprazole had been 1 day before admission. She denied any history of trauma or intramuscular injections. She exhibited tremor in all extremities, mild muscle rigidity, psychomotor retardation, diaphoresis, and altered mental status, including disorientation to date and place. She was also agitated and uncooperative. Her temperature was 100°F with blood pressure varying between 109/72 and 135/79 mm Hg, and tachycardia at 118 bpm. Laboratory studies included a mild leukocytosis of 14,000/mm3, hemocrit of 44%, and a creatine phosphokinase of 866 U/L (reference range 0–250); an additional CPK 6 hours after admission was 781 U/L. Electrolytes showed sodium of 137 mEq/L, potassium of 3.6 mEq/L, chloride of 104 mEq/L, bicarbonate of 26 mEq/L, blood urea nitrogen of 14 mg/dL, creatinine of 1.2 mg/dL. Urinalysis showed a specific gravity of 1.03 and no evidence of urinary tract infection. Her liver-associated enzymes were normal and urine toxicology screen was normal. Head CT and chest x-ray were normal. CSF analysis revealed a slightly elevated protein.

During her hospital course, she was treated for a presumptive diagnosis of NMS. Aripiprazole was held. She was rehydrated, received lorazepam 0.5 mg PRN Q6H for agitation and bromocriptine 2.5 mg BID for rigidity. On hospital day 2, she continued to be tremulous and disoriented, but her rigidity was decreased. CPK was then 474 U/L. On hospital day 4, the rigidity had resolved, CPK was 168 U/L, but she continued to be tremulous. Lorazepam was changed to a scheduled dose of 1 mg Q6H. On hospital day 5, her tremor had improved and CPK was 129 U/L. She still endorsed her delusional thoughts. She was not to have developed a urinary tract infection and was started on intravenous antibiotics. CPK was 93 U/L and 74 U/L on hospital days 7 and 8. On hospital day 9, she was transferred to a psychiatric facility.

COMMENT

This report describes a patient with methamphetamine dependence and a recent-onset psychosis treated with aripiprazole who met the DSM-IV-TR criteria for NMS. There have been 3 reported cases of aripiprazole-associated NMS.6,7 Many of the recent cases of NMS with atypical antipsychotic drugs involve patients who are highly susceptible because of previous NMS episodes, extrapyramidal symptoms,
treatment failures and risks associated with switching antipsychotics.\textsuperscript{1}

The risk of developing NMS seems to be related to the degree of \(D_2\) receptor blockade; with the atypical antipsychotics, this risk is less compared with the typical antipsychotics.\textsuperscript{2} Aripiprazole’s unique pharmacologic action (partial agonist at the \(D_2\) receptor, agonist at the 5-HT\(_{1A}\) receptor, and antagonist 5-HT\(_{2A}\) receptor) has been suggested to decrease the risk for extra-pyramidal side effects compared with other atypical antipsychotics, and similar to placebo.\textsuperscript{3,4} In view of our patient’s case, this may raise an issue in further evaluating the role of \(D_2\) blockade in the development of NMS given that aripiprazole is a \(D_2\) partial agonist, or to consider other contributing factors. Such cofactors might include genetic predisposition, environmental injury, and iatrogenic pharmacologic insult.\textsuperscript{5} Spivak et al.\textsuperscript{6} reported a case on NMS after withdrawal of the antipsychotics fluphenazine and penfluridol and the anticholinergic trihexphenidyl. Similarly, a case reported by Rosse and Ciolino\textsuperscript{7} showed worsening of NMS after simultaneous discontinuation of haloperidol and amantadine. These cases, with the onset on NMS after discontinuation of dopamine blocking antipsychotics, could be helpful in explaining NMS with the dopamine partial agonist aripiprazole.

Consensus support for the acute management of NMS includes discontinuation of the antipsychotic and provision of supportive therapy, such as IV hydration and close monitoring. Other interventions such as dantrolene, bromocriptine, and electroconvulsive therapy have been suggested to improve and shorten the duration of NMS. However, in the absence of prospective, controlled clinical trials and with the heterogeneity of reported cases, it is difficult to suggest one evidence-based treatment over another.\textsuperscript{8,9} This patient responded well to supportive therapy, lorazepam 0.5 mg PRN which was increased to 1 mg Q6H, and bromocriptine 2.5 mg BID.

This case illustrates the challenges of diagnosis of NMS-spectrum illness in patients using atypical antipsychotic agents. This patient was exposed early in treatment to a 30-mg daily dose of aripiprazole (rather than more conservative doses), which may have added to her risk. She did not present with extreme hyperthermia, grossly elevated CPK, and “lead-pipe” muscle rigidity, which would make the diagnosis of NMS unmistakable. Nonetheless, the onset of symptoms meeting DSM-IV-TR criteria for NMS within 2 weeks for first exposure to an antipsychotic, the resolution of her symptoms with discontinuation of aripiprazole and management with lorazepam, bromocriptine, and supportive care supports a diagnosis of presumed aripiprazole-associated NMS. There is a risk of increasing psychosis with bromocriptine; we used a low dose targeted to address the initial rigidity, which resolved in several days. Psychiatrists prescribing aripiprazole are advised to be alert to the possibility of NMS as experience is accumulated with this new antipsychotic agent.

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REFERENCES

An Open-Label Trial of Adjunctive Oxcarbazepine for Bipolar Disorder

To the Editors:

We recently conducted a small pilot study to evaluate the safety and efficacy of oxcarbazepine as an adjunctive treatment of Bipolar I disorder in outpatients with inadequate clinical response (including inadequate efficacy or intolerable side effects) to standard mood stabilizers. Oxcarbazepine, the 10-keto analogue of carbamazepine, has recently been considered as a safer, more tolerable, equally efficacious adjunctive alternative to carbamazepine in the common situation where monotherapy proves inadequate for bipolar patients.\textsuperscript{1,2} The limited research that has been done on the long-term efficacy of adjunctive oxcarbazepine has suggested that its antimanic properties exceed its antidepressant properties.

Our study, approved by the institutional review board and requiring written informed consent, was an open-label trial with 20 outpatients being treated for Bipolar I disorder in a university-based psychiatry department. Patients were eligible for inclusion if they had no other Axis I diagnoses and demonstrated active mood dysregulation despite treatment with standard mood stabilizers of adequate dose and duration, as evidenced by a Hamilton Depression Inventory\textsuperscript{3} (HAM-D) score of \(\geq15\) and/or a Young Mania Rating...