Maryland Medicaid Pharmacy Program

Pharmacy News&Views

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Maryland Department of Health and Mental Hygiene /Office of Systems, Operations and Pharmacy

Clinically Significant Drug Interactions Involving Antipsychotics and Anticonvulsants

Antipsychotics and prolonged QTc

Antipsychotics are known agents that prolong the QTc interval, which exposes patients to the risk of potentially fatal ventricular arrhythmias[1]. Most antipsychotic agents effect the rapid-potassium channels, which are crucial to the repolarization of cardiac ventricular muscles during the cardiac action potential[2]. Prolongation of the QTc is associated with the development of Torsades de Pointes and cardiac death. Many medications have been withdrawn from the US market by the Food and Drug Administration (FDA) due to QTc prolongation, including cisapride (Propulsid®) and terfenadine (Seldane®)[3].

QTc prolongation associated with antipsychotic use varies between agents, with thioridazine, haloperidol (IV) and ziprasidone having the most literature to support a Black Box Warning. Fluphenazine, haloperidol (PO/IM), and risperidone have a moderate risk. Olanzapine and quetiapine present a low risk, with aripiprazole having the lowest, minimal risk in this drug class. The risk is considered to be dose-dependent, with higher doses associated with an increased risk.

Drug interactions are a significant factor in drug exposure of antipsychotics. Most antipsychotics are metabolized through the cytochrome P450 system, with 3A4 and 2D6 being major pathways[4]. Use with inhibitors of these pathways (i.e. "azole" antifungals) can greatly increase the risk of QTc prolongation in otherwise stable patients. This risk is also increased with concomitant use of other drug classes with QTc prolongation potential (i.e. "quinolone" antibiotics, methadone).

Cytochrome P450 Inhibitors

3A4	2D6
amiodarone	amiodarone
diltiazem	fluoxetine
"azole" antifungals *(fluconazole, itraconazole, ketoconazole)*	haloperidol
macrolides *(excluding azithromycin)*	paroxetine
protease inhibitors *(ritonavir)*	propafenone
omeprazole	ritonavir
verapamil	sertraline
grapefruit juice	thioridazine

Anticonvulsants and skin reactions

Anticonvulsants are known agents indicated in the development of cutaneous reactions[5]. More serious reactions include Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), and Stevens-Johnson syndrome (SJS). SJS, a form of Toxic Epidermal Necrolysis (TEN), can be life-threatening if not caught and treated immediately. Both reactions include systemic symptoms of fever and fatigue, in addition to worsening skin lesions.

Valproate, lamotrigine, phenytoin and carbamazepine are commonly indicated in the development of skin reactions, though case reports are available for all agents in this class, including levetiracetam, oxcarbazepine and zonisamide. Skin reactions may be seen immediately or may be delayed up to 3 months from

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exposure to the medications. A dose-dependent risk has been established, with higher doses having a higher risk of skin reactions.

Drug interactions leading to increased drug concentrations are established for many anticonvulsants. Concomitant anticonvulsant use, which is not uncommon, is a risk factor for developing cutaneous reactions, in addition to other neurologic concerns. Interactions are commonly seen with the use of valproic acid/divalproex sodium, as it is an inhibitor of the cytochrome P450 system, as well as other drug metabolism pathways. Specific dosing considerations are outlined for most anticonvulsants to reduce the risk of serious adverse reactions[1].

Pharmacist Interventions for Clinically Significant Drug Interactions

Pharmacist's dispensing at point-of-sale (POS) patient encounters should use the proper drug utilization review (DUR) codes when reviewing these drug interactions. **Alerting the prescribing physician when a major or significant interaction is essential to patient care, in addition to counseling the patient on the issue and offering self-monitoring parameters.** Since many drug interactions occur with acute medication use (i.e. antibiotics for acute infections) it is important that the pharmacist be cognizant of these interactions and able to provide information to other healthcare providers to prevent adverse events from occurring.

As the community pharmacist is well aware, the Maryland Medicaid Pharmacy Program (MMPP) performs Prospective Drug Utilization Review (ProDUR) on submitted claims. ProDUR alerts are designed to prevent and reduce adverse drug interactions and therapeutic duplications. DUR intervention codes include:

DUR Intervention and Outcome Codes

Intervention Codes		Outcome Codes	
MO*	Provider consulted	1A	Filled as is, false positive
RO*	Pharmacist consulted	1B	Filled as is
PO*	Patient consulted	1C	FIlled with different dose
*second character is a zero		1D	FIlled with different directions
		1E	Filled with different drug
		1F	Filled with different quantity
		1G	FIlled, prescriber ok'd

Please remember to always alert the patient to these interactions when patient counseling is offered. Patient self-monitoring is an important step in preventing adverse drug events.

References

1. Micromedex 2.0. TruvenHealth Analytics, Inc.; 2015. Greenwood Village, CO. Solutions; 2015. Available at http://micromedexsolutions.com. Accessed on March 20, 2015.
2. Beach SR, et al. QTc Prolongation, Torsades de Pointers, and Psychotropic Medications. Psychosomatics 2013: 54; 1-13.
3. Food and Drug Administration (FDA). Available at http://www.fda.gov. Accessed March 20, 2015.
4. Ogu C and Maxa J. Drug interactions due to cytochrome P450. Proc (Bayl Univ Med Cent). 200 Oct; 13(4): 421-423.
5. DiPiro, J. T. (2005). *Pharmacotherapy: A pathophysiologic approach*. New York: McGraw-Hill Medical.

Emergency Supply of Medications

When a "non-preferred medication" denial message is received on a submitted fee-for-service claim, the pharmacy should contact the prescriber to either change the medication, or have the prescriber obtain the necessary Prior Authorization (PA). It would be beneficial for the pharmacist to advise the prescriber of alternative drug(s) that do not require a PA. The Preferred Drug List (PDL) is available online at **https://mmcp.dhmh.maryland.gov/pap/SitePages/Preferred%20Drug%20List.aspx**, or through Epocrates. Normally the prescriber can obtain a PA with a phone call to 1-800-932-3918.

When the prescriber is not available to obtain a PA, and the pharmacist in their professional judgment determined that the prescription is needed on an emergency basis, they should contact the Xerox call center at 1-800-932-3918 and request authorization to dispense a 72-hour emergency supply.

The pharmacist should use professional judgment in determining whether an emergency supply is needed. Please take into account the patient's diagnostic and drug history, information about what medications the patient has on hand, and possible recent hospitalization, as well as any mobility, transportation or communication issues that make returning to the pharmacy difficult or expensive.

During the 72-hour window, the pharmacist is to contact the prescriber who must obtain prior authorization before the remainder of the prescription can be dispensed. After prior authorization has been established, the pharmacist can dispense the remainder of the prescription. In the case of sprays, inhalers, eye or ear drops, creams, ointments, antibiotics, etc., it may be necessary to dispense the entire prescription as an emergency supply due to the way the drug is packaged or administered.

A 30-day supply is allowed for atypical antipsychotic medications while awaiting prior authorization for a non-preferred or Tier 2 drug.

For HealthChoice MCO members requiring an emergency supply of non-mental health and non-antiretroviral drugs, the pharmacist must contact the appropriate MCO Pharmacy Benefit Manager and follow their procedures before dispensing an emergency supply.

If at all possible do not let patients leave the pharmacy without medication if there is concern that the patient will be unwilling or unable to return at a later time that day after prior authorization is approved.

Tier 2 and Non-Preferred Antipsychotics for Patients Age 18 Years and Older

The following clinical criteria must be met to obtain prior authorization (PA) for non-preferred and Tier 2 antipsychotics. All other existing policies such as those regarding generic substitution and quantity limit (including dose optimization) continue to apply to these drugs as well. ***Note: Patient will be grandfathered if patient has been on the prescribed drug for greater than 30 days in the previous 120 days.***

Criteria for immediate approval upon review:
- The medication was started on an inpatient unit/other acute care setting; OR
- All preferred antipsychotics are medically contraindicated for the patient.

Other requests will be evaluated based on the following criteria:
- The patient has had an adequate trial (at least 6 weeks at recommended dose) of at least one preferred antipsychotic drug where FDA indicated; AND
- The patient has a FDA indicated diagnosis for the requested medication; AND
- The requested medication complies with the FDA package insert for dosage and frequency.

The use of pharmaceutical samples will not be considered when evaluating the patient's medical condition or prior prescription history for drugs that require prior authorization. All requests are reviewed by a psychiatric clinical pharmacist at the Maryland Medicaid Pharmacy Program or its designee.

Requests for specific drugs/dosage forms

When a drug is available in an oral tablet or capsule dosage form, all other dosage forms (excluding injectable) will only be approved if the patient has medical justification(s) or condition(s) that prevents him/her from taking an oral tablet or capsule.

Invega® oral tablet: Authorization will only be approved if the patient has medical justification for not being able to take risperidone, or if the patient is being prepared for the Invega Sustenna®, then up to a 30 day supply of the tablets will be approved.

More information can be found at the MMPP website at: **http://mmcp.dhmh.maryland.gov/pap/SitePages/paphome.aspx.**

Maryland Department of
Health and Mental Hygiene
Office of Systems,
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Pharmacy News & Views

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Boyd Rutherford, ***Lt. Governor***
Van Mitchell, ***Secretary, DHMH***

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Advisory Keeps You in the Know

Get the latest updates regarding pharmacy issues through the Maryland Medicaid Pharmacy Program (MMPP) e-mail notification service. Called the *Advisory*, these communications provide the pharmacy community with the most up to date information.
Advisories can be found at this link:
http://mmcp.dhmh.maryland.gov/pap/SitePages/paphome.aspx

Please contact the MMPP representative at ***410-767-1455*** if you are currently not receiving e-mail *Advisories* through a pharmacy organization to which you belong.
You can sign up to receive Advisories and the MMPP News & Views via e-mail by going to the website:
www.marylandmedicaidpharmacyinformation.com
and follow the links to enter your e-mail address.

TELEPHONE NUMBERS

Xerox Technical Assistance and Preauthorizations
1-800-932-3918
24 hours a day, 7 days a week

Maryland Medicaid Pharmacy Access Hotline
1-800-492-5231 *(select option three)*
Monday-Friday, 8:00 am to 5:00 pm

Kidney Disease Program
1-410-767-5000 or 5002
Monday-Friday, 8:00 am to 5:00 pm

Breast & Cervical Cancer Diagnosis and Treatment
1-410-767-6787
Monday-Friday, 8:00 am to 4:30 pm

Maryland AIDS Drug Assistance Program
1-410-767-6535
Monday-Friday, 8:30 am to 4:30 pm

Peer Review Program
1-855-283-0876
Monday-Friday, 8:00 am to 6:00 pm
with exception of State Holidays