MARYLAND Department of Health

Office of Systems, Operations and Pharmacy
MARYLAND MEDICAID PHARMACY PROGRAM

Pharmacy News & Views

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Clinically Significant Drug Interactions: Opioid-related Deaths Associated with Gabapentin Use

It has been well publicized that opioids have multiple drug interactions that lead to enhanced central nervous system (CNS) and respiratory depression. In addition to synergistic effects seen with concurrent use of opioids and benzodiazepines and muscle relaxants, patients that receive prescription opioids while on concomitant gabapentin treatment have an increased risk of death related to opioids, according to data from a recent study. A case-control study from Ontario, Canada, reviewed over two million participant records to identify those with overlapping use of an opioid and gabapentin over a 15-year period. The objective of the study was to determine the risk of accidental opioid-related mortality when gabapentin is co-prescribed. Those included in the analysis had to have an active prescription for continued use of an opioid at the time of death and use of gabapentin within 120 days of death. Cases were excluded for a diagnosis of hospice or end-of-life care, as well as those with a history of opioid overdose determined to be a suicide or homicide. The resulting cases identified those individuals prescribed opioids and gabapentin for chronic non-malignant pain only. Results of the study showed that the odds of an opioid-related death were increased 49% when gabapentin had been used within 120 days. Further, the investigators discovered a dose-dependent trend regarding gabapentin use. Gabapentin dose was characterized according to the following structure, which is partially based on prescribing information available for all gabapentin products:

Gabapentin Dosing Scale	
Dosing Level	**Dosage**
Low	< 900 mg/day
Moderate	900 – 1,799 mg/day
High	> 1,800 mg/day

Those who were characterized as having a moderate or high dose usage of gabapentin, when combined with opioids, had an associated 60% increased odds of opioid-related death compared to those using opioids alone. Further, those identified as using very-high dose gabapentin (> 2,500 mg per day) had close to a two-fold risk of opioid-related death. Those receiving a low dose of gabapentin did not appear to have an increased risk of opioid-related death in this analysis.

Prescription use of gabapentin, and other non-opioid analgesics, has increased in response to the initiatives put forth to combat the growing opioid epidemic. Most guidelines have recommended the use of these adjuvant agents to limit opioid use, either through abstinence of opioids or through the opioid-sparing effect adjuvant analgesics provide. Many of these agents have had updated labeling over the past few years to alert healthcare providers to the potential risks associated when co-prescribed with opioids. Gabapentinoids (gabapentin, pregabalin) labeling has been updated to include the pharmacodynamic and pharmacokinetic interactions seen when used with opioids. Since both agents have CNS and respiratory depression as adverse drug events when used as a single agent, this effect can be exponentially enhanced when used together. Gabapentin levels are also increased when used with opioid analgesics, likely due to decreased gastrointestinal mobility and increased availability and absorption of gabapentin. The theoretical potential has been a concern and now has some evidence of real-life applications.

A review article recently published in *Pain Week Journal* (separately presented at PAINWeek 2017) highlighted concerns regarding gabapentin and pregabalin (gabapentinoids) misuse and abuse. Prevalence of abuse or misuse of gabapentinoids was 165% increased from previous years based on a cohort from the Appalachian area of the United States. Pregabalin currently carries a

Schedule V status, owing to the potential for abuse. Gabapentin products currently do not carry a schedule that implies there is risk of abuse.

The opioid epidemic continues to evolve across the United States, and Maryland is no exception.. With new information available regarding other agents of abuse or misuse, it is important for healthcare providers to remain abreast of updated information and national trends, and work to implement procedures within their practice that will help identify potential risks related to opioid therapy.

For more information regarding Maryland's response to the opioid epidemic, including tools to identify and prevent opioid overdose, please visit the Maryland Department of Health Behavioral Health Administration at:
https://bha.health.maryland.gov/Pages/Index.aspx

Naloxone products are available for anyone at risk of opioid-related adverse effects through a standing order from the Maryland Department of Health (https://bha.health.maryland.gov/NALOXONE/Pages/Statewide-Standing-Order.aspx). Prescriptions for naloxone for Medicaid participants are paid by the Maryland Medicaid fee-for-service (FFS) benefit. Covered products include naloxone injectable formulations and Narcan nasal spray.

References:

1. *Gomes T, Juurlink DM, Antoniou T, Mardan MM, Paterson JM, van den Brink W (2017). Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study. PLoS Med 14(10).*

2. *Kominek C (2018). What's all the GABA about? Pain Week Journal. http://www.painweek.org/journals/whats-all-the-gaba-bout.html*

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Screening and Treatment for Vitamin D Deficiency – Practice Guideline Update

In February 2018, the American Academy of Family Physicians (AAFP) released new findings from a recent review of available literature regarding vitamin D supplementation and long-term health benefits and harms. Within the past decade, screening of vitamin D levels (25-OH-D) in community practice has become commonplace in asymptomatic patients. It was hypothesized that correction of vitamin D deficiency prevent cancer or cardiovascular disease, prevent fractures and even prolong life in the general population. Other benefits of using vitamin D for the treatment of chronic conditions, from depression to chronic pain, were also considered. In response, assessment and treatment of vitamin D levels became a common practice, with vitamin D blood concentrations becoming the fifth most common laboratory test ordered in 2014. Now, the AAFP, in addition to the US Preventive Services Task Force (USPSTF), is pulling back on the routine monitoring of vitamin D levels in the general population. Strong evidence supports discontinuing use of monitoring or treatment measures for chronic condition of depression, fatigue, osteoarthritis or chronic pain. Both agencies also strongly recommend against the use of routine vitamin D supplementation without a compelling indication (e.g. osteoporosis, chronic kidney disease). Furthermore, adequate evidence has been found showing that vitamin D supplementation does not reduce the risk of cancer, diabetes or death in a community population nor does it reduce fractures in individuals without a high risk of fractures. While toxicities from overexposure to vitamin D supplements is rare, the costs associated with laboratory monitoring and treatment are not justified based on available outcomes.

References:

1. *LeFevre M and LeFevre N. Vitamin D Screening and Supplementation in Community-Dwelling Adults: Common Questions and Answers. Am Fam Physician. 2018 Feb 15; 97(4): 254-260.*

2. *Final Recommendation Statement: Screening for Vitamin D Deficiency in Adults. U.S. Preventive Services Task Force. November 2014 https://www.uspreventiveservicestaskforce.org/Announcements/News/Item/final-recommendation-statement-screening-for-vitamin-d-deficiency-in-adults*

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Updates on Available Treatments for HIV-1

Several new products have been approved by the Food & Drug Administration (FDA) for the treatment of HIV-1. Many products include new combinations of existing agents as well as some newer therapies. All antiretrovirals for the treatment of HIV are carved out of the Managed Care Organization (MCO) benefit and paid by the Fee-for-Service (FFS) program. Pharmacists play a crucial role in the management of antiretroviral therapies resulting in improved patient outcomes, including enhanced medication adherence by counseling the patient regarding correct dosing frequency and product administration, as well as monitoring for any interacting drug products that may alter the efficacy of the antiretroviral therapy.

Approvals from the first quarter of 2018 are listed below. Product labeling and approval information is available on the FDA website (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm) as well as via a mobile app available for download for both Apple and Android products (Drugs @ FDA Express). Appropriate therapeutic use and guidelines for treatment are available for free at the US Department of Health and Human Services and National Institute of Health website: https://aidsinfo.nih.gov

New Products for Treatment of HIV

Brand	Generic	Manufacturer	Dosing	Product Attributes
Symfi ™	efavirenz 600mg/ lamivudine 300mg/ tenofovir disoproxil fumarate 300mg	Mylan	One tablet by mouth once daily at bedtime *(Three drug combination NNRTI and NRTI complete regimen for treatment-naïve)* Contraindicated with Zepatier due to loss of Hepatitis C antiviral activity	Adults/pediatrics > 40 kg
Symfi Lo ™	efavirenz 400mg/ lamivudine 300mg/ tenofovir disoproxil fumarate 300mg			Adults/pediatrics > 35 kg
Cimduo ™	lamivudine 300mg tenofovir disoproxil fumarate 300mg	Mylan	One tablet by mouth once daily *[Two drug combination (NRTI)]*	Adults/pediatrics > 35 kg *Must be used in combination with other antiretrovirals (not NRTI) for a complete regimen*
Biktarvy ®	bictegravir 50mg/ emtricitabine 200mg/ tenofovir alafenamide fumarate 25mg	Gilead	One tablet by mouth once daily *[Three drug combination INSTI and NRTI for treatment-naïve or treatment experienced who are virologically suppressed (HIV RNA < 50 copies per mL) on another regimen and stable for 3 months]*	bictegravir is a new molecular entity in the integrase strand transfer inhibitor (INSTI) class of antiretrovirals
Trogarzo ™	ibalizumab-uiyk	Taimed Biologics	IV infusion every 2 weeks Loading dose 2,000mg Maintenance dose 800mg	Multidrug resistant HIV to at least one agent in each class (NNRTI, NRTI and PI) Continue maintenance ARV regimen

MARYLAND
Department of Health

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Pharmacy
News & Views

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30-Day Emergency Supply of Atypical Antipsychotic Agents

When the prescriber is not available to obtain prior authorization for an antipsychotic medication that is non-preferred or second tier, the pharmacist can obtain a one-time only authorization to dispense up to a 30-day emergency supply.

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.

To obtain authorization for an emergency supply of an antipsychotic, call Conduent Technical Assistance at 800-932-3918. During the 30-day window, the pharmacist must notify the prescriber of the need to obtain a PA before the prescription can be filled a second time and make a note for his or her records of the date, time and person contacted at the prescriber's office.

Tier 2 and Non-Preferred Antipsychotic Review Process

All claims for Tier 2 or non-preferred antipsychotics for patients age 18 or older require authorization. The claim will deny at point of service and will not process. An electronic message will display on your system with instructions as to how to proceed. The Tier 2 and Non-Preferred Prior Authorization Form can be found at:
https://mmcp.health.maryland.gov/pap/docs/ANTIPSYCHOTIC%20PA%20FORM%20.pdf

TELEPHONE NUMBERS

- **Conduent Technical Assistance**
  1-800-932-3918
  24 hours a day, 7 days a week
- **Maryland Medicaid Pharmacy Access Hotline**
  1-800-492-5231 (option three)
  Monday-Friday, 8:00 am - 5:00 pm
- **Kidney Disease Program**
  1-410-767-5000 or 5002
  Monday-Friday, 8:00 am - 5:00 pm
- **Breast and Cervical Cancer Diagnosis and Treatment**
  1-410-767-6787
  Monday-Friday, 8:00 am - 4:30 pm
- **Maryland AIDS Drug Assistance Program**
  1-410-767-6535
  Monday-Friday, 8:30 am - 4:30 pm
- **Peer Review Program**
  1-855-283-0876
  Monday-Friday, 8:00 am - 6:00 pm