

ISMP Adverse Drug Reactions

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Joel Shuster, PharmD, BCPP*

The purpose of this feature is to heighten awareness of specific adverse drug reactions (ADRs), to discuss methods of prevention, and to promote reporting of ADRs to the FDA's MEDWATCH program (800-FDA-1088). If you have reported an interesting preventable ADR to MEDWATCH, please consider sharing the account with our readers. Write to Dr. Shuster at ISMP, 1800 Byberry Road, Suite 810, Huntingdon Valley, PA 19006 (call 215-947-7797; fax 215-914-1492; e-mail joel.shuster@tenethealth.com). Your report will be published anonymously unless otherwise requested. This feature is provided by the Institute for Safe Medication Practices in cooperation with the FDA's MEDWATCH Program and Temple University School of Pharmacy. ISMP is an FDA MEDWATCH partner.

COGNITIVE IMPAIRMENT WITH STATINS?

A group of pharmacists and physicians from Mississippi recently published a report about two patients who developed mem-

ory impairment and/or cognitive decline with the use of two 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins").¹

The following is a summary of one of their case reports.

A 68-year-old woman with a 20-year history of high blood pressure was referred for reevaluation of her therapy. She had been taking lisinopril, atenolol, and estradiol; hydrochlorothiazide was added for blood pressure con-

trol. When her lipid panel showed elevated levels, she was started on atorvastatin (*Lipitor*) 10 mg daily. After 6 weeks, her lipid levels were markedly improved.

About 9 months later, the patient's daughter noted that her mother was displaying "noticeable memory impairment, cognitive decline, and behavior changes." Apparently, the patient was forgetting scheduled appointments and began to neglect her physical fitness program, to which she had been quite dedicated. She complained of weakness in the extremities and a "lack of energy." Because the patient's daughter thought that the new symptoms started with the addition of the cholesterol-lowering drug, she told her mother to stop taking atorvastatin.

Within one week, the patient's physical and cognitive symptoms showed improvement. A month later, the patient was rechallenged with atorvastatin; 3 weeks later,

*Professor of Clinical Pharmacy Practice, Temple University School of Pharmacy, Philadelphia; Clinical Pharmacist, Medical College of Pennsylvania Hospital, Philadelphia; and Clinical Advisor and Trustee, Institute for Safe Medication Practices, Huntingdon Valley, PA 19006.

she demonstrated similar “cognitive impairment and other symptoms.” The drug was stopped again. When she was seen a few weeks later, she reported that she was better.

Because of a strong family history of cardiovascular problems, it was decided that the patient’s cholesterol level should be lowered. Simvastatin (*Zocor*) was begun at 20 mg daily. At the 7-week mark, the patient and her daughter noted the distinct return of memory impairment and cognitive decline. Again, the statin was stopped and symptoms resolved within 3 weeks.

The authors point out that there is only one other similar report in the literature, but that at least three of the package inserts for agents in this class state that memory loss is a potential adverse effect. They provide a short review of the many uses of the statin class and refer to the possible use of these agents in the prevention of Alzheimer’s disease, which is certainly paradoxical given this report.

PREMATURE EJACULATION AFTER DISCONTINUING AN SSRI

A 43-year-old male had been treated for depression with citalopram (*Celexa*) for one year.² Because of some decrease in libido and orgasmic delay, the patient requested that citalopram be discontinued. The dose was decreased from 20 mg to 10 mg for 1 month and then the drug was discontinued.

Within a week of stopping the antidepressant, “the patient noticed that, during sexual intercourse, his genitals seemed to be extremely sensitive and orgasm was achieved within approximately 1 minute.” The premature ejaculation continued over the next

few weeks. Citalopram was restarted at the 10 mg dose level and the symptoms resolved. However, continued attempts at even lower and slower tapering doses led to the same symptomatology. The patient eventually returned to the 20 mg dose of citalopram because his depression and irritability resurfaced. He continued to have decreased libido and mild orgasmic delay.

The patient tried escitalopram (*Lexapro*) when it became available, but this agent caused insomnia and decreased libido. He began taking citalopram again and still suffers with its sexual adverse effects. The authors of the report state that the patient “found these adverse effects preferable to a recurrence of depressed mood or premature ejaculation and did not wish to change his therapy.”

The authors believe that their report is the first to describe premature ejaculation occurring after discontinuation of an SSRI. They provide a brief review of the proposed mechanisms by which serotonergic antidepressants cause sexual dysfunction.

ADVERSE REACTIONS TO TRIMETHOPRIM/SULFAMETHOXAZOLE IN PATIENT WITH AIDS

A 37-year-old woman with AIDS was admitted to a hospital with generalized weakness, fever, and nonproductive cough of 3 weeks’ duration.³ She had not been taking her prescribed antiretroviral therapy or other prophylactic medications, which consisted of zidovudine/lamivudine, amprenavir, ritonavir, itraconazole, trimethoprim/sulfamethoxazole (TMP/SMX), and azithromycin. She had been treated in the hospital 8 months earlier for disseminated histoplasmosis. Her treatment had

consisted of IV amphotericin B lipid complex followed by oral itraconazole.

The patient underwent extensive laboratory testing. An abdominal ultrasound “showed marked hepatomegaly, with the right lobe measuring 18 cm in length.” It was presumed that the patient had a relapse of disseminated histoplasmosis. She was started on amphotericin B lipid complex. Because she had a 3-week history of a non-productive cough and no prophylaxis for *Pneumocystis carinii* pneumonia (PCP), TMP/SMX was initiated as empiric therapy at an IV dose of 15 mg/kg/day. Ibuprofen and diphenhydramine were used as premedicants for her amphotericin infusions. The only other medication ordered for this patient was acetaminophen for fever.

Two days after these medications were started, the patient developed “a high-frequency tremor that involved both upper extremities, was present at rest, and worsened with activity.” Her serum creatinine had risen to 5.6 mg/dL (normal 0.5 to 1.5 mg/dL) from her admission value of 2.5 mg/dL. Her serum potassium was also increased. One day later, the serum creatinine was 5.9 mg/dL. Ibuprofen and TMP/SMX were discontinued because of concern about renal toxicity.

On the fifth day after amphotericin and TMP/SMX were first administered, the patient developed severe abdominal pain, nausea, and vomiting. Her abdomen was distended and extremely tender. Her tremor had worsened. Lab findings revealed increased amylase and lipase levels. A diagnosis of acute pancreatitis was made after a computed tomography scan of the patient’s abdomen.

Within 72 hours of discontinu-

ing the TMP/SMX, the patient's abdominal symptoms and tremor resolved. The amylase and lipase levels fell to half of their elevated values and the serum creatinine fell to baseline over 5 more days. The histoplasmosis diagnosis was confirmed by a "strongly positive" urinary assay for *Histoplasma capsulatum*. The patient improved after receiving a total of 14 days of amphotericin therapy. She was given oral fluconazole for continued treatment of histoplasmosis and dapsone as PCP prophylaxis.

The authors discuss the high incidence of ADRs associated with TMP/SMX therapy in patients with AIDS. They state that tremor, pancreatitis, and adverse renal effects have all been reported with this combination agent. They believe that their report is the first that describes all three of these problems in the same patient. The authors describe the adverse effects of the sulfamethoxazole and trimethoprim moieties and provide a useful bibliography.

NEUTROPENIA ASSOCIATED WITH PIPERACILLIN-TAZOBACTAM

A medical group in Spain recently assessed hospital records over a 7-year period and found 41 cases in which patients were treated for bone-related infections with the combination agent piperacillin-tazobactam (*Zosyn* in the US).⁴

The authors reported that 34% of the patients developed neutropenia. Four of the cases were considered severe and three patients required therapy with granulocyte colony-stimulating factor. The most important factor in the development of neutropenia seemed to be a high cumulative dose of the antibiotic combination. Because bone-related infections require long-term therapy with appropriate antibiotics, the mean course of therapy

with these patients was almost 27 days.

The authors pointed out that other reviews of this therapy have not mentioned neutropenia. They state that prior studies have only looked at therapies lasting less than 2 weeks and strongly recommend that frequent hematologic monitoring be performed in any patient receiving piperacillin-tazobactam for more than 14 days.

HYPERTENSIVE CRISIS WITH ANTIDEPRESSANT

A 37-year-old woman was being treated for "anxiety, depression, and alcohol abuse" with a combination of quetiapine and disulfiram.⁵ She had been on this regimen for 6 weeks. Her blood pressure was normal. Because of worsening anxiety, venlafaxine and risperidone were added. (Editor's note: Quetiapine and risperidone are not indicated for anxiety states and appear to be poor choices for therapy in a patient with no history of psychosis.) After using the new medications for a little more than a week, the patient developed blurred vision. Her psychiatrist discontinued risperidone.

The patient's eye problem continued, so she went to an ophthalmologist. At the eye clinic, her blood pressure was measured at 220/140 mm Hg and "cotton wool spots were identified in both eyes." She was admitted to the hospital, her medications were held, and labetalol and nitroprusside were given intravenously to lower her blood pressure. A complete workup found no renal disease, but a magnetic resonance imaging of her brain demonstrated changes "consistent with hypertensive encephalopathy." The patient stayed in the hospital for 3 days and was discharged with oral metoprolol therapy for hypertension.

The authors suggested that the disulfiram may have inhibited the metabolism of venlafaxine through its inhibiting effect on the CYP3A4 enzyme. The patient received only 75 mg of venlafaxine daily. Venlafaxine is known to cause a slight increase in diastolic blood pressure in a small percentage of normal patients. The authors warn against using inhibitors of CYP3A4 in combination with this antidepressant.

IMATINIB-ASSOCIATED PULMONARY ALVEOLAR PROTEINOSIS

Recently, a brief letter was sent to the editors of *The American Journal of Medicine* describing a case of a 29-year-old woman who developed pulmonary alveolar proteinosis after receiving treatment for chronic myelogenous leukemia (CML).⁶

The patient was treated for CML with hydroxyurea for 3 years. One year later, imatinib mesylate (*Gleevec*) was started at a dose of 400 mg daily. After a year of imatinib therapy, the patient developed dyspnea on exertion and a dry cough. She underwent bronchoscopy, which revealed pulmonary alveolar proteinosis. Imatinib mesylate was discontinued, and she was treated with an application of hydroxyurea and therapeutic lavage. She had a good response and her symptomatology improved.

The authors pointed out that the alveolar proteinosis may have been related to the CML itself. However, because the symptoms developed while the patient was receiving imatinib and resolved after its discontinuation, the authors suggested that this may be a new adverse effect that must be considered when using the new and rather safe agent.

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