ISMP Adverse Drug Reactions

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Trichotillomania Associated With Aripiprazole

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and Myungsun Ro¹**

Abstract

The purpose of this feature is to heighten awareness of specific adverse drug reactions (ADRs), discuss methods of prevention, and promote reporting of ADRs to the US Food and Drug Administration's (FDA) MedWatch program (800-FDA-1088). If you have reported an interesting, preventable ADR to MedWatch, please consider sharing the account with our readers. E-mail Dr. Mancano michael.mancano@temple.edu. Your report will be published anonymously unless otherwise requested. This feature is provided by the Institute for Safe Medication Practices (ISMP) in cooperation with the FDA's MedWatch program and Temple University School of Pharmacy. ISMP is an FDA MedWatch partner.

Lithium-Induced Cardiomyopathy¹

A 59-year-old female presented to the emergency department with a chief complaint of chest pain for longer than 24 hours and occasional breathing difficulties with moderate activity over the past 4 weeks that was sometimes associated with chest pain lasting less than 5 minutes.¹ While in the emergency department, she had an electrocardiogram (ECG) that showed a sinus rhythm and a left bundle branch block, in addition to a normal blood test, unremarkable troponin levels, CHEM-7, complete blood cell count (CBC), and a lithium level of 0.9 mEq/L (therapeutic range, 0.6–1.2 mEq/L). The patient was diagnosed with heart failure and was started on aspirin, furosemide, and an angiotensin-converting enzyme (ACE) inhibitor.

A medication history revealed the patient had been receiving lithium and low doses of trazodone and lormetazepam for a 15-year history of bipolar affective disorder. She had good adherence to her medications, always went to follow-up appointments, and had been mentally stable for the past 12 years on this current regimen. She had routine blood tests that revealed a normal lithium level of 0.9 mEq/L, normal thyroid function tests, and normal renal function tests as well.

At a follow-up 4 months after her initial diagnosis of heart failure, she presented with breathing difficulties and was classified into class II according to the functional classification of the New York Heart Association (NYHA). A

transesophageal echocardiography showed severe dilation of her left ventricle with severe systolic dysfunction and an ejection fraction of 20%–30%. Other diagnoses were considered, such as ischemic cardiomyopathy with multivessel coronary artery disease versus dilated cardiomyopathy (DCM) related to lithium toxicity. A cardiac computed tomographic (CT) scan and another transesophageal echocardiography were performed but no coronary vessel lesions were found, just dilation of the left ventricle. This suggested that DCM related to lithium toxicity was the cause. The patient was started on low-dose β -blockers and was advised to discontinue lithium. The patient was reluctant but agreed to a gradual reduction.

At another follow-up 4 months later, the patient's lithium level was 0.4 mEq/L and she was reclassified to NYHA class I due to an improvement in her breathing. A magnetic resonance imaging (MRI) scan showed an improvement in systolic function evidenced by an ejection fraction of 40%.

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The family discussed the declining mental health of their family member. Eighteen months after this concern, the patient was admitted to a psychiatric ward for a manic relapse. Her lithium levels at this time were 0.2 mEq/L and she was switched to a different mood stabilizer, valproic acid. The patient went into remission once her blood levels of valproic acid reached 80 ng/dL (therapeutic range, 50-125 ng/dL). One month after the complete discontinuation of lithium, the patient's breathing difficulties were less severe and her ejection fraction improved further to 45%.

It is thought that lithium affects cardiac conduction and could decrease myocardial systolic function. It can cause many cardiac affects from benign T-wave flattening to cardiac collapse. However, serious cardiac toxicity is rare and usually only occurs in patients with underlying cardiac disease. Using the Naranjo algorithm, it is thought that this patient was suffering from DCM secondary to lithium toxicity evidenced by previous reports about it; all other causes were ruled out, and the patient experienced obvious improvement when lithium was stopped. This patient scored a 5 using the Naranjo algorithm, which shows that lithium probably caused DCM, but there is no way at this time to entirely confirm this diagnosis. Some studies have shown that lithium toxicities can be caused by an increase in the level of plasma and urine norepinephrine, whereas other studies have shown that it can be related to an increase in thyroid-stimulating hormone, but again there is no clear/accurate way to diagnose DCM.

In conclusion, the authors hope this possible life-threatening side effect is considered for all patients on long-term lithium use. Health care professionals should watch patients for difficulty in breathing and any weakness. If these do occur, the patient should be referred to a cardiologist right away. In addition, always ask the patient about any underlying heart disease before starting lithium treatment. It requires a multidisciplinary approach to treat the patient effectively and give them the best care possible.

Fixed Drug Eruption Due to Cetirizine, Levocetirizine, and Hydroxyzine²

A 21-year-old man presented with a chief complaint of multiple itchy erythematous and edematous plaques over the past 2 days covering his lips, trunk, and upper and lower extremities. These plaques developed within an hour after taking levocetirizine 5 mg for allergic conjunctivitis. The patient described a previous medical episode 5 years prior, in which he was given topical steroids that led to postinflammatory hyperpigmentation. The patient's medical records revealed, he was previously taking cetirizine, levocetirizine, nimesulide (a nonsteroidal anti-inflammatory drug [NSAID]), acetaminophen, trimethoprim/sulfamethoxazole, and doxycycline before the episodes. He was prescribed these medications for cold, cough, fever, sore throat, headache, and allergic conjunctivitis. A diagnosis of a fixed drug

eruption to levocetirizine was given and the topical steroid mometasone furoate 0.1% was applied once daily for treatment. The lesions resolved within 1 week.

The patient was admitted to the hospital and was challenged with all suspected drugs using the standard oral provocation method. Pigmented lesions reactivated in the form of itching and erythema within 1 hour with one-eighth of the dose of cetirizine and levocetirizine on two different occasions over 10 days. In addition to this, new itchy erythematous plaques developed over the trunk and extremities. Oral provocation tests with loratadine, desloratadine, and fexofenadine were negative. The patient refused more provocation tests, but a lesional patch test with hydroxyzine in 10% petrolatum was positive at 48 hours as an itchy erythematous plaque. After these tests, the patient was instructed to avoid cetirizine, levocetirizine, and hydroxyzine in the future.

The authors state that antihistamines have been the first-line drug for allergic diseases and are one of the most commonly prescribed drug classes. The H₁ antihistamines are broken down into multiple groups with cetirizine, levocetirizine, and hydroxyzine falling into the piperazine derivative group. Very rarely are cutaneous side effects, more specifically fixed drug eruptions, seen with these drugs. It should be noted that in vivo, 45% of hydroxyzine is metabolized into cetirizine and then into the R-enantiomer of cetirizine, levocetirizine.

Nivolumab-Induced Myasthenia Gravis³

A 76-year-old woman with an 8-year history of stage IV non-small-cell lung cancer (NSCLC) had recently initiated therapy with nivolumab. After receiving her second dose of nivolumab, she experienced left ptosis (drooping or falling of the upper eyelid). In addition, after receiving her second dose of nivolumab, the patient complained of mild fatigue on day 23 of treatment and on day 26 she presented again with left ptosis. Her medical examination and blood work was normal except for elevated aspartate transaminase of 424 IU/L (normal range, 13-37 IU/L), alanine transaminase (ALT) of 329 IU/L (normal range, 8-45 IU/L), and creatinine kinase of 6566 IU/L (normal range, 49-189 IU/L). Increased creatinine kinase associated with myasthenia gravis (MG) is only seen in about 0.9% of patients. She had some decreased grip strength, but that was believed to be due to her preexisting cervical spondylosis. Her quantitative MG score was 7. According to the Myasthenia Gravis Foundation of America I, the patient was categorized as having mild generalized MG evidenced by a normal anterior mediastinum without obvious thymoma, found through a chest computed tomography, and an improvement in her muscle weakness after an edrophonium test. Myasthenia gravis is an autoimmune neuromuscular disease produced by autoantibodies against acetylcholine receptors. Specifically, MG caused by immune checkpoint inhibitors, such as nivolumab, has an unclear mechanism, but the authors believe that it may be due to

autoreactive T-lymphocyte activation through the blockade of programmed cell death 1 (PD-1).

At follow-up, the patient's creatinine kinase was decreased, but on the 29th day, she developed diplopia and dysphagia. Rapid diplopia and dysphagia are a sign of myasthenic crisis or an acute exacerbation. She was given intravenous immunoglobulin (IVIG) for 2 days, but her condition worsened as she developed shortness of breath and severe dysphagia. This respiratory failure demonstrates a potential risk for severe myasthenic crisis. The patient had an arterial blood gas analyses and it was found that her partial pressure of oxygen in arterial blood was 65.7 mm Hg (normal range, 75-100 mm Hg), partial pressure of carbon dioxide in arterial blood was 64.6 mm Hg (normal range, 38-42 mm Hg), and a pH of 7.295 (normal range, 7.38-7.42). Her condition continued to deteriorate, and she needed noninvasive positive pressure ventilation (NIPPV) and three sessions of plasma exchange (PE) therapy. Her anti-acetylcholine receptor antibody (ARAB) was 1.5 nmol/L (normal range, <0.2 nmol/L) and her anti-muscle-specific tyrosine kinase antibody level was normal. The patient was diagnosed with complicated myasthenic crisis caused by nivolumab evidenced by eyelid ptosis, cervical muscle weakness, and high ARAB levels.

After this diagnosis, the patient was treated with four sessions of immunoadsorption plasmapheresis (IA) therapy and IVIG for 5 days. Her symptoms improved and NIPPV was withdrawn on the 65th day. She received prednisolone 10 mg/day and her forced vital capacity increased to 94.2% with a quantitative MG score of 6.

Nivolumab, a fully human IgG4 monoclonal antibody which binds to the PD-1 receptor, blocking the interaction with its ligands (PD-L1 and PD-L2) and restoring immune competence against tumor cells. The authors stated that the occurrence of MG was studied for nivolumab in a postmarketing surveillance safety study from July 2014 to February 2017, and the total incidence rate was only 0.1%. When a comprehensive literature search was conducted of relevant published studies, it was found that MG in patients receiving nivolumab was associated with a median age of 75, predominantly melanoma patients, while NSCLC was the second most common oncologic condition. There were only 11 cases of MG caused by anti-PD-1 antibodies, such as nivolumab. The onset in these cases occurred mostly in the early phase between 1 and 4 cycles. In addition to this, the authors also found 4 case reports in which patients with previous MG were treated with nivolumab; these patients experienced disease flares.

In conclusion, oncologists should consider the safety aspect of nivolumab before prescribing it to patients. The clinical features of MG caused by nivolumab are different from classical MG evidenced by early onset once an immune checkpoint inhibitor is started; it varies from mild to severe, and once the disease progresses, it is usually associated with high frequencies of myasthenic crisis or acute exacerbations, and creatine kinase (CK) elevations. Careful monitoring is

necessary with nivolumab because symptoms can look mild; CK should be monitored as well as the patient should be asked about muscle weakness.

Nivolumab-Induced Cholangitic Liver Disease⁴

A 79-year-old man began taking up to 4 courses of nivolumab to treat progressive metastatic NSCLC. Nivolumab is typically dosed 240 mg once every 2 weeks or 480 mg once every 4 weeks until disease progression or unacceptable toxicity for NSCLC. On day +62 from the initiation of nivolumab, the patient presented to the hospital with itching and jaundice. Lab results showed grade 4 elevation in total bilirubin and gamma-glutamyl transpeptidase (GGT) and grade 3 elevation in alkaline phosphatase (AP) and ALT levels. Upon assessment, biliary tree distention, liver metastases, portal thrombosis, viral infections, and storage diseases were excluded. The patient did not have a history of concomitant potentially hepatotoxic medications or herbal products, autoimmune disorders, past liver damage, or history of liver disease, and gamma-globulin values appeared normal. All autoantibodies were negative except antinuclear antibodies, and human leukocyte antigen-DR11 was detected. A percutaneous liver biopsy and pathology report showed drug-induced liver damage with features of cholangitis.

Subsequently, nivolumab was discontinued and the patient started on methylprednisolone (1 mg/kg) and ursodeoxycholic acid (UDCA) (15 mg/kg) on day +2 from hospitalization. At 14 weeks, the bilirubin levels reached normal range; however, grade 3 elevation of GGT and grade 1 elevation of AP/ALT persisted at 16 weeks. The steroid dose was lowered to 5 mg daily and UDCA was continued at the same dose. On day 152 since the start of nivolumab, the patient died due to progressive disease.

The authors stated there have been reports of immune-related liver toxicity associated with nivolumab treatment, but cholestatic forms have not been previously described. In this patient's case, the time to onset was similar to that reported in the registration trials, although the time to resolution was longer. It is common to use steroids in the treatment autoimmune hepatitis/cholangitis and nivolumab-induced liver injury; however, the responses to steroids can be variable. Currently, we do not fully understand the mechanism of nivolumab-induced liver injury. It can be reasoned that nivolumab-induced liver injury represents heterogeneous forms of immune-mediated liver damage that ranges from autoimmune hepatitis to forms with cholangitic liver disease. Because these may manifest in different ways due to various clinical, biochemical, and histopathologic features, the cases may result in different outcomes and require different therapeutic strategies. In this case, it is likely that nivolumab may have led to the cholangitic liver disease by an immune-mediated mechanism and subsequent hepatocellular damage. To detect earlier cholestatic liver

disease, it is recommended to monitor the GGT and AP levels in addition to transaminases and bilirubin.

Torsade de Pointes Caused by Psychiatric Polypharmacy⁵

A 69-year-old Caucasian man presented to the hospital with a chief complaint of altered mental status and generalized weakness, with ingestion of an unknown quantity of diphenhydramine multiple hours before presentation. His medical history includes bipolar disorder, coronary heart disease (status: post 4-vessel coronary artery bypass 6 months before presentation), ischemic cardiomyopathy (15% ejection fraction), biventricular permanent pacemaker/internal cardioverter defibrillator, hypertension, type 2 diabetes, moderate aortic stenosis, and cannabis/tobacco use disorder. According to previous mental health notes, the patient's mental diagnosis has varied between a psychotic disorder (schizophrenia) and more consistently a bipolar disorder with past reports of hyperreligiosity, hypomania, and hypersexual behavior. On admission, the ECG results showed polymorphic ventricular tachycardia consistent with Torsade de Pointes (TdP). Bolus amiodarone was administered, and the patient became sedated and intubated. Routine ECG monitoring displayed QTc readings were 504, 547, 747, and 525 (ms) during the first 24 hours after admission. The patient's troponin level was measured at 1.77 ng/mL (normal range, <0.01 ng/mL), potassium at 3.5 mmol/L (normal range, 3.5-5.0 mmol/L), and magnesium at 2.0 mg/dL (normal range, 1.6-3.0 mg/dL).

A review of the patient's outpatient medications included lorazepam, fluoxetine, fluphenazine, ropinirole, and diphenhydramine. Patient had been on fluphenazine for 1 year prior to admission. According to the institution's pharmacy records, amiodarone, digoxin, potassium, clopidogrel, and carvedilol had not been refilled for several months, which indicated a possible significant nonadherence issue. In addition, the patient had been prescribed a 7-day course of ciprofloxacin for the treatment of a urinary tract infection approximately 1 month ago. Based on the medication history, all outpatient medications with known QTc prolonging effects were held at the time of admission, including fluoxetine and fluphenazine. In addition, a serum fluoxetine level was obtained to assess toxicity and because of its extended half-life.

In response to concerns and symptoms of acute hyperactive delirium, the patient was initiated on olanzapine which has sedative effects and relatively low risk for QTc prolongation. After 2 oral doses of olanzapine 5 mg separated by approximately 12 hours, polymorphic ventricular tachycardia/TdP reappeared on ECG with a QTc measurement of 722 ms. The patient was administered intravenous magnesium and one manual defibrillation shock, which returned him to normal sinus rhythm. After the recurrence of TdP, delirium management was transitioned to lorazepam rather than antipsychotics, which kept the patient stable throughout his hospital course.

While in the hospital, the patient received continuous psychiatric care and an assessment of outpatient medications that have cardiovascular concerns and delirium management effects. In addition, fluoxetine and fluphenazine were discontinued due to the risk of QTc prolongation, although normal serum fluoxetine and norfluoxetine levels were present.

The authors noted that this case report describes an acute, confirmed TdP stemming from the use of multiple medications with the potential for QTc prolongation, active risk factors, and medical comorbidities. As recommended by the current schizophrenia guidelines by the American Psychiatric Association, every patient undergoing significant dose changes in medications known to cause TdP should receive ECG monitoring follow-up.

Trichotillomania Associated With Aripiprazole⁶

A 16-year-old boy diagnosed with attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (multiple physical fights) since age 10 was prescribed aripiprazole. The initial dose was 2.5 mg/day for 1 week which was increased to 5 mg/day. At the follow-up visit, the patient reported hair loss on his right vertex scalp that occurred approximately 1 week after aripiprazole initiation. The baseline laboratory values were reported within normal ranges, and physical examination found no other abnormality. At a subsequent visit with the dermatologist to evaluate his hair loss, the patient revealed an uncontrollable urge to pull out his hair (trichotillomania) and a sense of relief after pulling his hair out. Aripiprazole was discontinued and after 2 days of stopping aripiprazole, the symptoms disappeared. The patient was followed up for 2 months with no medication and then methylphenidate was initiated for his ADHD. No urge or behavior of pulling out hair has been reported, and the hair started to grow back on his vertex scalp.

The authors evaluated that in this patient, the appearance of trichotillomania seemed to only correlate with the use of aripiprazole; it is suggested that aripiprazole is indeed associated with the behavior. The patient had never experienced trichotillomania in the past and did not experience any stressful social life events, which is one of the important factors in the cause of trichotillomania. Trichotillomania associated with atypical antipsychotics is not well elucidated in the literature. Animal studies have shown that depletion of serotonin (5-HT) has been associated with impulsivity and repetitive motor behavior, which are the characteristics of obsessive-compulsive disorder, impulsive control disorder symptoms, and trichotillomania. By this reason, although selective serotonin reuptake inhibitors (SSRIs) are often believed to be effective in the treatment of trichotillomania, recent research findings actually have shown that hair pulling occurs unconsciously and does not respond well to SSRIs. This may be caused by

dopaminergic pathways acting on the mesolimbic system to trigger trichotillomania, and studies have shown antipsychotics olanzapine, haloperidol, and aripiprazole to be effective therapies.

Aripiprazole is a second-generation antipsychotic agent that behaves as a partial agonist at D2, D3, and 5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors. At low doses, aripiprazole may also act as an agonist rather than an antagonist at dopamine receptors. D3 receptors have been shown to play a crucial role in the pathophysiology of schizophrenia, major depressive disorder, and substance use disorder, but the patient's past medical history involves none of these. There has been some suggestion in the literature that D3 receptors may play a significant role in emerging impulse-control behaviors or obsessive-compulsive symptoms such as pathological gambling, hypersexuality, binge and compulsive eating, compulsive shopping, excessive hobbies, and excessive controlling. In this case, the patient's underlying comorbidity of ADHD may have been a factor in the dopaminergic changes associated with trichotillomania.

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