



NATIONAL PBM BULLETIN

MAY 13, 2016

DEPARTMENT OF VETERANS AFFAIRS
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
VISN PHARMACIST EXECUTIVES (VPEs), AND THE CENTER FOR MEDICAL SAFETY (VA MedSAFE)

ANTIPSYCHOTIC AGENTS AND SAFETY ISSUES

ARIPIRAZOLE AND IMPULSIVE BEHAVIOR

I. ISSUE

FDA reports uncontrollable and excessive urges for gambling, shopping, binge eating and sexual behavior associated with the use of aripiprazole (Abilify, Abilify Maintena, Aristada).

II. BACKGROUND

Aripiprazole (Abilify, Abilify Maintena, Aristada) is an atypical antipsychotic indicated for the treatment of schizophrenia, bipolar disorder, depression (adjunctive treatment), irritability associated with autistic disorder, and Tourette's disorder.

III. DISCUSSION

FDA identified 184 case reports (167 FDA Adverse Event Reporting System [FAERS] cases and 17 medical literature cases) between November 2002 through January 2016, indicating an association between aripiprazole and impulse-control problems: pathological gambling (n=164); compulsive sexual behavior (n=9); compulsive buying (n=4); compulsive eating (n=3); and multiple impulse-control problems (n=4).

Of the 167 FAERS cases:

- Compulsive behavior began after initiating aripiprazole treatment and resolved within days to weeks of dose reduction or discontinuation.
- None had a history of pathological gambling, compulsive sexual behavior, binge eating, or compulsive shopping prior to starting treatment.
- None had concurrent substance abuse disorder or symptoms of mania at the time they developed impulse-control problems.

Of the 17 cases from the medical literature:

- All cases resolved completely when aripiprazole was discontinued.
- Four cases reported reactivation of compulsive behaviors within days to weeks when aripiprazole was restarted.

IV. PROVIDER CONSIDERATIONS/RECOMMENDATIONS

Healthcare professionals should:

- Inform patients and caregivers of the risk of impulsive behavior, such as uncontrollable and excessive urges for gambling, shopping, binge eating and sex associated with the use of aripiprazole (Abilify, Abilify Maintena, Aristada).
- Ask patients whether they are experiencing new or increasing urges while receiving this agent.
- Closely monitor for new or worsening uncontrollable urges in patients at higher risk for impulse-control problems, including: those with a personal or family history of obsessive-compulsive disorder, impulse-control disorder, bipolar disorder, impulsive personality, alcoholism, drug abuse, or other addictive behaviors.
- Consider reducing the dose or stopping the medicine if new or increased impulsive or compulsive behaviors develop.
- Be aware that impulsive behaviors have been reported with dopamine agonists used to treat restless syndrome and Parkinson disease. Aripiprazole has been prescribed off-label to treat Parkinson-related behavior disturbances because of its partial agonist activity at the D2 receptors.
- Recognize that aripiprazole might be prescribed for other off-label indications, such as:
 - Dementia, as aripiprazole is often used to treat behavioral disorders despite the boxed warning.
 - PTSD as second generation antipsychotics are still prescribed.
 - Chorea of Huntington Disease
 - Cocaine dependence
 - Trichotillomania



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ANTIPSYCHOTIC AGENTS AND SAFETY ISSUES *(continued from page 1)*

Providers should continue to report any adverse reactions with the use of aripiprazole products by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, or by mail).

V. REFERENCES

1. FDA Drug Safety Communication: FDA warns about new impulse-control problems associated with mental health drug aripiprazole (Abilify, Abilify Maintena, Aristada). <http://www.fda.gov/Drugs/DrugSafety/ucm498662.htm>. (Accessed May 3, 2016)

OLANZAPINE AND DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

I. ISSUE

FDA reports Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) associated with the use of olanzapine (Zyprexa, Zyprexa Zydis, Zyprexa Relprevv, and Symbyax, and generics) and will add a new warning concerning this to the label of all olanzapine-containing drugs.

II. BACKGROUND

Olanzapine (marketed as Zyprexa, Zyprexa Zydis, Zyprexa Relprevv, and Symbyax, and generics) is an antipsychotic used to treat schizophrenia, bipolar disorder, depression associated with bipolar 1 disorder, and treatment resistant depression. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a potentially fatal drug reaction with a mortality rate of up to 10%. Although pathogenesis is unclear, genetic and immunologic factors, such as detoxification defects in the drug metabolism pathway may result in toxic metabolite formation and an immune response.

III. DISCUSSION

FDA identified 23 cases of DRESS reported with olanzapine worldwide since 1996. Of the 23 cases:

- Median time to onset was approximately 19 days after initiation of treatment with olanzapine.
- Median duration of olanzapine treatment was 2 months.
- Median olanzapine dose was 20mg per day, however DRESS was reported at doses as low as 5mg per day.
- 1 fatality occurred from acute cardiac failure related to olanzapine. The patient had an initial episode of DRESS followed by a relapse during hospitalization.
- 22 nonfatal cases reported a serious outcome and 18 of these required hospitalization.
 - 9 cases reported resolution of symptoms after discontinuation of olanzapine.
 - 1 reported recurrence of DRESS after restarting olanzapine.
 - 6 reported positive confirmatory test results and work-up specific for olanzapine reactions.

IV. PROVIDER CONSIDERATIONS/RECOMMENDATIONS

The FDA recommends that healthcare professionals should:

- Inform patients about the risk DRESS associated with the use of olanzapine-containing products.
- Explain the signs and symptoms of DRESS to patients and tell them when to seek immediate care if signs and symptoms occur, such as :
 - Cutaneous reaction (such as rash or exfoliative dermatitis) that can spread to all parts of the body.
 - Eosinophilia (higher-than-normal number of infection-fighting white blood cells called eosinophils that can cause inflammation, or swelling)
 - Fever
 - Lymphadenopathy (swollen lymph glands in the neck, armpits or face)



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ANTIPSYCHOTIC AGENTS AND SAFETY ISSUES *(continued from page 2)*

OLANZAPINE AND DRUG REACTION WITH EOSINPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

- One or more systemic complications such as hepatitis, myocarditis, pericarditis, pancreatitis, nephritis, and pneumonitis (injury to organs including the liver, kidneys, lungs, heart, or pancreas, and can lead to death).
- Instruct patients to not stop taking olanzapine or change their dose without first talking to their health care professional and that sudden stopping of the medicine can be harmful without direct supervision.
- If DRESS is suspected, providers should discontinue olanzapine treatment immediately.
- Since there is currently no specific treatment for DRESS, the important ways to manage DRESS are early recognition of the syndrome, discontinuation of the offending agent as soon as possible, and supportive care. Treatment with systemic corticosteroids should be considered in cases with extensive organ involvement.
- Recognize other off-label uses of olanzapine, such as:
 - Chorea of Huntington Disease
 - Delusional parasitosis
 - Stuttering
 - Tardive dyskinesia
 - Tourette's syndrome

Providers should continue to report any adverse reactions with the use of olanzapine products by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, or by mail).

V. REFERENCES

1. FDA Drug Safety Communication: FDA warns about rare but serious skin reactions with mental health drug olanzapine (Zyprexa, Zyprexa Zydis, Zyprexa Relprevv, and Symbyax). <http://www.fda.gov/Drugs/DrugSafety/ucm499441.htm>. (Accessed May 10, 2016)

ACTIONS

- **Facility Director** (or physician designee): Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives**: Forward this document to all appropriate providers and health care staff (e.g., **primary care providers, mental health specialists, including contract providers, etc.**). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D**: Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).