MARYLAND DEPARTMENT OF HEALTH
Medicaid Pharmacy Program

Pharmacy NEWS AND VIEWS

May 2019

Review of Stimulants Used for Attention-Deficit/Hyperactivity Disorder (ADHD)

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the more common behavior disorders diagnosed in children. The Centers for Disease Control and Prevention (CDC) reported in 2016 that 6.1 million children aged 2-17 had been diagnosed with this disorder, which is about 10% of this population in the United States.[1] In addition to behavioral interventions, stimulants such as amphetamines and methylphenidate, continue to be first line pharmacotherapy.[2] Multiple formulations of these drugs are available for use (Table 1).[3] General dosing guidelines recommend using lower doses as initial therapy and titrating to the lowest effective, tolerated dose. The use of extended release products provides a more stable level throughout the day and prevents frequent dosing throughout the day. This can be especially important for school aged children, so that administration at school is not necessary. Supplemental doses in the form of immediate release products can also be prescribed for use in the afternoon to aid in evening control of symptoms with less impact on sleep. Monitoring for efficacy is important as the dose may need to be adjusted over time.

All products have similar adverse effect profiles. These include nausea, reduced appetite/weight loss, insomnia, headache, dyskinesia/movement disorders, and cardiovascular effects including increased blood pressure and heart rate. Additionally, all products are classified as controlled substances (C2) and have a high risk of abuse and dependence. Since ADHD is considered a chronic condition, monitoring for side effects and overall health is an important aspect of care in this population.

Table 1: Available Stimulants for ADHD

Drug Compound	Available Products	Maximum Daily Dose (general)*
Amphetamine salt combo	Adderall, Adderall XR, Adzenys ER/ODT, Dyanavel XR, Mydayis ER	Immediate release: 40 mg Extended release: 30 mg
Amphetamine sulfate	Evekeo	40 mg
Dextroamphetamine	Dexedrine, Dexedrine ER, Zen-zedi	40 mg
Dexmethylphenidate	Focalin, Focalin XR	Immediate release: 20 mg Extended release: 40 mg
Lisdexamfetamine	Vyvanse	70 mg
Methylphenidate	Aptensio, Concerta, Contempla XR ODT, Daytrana, Metadate, Methylin, Quillichew ER, Quillivant XR, Ritalin, Ritalin LA, Ritalin SR	Transdermal: 30 mg Oral: 60 mg

**Maximum dose may vary by product and age. Generally lower doses recommended for younger patients.*

References:

[1]Attention-Deficit/Hyperactivity Disorder. Center for Disease Control and Prevention. Available at www.cdc.gov/ncbddd/adhd/index.html. Accessed April 15, 2019.

[2]ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. *Pediatrics* 2011; 128: 1007-1022.

[3]IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at www.micromedexsolutions.com (cited: *April 15, 2019*).

Automatic Refills for Maryland Medicaid Participants

In March 2014, regulations were updated regarding the automatic refill process for Maryland Medicaid. Currently, a pharmacy provider must have written authorization from the participant (or their designee) in order to automatically refill any prescription (see COMAR 10.09.03.03N and 10.09.03.05 C2c). While this is a beneficial process for adherence to medication regimens, it can increase the incidence of duplication of therapy, especially if a dose adjustment or change in medication therapy is made. Additionally, removing old or outdated prescriptions from the automatic refill process is recommended to prevent duplicate therapy and an increased risk of adverse effects.

During the Prospective Drug Utilization Review (ProDUR) process it is important to review the medication profile and input the appropriate ProDUR codes. Pharmacists should continue to input the correct Intervention and Outcome codes at the Point of Sale (POS).

DUR Intervention Codes

MØ*	Provider consulted
RØ*	Pharmacist consulted
PØ*	Patient consulted

**second character is a zero, not the letter "O"*

DUR Outcome Codes

1A	Filled as is, false positive
1B	Filled as is
1C	Filled with different dose
1D	Filled with different directions
1E	Filled with different drug
1F	Filled with different quantity
1G	Filled, prescriber ok'd

Coming Soon!

Maryland Medicaid Pharmacy Program will be implementing quantity limits on stimulants.

Stay tuned for more information!

Risks Associated with Concomitant Use of Opioids and Benzodiazepines

With more information being reported regarding medication overdose mortality and morbidity, the risks associated with opioid use continues to be a significant concern. While many agents can interact with opioids and enhance the central nervous system (CNS) depressant effects, concurrent benzodiazepine use is of particular concern. Benzodiazepines, when used alone, exert similar CNS depressant effects of opioids, including decreased respiratory rate and sedation. A review of overdose statistics for the State of Maryland revealed that the majority of benzodiazepine related deaths occurred in combination with an opioid, including fentanyl, prescription opioids and heroin.[1] The National Institute on Drug Abuse (NIDA) reports that more than 30 percent of opioid overdoses involve benzodiazepines.[2] NIDA also cites studies that show combined use of opioids and benzodiazepines increases the risk of death up to 10 times of that when opioids are used alone.

Based on these reports, the Centers for Disease Control and Prevention (CDC) issued a guidance statement regarding opioid prescribing in 2016.[3] One of the recommendations included limiting the prescribing of opioids and benzodiazepines whenever possible. This recommendation was included in the 2018 update as well. Further, the CDC also recommends the use of a prescription drug monitoring program (PDMP) to assess the use of all controlled substances when prescribing opioids to assess overall medication use and associated risks. In Maryland, prescribers and pharmacy providers are required to have access to the PDMP. Further, the PDMP Use Mandate that took effect July 1, 2018, requires periodic monitoring by providers or delegated users for prescribers and by pharmacists.[4] Additionally, the recent approval of the SUPPORT Act (H.R.6) requires Medicaid programs to monitor concurrent use of these agents.[5]

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.

References:

[1]Maryland Department of Health Behavioral Health Administration – Overdose Data and Reports. Drug and Alcohol-Related Intoxication deaths in Maryland, 2017. https://bha.health.maryland.gov/overdose_prevention/pages/data-and-reports.aspx

[2]National Institute on Drug Abuse. Benzodiazepines and Opioids – Revised March 2018. www.drugabuse.gov/drugs-abuse/opioids/benzodiazepines-opioids

[3]Centers for Disease Control and Prevention – Opioid Overdose. www.cdc.gov/drugoverdose/index.html

[4]Maryland Department of Health Behavioral Health Administration – Prescription Drug Monitoring Program. https://bha.health.maryland.gov/pdmp/Pages/Home.aspx

[5]H.R.6 – Support for Patients and Communities Act. www.congress.gov/bill/115th-congress/house-bill/6

Metabolic Adverse Effects with Atypical Atipsychotic Use

Metabolic syndrome is a group of risk factors that increase the risk for heart disease and includes hypertension, dyslipidemia, obesity and diabetes.[1] While this combination of risk factors can occur in any patient, it is more prevalent in those with a mental disorder, specifically schizophrenia. This may be due to general lifestyle behaviors, but in this population an identified factor includes the use of atypical antipsychotics[2].

Atypical antipsychotics, such as olanzapine and risperidone, differ from typical antipsychotics in that they have less of an effect at dopamine receptors and have greater effects through serotonin, muscarinic and histamine receptors. While this is beneficial in decreasing, though not eliminating, the risk of extrapyramidal symptoms (dystonias, akathisia, tardive dyskinesia), other adverse effects may be more common. For instance, products that have a high affinity for H1 and 5-HT2c receptors, such as clozapine and olanzapine, have been linked to the highest risk for weight gain.[2] Since each agent has a unique receptor binding profile, a direct link to side effects has been difficult to establish, but overall trends have been observed. These effects are likely a combination of multiple pathways.

Risk of Metabolic Adverse Effects

Drug	Weight Gain	Dyslipidemia	Hyperglycemia
Clozapine	Severe	Severe	Severe
Olanzapine	Severe	Severe	Severe
Risperidone	Intermediate	Low	Low
Quetiapine	Intermediate	Intermediate	Intermediate
Ziprasidone	Low/Neutral	Low/Neutral	Low/Neutral
Aripiprazole	Low/Neutral	Low/Neutral	Low/Neutral
Iloperidone	Intermediate	Low/Neutral	Low/Neutral
Paliperidone	Low	Low	Low
Asenapine	Low/Neutral	Low/Neutral	Low/Neutral
Lurasidone	Low/Neutral	Low/Neutral	Low/Neutral

Appropriate monitoring is essential to manage the increased risk of heart disease morbidity and mortality when using atypical antipsychotics. Baseline risk should be assessed prior to initiating treatment, and at minimum should include: Body Mass Index (BMI), waist circumference, blood pressure, Hemoglobin A1c, fasting plasma glucose and fasting lipid panel.[3] Additionally, BMI, waist circumference and blood pressure should be assessed at every visit or at least monthly for the first three months of treatment. Laboratory parameters should be assessed at three months and then at minimum annually. More frequent monitoring may be necessary based on other risk factors. Additionally, those using atypical antipsychotics should be instructed to make other lifestyle changes to decrease cardiovascular risk factors, to include following a heart healthy diet, abstaining from tobacco use and increasing physical activity.

It is important to note that these side effects are not necessarily dose dependent, and may occur at low doses. Also, some effects, such as weight gain, may be more pronounced in certain sub-populations (e.g. children and adolescents, treatment-naïve). This is of particular concern as atypical antipsychotics are commonly used off-label at low doses for a variety of conditions. The risk of metabolic syndrome associated with these agents, along with potential inappropriate monitoring, should be considered when using atypical antipsychotics for any indication.

References:

[1]National Heart, Lung and Blood Institute (NIH). Metabolic Syndrome. Available at: /www.nhlbi.nih.gov/health-topics/metabolic-syndrome. Accessed April 17, 2019.

[2]Riordan HJ, et al. Atypical Antipsychotics and Metabolic Syndrome in Patients with Schizophrenia: Risk Factors, Monitoring, and Healthcare Implications. *Am Health Drug Benefits* 2011; 4(5): 292-302.

[3]Zeier, K, et al. Recommendations for lab monitoring of atypical antipsychotics. Curr Psychiatry 2013; 12(9): 51-54.

Appropriate Dosing of Gabapentin

Gabapentin, licensed under the brand name Neurontin®, was first approved in 1993 by the Food and Drug Administration (FDA) as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy.[1] At the time, this novel agent was thought to be relatively safer compared to other antiepileptics and did not require drug concentration monitoring for efficacy and safety. Over the next 25 years, approved indications expanded to include use in pediatric patients as an antiepileptic and for the treatment of postherpetic neuralgia.[2] Other formulations of gabapentin have been approved (Horizant, Gralise) and include treatment of Restless Leg Syndrome.[3,4] A review of clinical trials and prescribing patterns shows that gabapentin is used for many other ailments, including diabetic peripheral neuropathy, fibromyalgia, hemodialysis associated pruritus, hot flashes and post-operative pain.

While the exact mechanism of action of gabapentin is not fully known, it is a compound that is structurally similar to gamma-aminobutyric acid (GABA), a neurotransmitter. Gabapentin does not bind to GABA receptors and does not interfere with endogenous GABA binding, uptake or degradation. Studies show that gabapentin binds to voltage-activated calcium channels, resulting in a presynaptic inhibition of excitatory neurotransmitter release, and exhibits an overall inhibitory effect on neuronal transmission. This effect can explain therapeutic use of the agent as an antiepileptic and analgesic.

Recommended dosing of gabapentin is diagnosis-dependent, and overall the maximum daily dose is 3,600mg. In some instances, studies have shown no additional benefit of using higher doses, but did show an increased rate of adverse effects. For the immediate release formulations, doses should be divided throughout the day and should occur no less frequently than every 12 hours, for those with normal renal function. Gabapentin is not intended to be used on an "as needed" basis as this has not been proven effective for any indication. When not titrated and administered correctly, adverse effects of dizziness, somnolence and nausea are more likely to occur.

Gabapentin absorption is dose dependent and decreases with higher doses.

Gabapentin dose (oral)	Bioavailability
900 mg	60%
1200 mg	47%
2400 mg	34%
3600 mg	33%

Since gabapentin is not metabolized and is excreted as unchanged drug in the urine, dose adjustments must be made in those with impaired renal function.

The extended-release formulations, which are not interchangeable with immediate release formulations, have different dosing recommendations, including use in renal impairment. Gralise® is not indicated with an estimated creatinine clearance of less than 30 ml/min or with hemodialysis. Horizant® provides dosing recommendations for the two approved indications of restless leg syndrome and post-herpetic neuralgia.

When reviewing prescription records for gabapentin use, proper indication and dosing should be reviewed for each patient. Additionally, counseling on the dose titration and potential adverse effects should be provided to maximize benefit when using gabapentin.

References:

[1]Gabapentin. In: IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at www.micromedexsolutions.com (cited: April 15, 2019).

[2]Neurontin [**package insert**]. New York, NY : Parke-Davis; rev 2017.

[3]Gralise [**package insert**]. Menlo Park, CA : Depomed, Inc.; rev 2012.

[4]Horizant [**package insert**]. Research Triangle Park, NC : GlaxoSmithKline; rev 2013.

Creatinine Clearance (est., ml/min)	Daily Dose (mg)	Dosing Frequency
≥ 60	900 - 3600	Three times daily
> 30 – 59	400 - 1400	Twice daily
> 15 – 29	200 - 700	Once daily
15	100 - 300	Once daily
Hemodialysis	125 - 350	Once after each HD session, in addition to maintenance dose

A 72-hour emergency supply of a non-preferred medication is available. Pharmacists should call

1-800-932-3918

to request authorization to dispense.

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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

Have you tried Formulary Navigator?

- Web-based open access – no login required!
- Multiple search options to find products by alphabet, brand and generic, and/or therapeutic class.
- More detailed information on product restrictions and prescribing requirements
- Easy access links to health plans **www.mmppi.com**

TELEPHONE NUMBERS

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