Maryland Medicaid Pharmacy Program

Pharmacy News&Views

October 2015

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

Clinically Significant Drug Interactions: A focus on Trazodone

Trazodone was first approved in 1981 under the brand name Desyrel®. It is classified as a triazolopyridine antidepressant and was the first drug in this class. The mechanism of action is thought to be related to the potentiation of serotonergic activity in the central nervous system (CNS). Trazodone also has a strong alpha adrenergic receptor antagonist effect. For this reason, it is thought to have an anti-anxiety effect, and has been studied for insomnia in depressed patients. Based on these studies, low dose trazodone is commonly utilized as an adjunct.

To accomplish antidepressant effects, the dosing of trazodone is recommended as 150 mg in divided doses to start, with a titration of up to 400 mg. In contrast, dosing for insomnia is limited to 50-100 mg daily at bedtime. It is not known what effect is seen with low dose trazodone in relation to antidepressant effects, or serotonergic effects, though based on the dosing recommendations it theoretically would be subtherapeutic effects, if used as monotherapy.

In This Issue

There are two major drug interactions of concern with the use of trazodone. The first is the increased risk of QTc prolongation when given concurrently with other medications known to prolong the QTc interval, or with medications that increase levels of trazodone *in vivo*. Drug interactions are mediated via the cytochrome P450 3A4 system, as trazodone is extensively metabolized via this pathway. Known inhibitors include cyclosporine, diltiazem, azole antifungals (fluconazole, ketoconazole, itraconazole), macrolide antibiotics (excluding azithromycin), omeprazole and protease inhibitors. Amiodarone inhibits CYP450 3A4 as well as prolongs the QTc interval. Other antiarrhythmics, such as disopyramide, dofetilide and sotalol, as well as other agents that prolong the QTc interval (haloperidol, ziprasidone, ondansetron), can have additive effects. The second major drug interaction is increased risk of serotonin syndrome with concomitant use of another medication that increases serotonin levels. These medications include antidepressants – specifically the selective serotonin reuptake inhibitors (SSRIs), as well as over-the-counter (OTC) agents like dextromethorphan and St. John's Wart. Signs and symptoms of serotonin syndrome include hyperthermia, myoclonus, tachycardia, mental confusion, hallucinations, and coma.

If a patient is prescribed trazodone it is important to complete a full prescription profile review, in addition to a comprehensive medication reconciliation to assess non-prescription or OTC medication use. Patient counseling on the risk of drug interactions, even with low dose trazodone, as well as signs and symptoms to monitor during treatment, should be provided to each patient to reduce the risk of harm.

<u>References:</u>

1. Trazodone. Micromedex 2.0. TruvenHealth Analytics, Inc.; 2015. Greenwood Village, CO. Solutions; 2015. Available at http://micromedexsolutions.com. Accessed on September 18, 2015.
2. Brogden RN et al. Trazodone: a review of its pharmacological properties and therapeutic use in depression and anxiety. Drugs 1981; 21(6): 401-429.
3. Kaynak H et al. The effects of trazodone on sleep in patients treated with stimulant depressants. Sleep Med 2004; 5(1): 15-20.

Updates to Clozapine REMS program

Clozapine, a medication used in the treatment of refractory schizophrenia, has an updated safety program. The Food and Drug Administration released a new Risk Evaluation and Mitigation Strategy (REMS) program to simplify reporting standards for prescribers, pharmacies and patients.

Important: Prescribers and pharmacies will need to be certified to participate in the new Clozapine REMS program, which is scheduled for implementation starting October 12, 2015. Instructions for certification appear at the bottom of this article. Beginning in December, you may not order or dispense clozapine unless your pharmacy is certified and the prescriber is certified, even if the patient is already receiving the medication.

The new program will replace existing programs maintained by individual drug manufacturers. Clozapine is known to cause neutropenia, a serious adverse event. The new program will be a centralized database for monitoring patients receiving therapy. The goal is to reduce the burden of reporting requirements, while maintaining the safe use of the medication. All current patients receiving clozapine should be transitioned into the new program automatically. Pharmacies and prescribers should make sure their patients' information transferred correctly after October 12, 2015. The reporting requirements will be simplified to use the Absolute Neutrophil Count (ANC) as a marker of neutropenia, instead of a full Complete Blood Count (CBC) panel to monitor white blood cell count (WBC). In addition, to simplifying reporting requirements, the new program will change the threshold for holding therapy to allow patients to continue on the medication if a clear benefit is seen. Also, patients who previously were ineligible for therapy due to benign ethnic neutropenia (BEN) will now be able to receive treatment.

To certify, prescribers and pharmacists must review the prescribing information for clozapine and the *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers.* They must also successfully pass the Knowledge Assessment for Healthcare Providers and complete and submit the Clozapine REMS Enrollment Form. These materials are available at
http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=351.

Additionally, beginning in December 2015, outpatient pharmacies will be required to obtain a pre-dispense authorization code to process clozapine prescriptions. More information can be found at
http://www.fda.gov/Drugs/DrugSafety/ucm461853.htm

A Review of Opioid Conversions

Opioid analgesics are commonly prescribed medications for short or long-term use in the management of moderate to severe pain. Dosing is usually individualized based on the patient and indication. For someone who is considered "opioid-naïve," lower starting doses are recommended for these medications to minimize the risk of serious adverse outcomes, including central nervous system (CNS) depression (manifested as drowsiness or sedation) and respiratory depression (slowed breathing). An opioid-naïve patient is someone who does not regularly take opioids on a consistent basis. They may have been exposed to opioids at some point, but their body has not built up a tolerance to the effects of the medication.

Opioid tolerance can be defined as a decrease in pharmacologic response following repeated or prolonged administration of opioids which occurs over time. There are many mechanisms of opioid tolerance, including pharmacokinetic (e.g. production of metabolites and metabolic enzyme activity) and pharmacodynamic (e.g. receptor binding and cross-sensitivity) aspects. Opioid tolerance is often seen in patients who suffer from chronic pain. For instance, in the prescribing information available for Oxycontin® from Purdue Pharma, opioid tolerance is defined as patients who ingest 60 mg of morphine per day (or the analgesic equivalent) for at least 1 week. Since opioid tolerance is unique to each patient, this dose and timeframe is a general rule, and some patients may require a lower dose or longer timeframe before tolerance is seen. Using the Equianalgesic Opioid Dosing table, you can extrapolate the dose of each individual drug converted to morphine oral equivalents. For instance, to achieve an equianalgesic dose of morphine 60 mg, a patient would need to ingest 40 mg of oxycodone (morphine:oxycodone ratio is 30:20, or 3:2), or 20 mg of oxymorphone (morphine:oxymorphone ratio is 30:10, or 3:1).

Equianalgesic Opioid Dosing Table

Drug	Equianalgesic Doses (mg)	
	Parenteral	Oral
Morphine	10	30
Buprenorphine	0.3	0.4 (sublingual)
Codeine	100	200
Fentanyl	0.1	NA
Hydrocodone	NA	30
Hydromorphone	1.5	7.5
Meperidine	100	300
Oxycodone	10*	20
Oxymorphone	1	10
Tramadol	100*	200

*parenteral oxycodone and tramadol are not available in this country

This table should only be used as a guide to estimate a patient's opioid use since it does not account for cross-sensitivity or other individual patient characteristics. In addition to opioids, patient-specific medication profiles can provide useful information to assess the risk of serious adverse events with opioids. Specific drug classes such as benzodiazepines and muscle relaxants potentiate the increased risk of CNS and respiratory depression when taken concurrently with opioids. Counseling the patient on the risk of side effects and signs and symptoms to be aware of while using opioids is an important part of the medication use process.

Another useful tool is the Prescription Drug Monitoring Program (PDMP). The Department of Health and Mental Hygiene (DHMH), Behavioral Health Administration (BHA) is responsible for oversight of the PDMP. The PDMP was created to assist healthcare providers and public health and law enforcement agencies in reducing the non-medical use, abuse and diversion of prescription drugs while preserving the professional practice of healthcare providers and legitimate patient access to optimal pharmaceutical-assisted care.

The PDMP collects and securely stores prescription information on drugs that contain controlled substances and are dispensed to patients in Maryland regardless of the method of payment. Claims paid by private third party insurers, Medicaid, Medicare and even prescriptions paid for in cash are uploaded by pharmacies throughout the state daily, and then included in the PDMP database.

Access to prescription data is made available at no-cost to physicians, nurse practitioners, pharmacists and others that provide pharmaceutical care to their patients.

By law, healthcare providers may only access information on patients under their care. Use of prescription information improves providers' ability to manage the benefits and risks of controlled substance medications and identify potentially harmful drug interactions.

The Maryland Medicaid Pharmacy Program (MMPP) encourages all providers to register with the PDMP and use the vital tool to ensure patient safety and provide for appropriate utilization of controlled substances. By viewing a patient's recent claims history, providers are able to see the patient's current medication regimen and avoid prescribing or dispensing dangerous drug combinations. More information can be found at the PDMP website: http://adaa.dhmh.maryland.gov/PDMP/SitePages/Home.aspx

References:

1.National Institute on Drug Abuse. The Science of Drug Abuse and Addiction. Available at: http://www.drugabuse.gov/drugs-abuse Accessed September 1, 2015.

2. McPherson ML. Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing. Amer Soc Health-System Pharm, Bethesda, MD, 2010.

3. Dumas EO and Pollack DM. Opioid Tolerance Development: A Pharmacokinetic/Pharmacodynamic Perspective. AAPS Journal 2008; 10(4): 537-551.

4. Purdue Pharma. (rev. 8/2015). Oxycontin: Highlights of prescribing information.

Prospective DUR Alerts for Therapeutic Duplication of Opioids

The community pharmacist is well aware that the Maryland Medicaid Pharmacy Program (MMPP) performs Prospective Drug Utilization Reviews (ProDUR) on submitted claims. ProDUR alerts are designed to prevent and reduce adverse drug interactions and therapeutic duplications. They do so by identifying two similar drugs, such as duplicate opioids. Concurrent use of a long acting opioid and a short acting opioid for breakthrough pain is clinically indicated in patients with an appropriate diagnosis and when the prescriber of both agents is the same.

When clinically appropriate, duplicate opioid claims can be overridden by the pharmacist and should only be overridden by the pharmacist, and not a technician.

When the prescriber has been consulted, the "M0" intervention code should be used. If the pharmacist has reviewed the patient's drug history profile the "R0" code can be utilized. The "P0" code is documented when the pharmacist has counseled the patient.*

The MMPP relies on the pharmacist to use his or her best clinical judgment in determining whether to use one of these overrides and deciding which intervention is appropriate to implement.

If a patient has prescriptions for two different opioids from different prescribers or two different short acting agents or two different long-acting agents, the prescriber should be contacted and made aware of the situation.

In addition, if claims are denied based on duplicate therapy or early refill alerts, cash payment for a Medicaid patient's prescription should not be accepted.

Get the latest updates on a variety of initiatives regarding the Maryland Medicaid Pharmacy Program at: https://mmcp.dhmh.maryland.gov/pap/SitePages/paphome.aspx

*DUR intervention codes include: M0 (Provider consulted), R0 (Pharmacist consulted), or P0 (Patient consulted). Outcome codes for the intervention include: 1A (filled as is, false positive), 1B (filled prescription as is), 1C (filled with different dose), 1D (filled with different directions), or 1E (filled with different drug), 1F (filled with different quantity), or 1G (filled, prescriber ok'd). Please remember to always alert the patient to these interactions while counseling the patient.

Free Continuing Education Seminar

Registration is open for the annual continuing education series, co-sponsored by the Maryland Department of Health and Mental Hygiene (DHMH), Maryland Medicaid Pharmacy Program (MMPP), Saint Agnes Healthcare and Health Information Designs, LLC (HID). The program will be from 7:30 am-1:00 pm on Saturday, October 24, 2015 at St. Agnes Hospital in Baltimore, Maryland. This program provides up to 4 (four) hours of live continuing education credits for prescribers and pharmacists. The program will provide attendees with information related to the treatment of substance use disorders, with a focus on buprenorphine therapy, as well as updates in the management of Hepatitis C. The event is free for attendees, but you must pre-register to attend.

Please visit http://www.marylandmedicaidpharmacyinformation.com/LiveEdMeetings.htm to register for this event. You may also sign up to receive this newsletter electronically at the same site.

Objectives

Substance Use Disorders

- Increase knowledge of epidemic of opiate use disorder.
- Increase knowledge of treatment of opiate use disorder.
- Define "clinical integration" related to substance use disorders.
- List self-reported physician barriers to prescribing buprenorphine.
- Describe a model of treatment that links opioid treatment programs with office-based buprenorphine prescribers.
- Be convinced that integrating treatment for opiate use disorder with medical care is beneficial (for patient, providers and the health system).

Hepatitis C

- Discuss the prevalence, natural history and healthcare impact of Hepatitis C.
- Review the recent advances in treatment of Hepatitis C.
- Explore financial consideration and public health impact of new therapies for Hepatitis C.
- Discuss the selection of appropriate HCV oral direct acting therapy and duration of therapy in HCV/HIV co-infected patients.
- Recognize antiretroviral management issues in HIV/HCV co-infected patients including drug-drug interactions.
- Discuss monitoring of patients on HCV therapy.

Program

- Integrating Buprenorphine Treatment of Opiate Use Disorder into Primary Care
  Michael Fingerhood, MD FACP, Director, Division of Chemical Dependence, Johns Hopkins Bayview Medical Center
- CoOP: A Collaborative Care Model Linking Office-Based Buprenorphine Prescribers with Specialty Treatment Clinics
  Kenneth B Stoller, MD, Director and Medical Director for Behavioral Health, Johns Hopkins Broadway Center for Addictions
- Hepatitis C: The Future is Here
  Darryn Potosky, MD, Director of Hepatology, University of Maryland School of Medicine
- Hepatitis C Management in the HIV Infected Patient
  Oluwaseun Falade-Nwulia, MBBS, MPH, Medical Director, Baltimore City Health Department, STD Clinic/HIV Early Intervention Initiative Program

Education Credits

A maximum of 4 CME and ACPE credits will be available for this program. For ACPE credits, pharmacists must provide a valid NABP#.

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

Pharmacy News & Views

Maryland Medicaid Pharmacy Program
201 West Preston Street, 4th Floor
Baltimore, Maryland 21201
1-800-492-5231 *(select option 3)*
http://mmcp.dhmh.maryland.gov/pap

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

Go Green!!!!

Sign up to receive the MMPP News & Views and Advisories via e-mail. Go to http://www.marylandmedicaidpharmacyinformation.com/

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