Drug Utilization Review (DUR) Newsletter

COLORADO
Department of Health Care Policy & Financing

Select HCPF Medication Use Policy Updates

WINTER 2021

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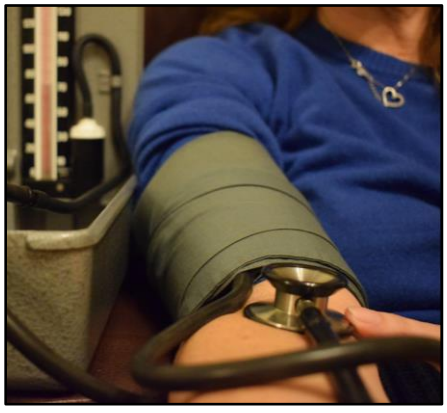
Do Cardiovascular Risks Exist for ADHD Drugs in Adults?

First-line stimulant class medications such as methylphenidate and amphetamine formulations are FDA-approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and narcolepsy.

It is estimated that 4.4% of U.S. adults experience some symptoms and disabilities of ADHD. However, adults receive 32% of all issued stimulant prescriptions.[1] Off-label treatment for conditions including weight management, fatigue related to depression, stroke, traumatic brain injury, or hypersomnolence due to obstructive sleep apnea (OSA) may account for the high prevalence of stimulant use in adults. Such conditions are frequently associated with history or risk of cardiovascular disease. Of note, OSA and other forms of sleep-disordered breathing have unfavorable effects on cardiovascular physiology, predisposing affected individuals to cardiovascular disease and cardiac arrhythmias.[2,3]

Due to reports of cardiovascular adverse events and observed physiological effects, the package inserts for stimulant drugs warn against use in patients with preexisting heart disease or cardiac structural abnormalities due to risk of sudden death, stroke, and myocardial infarction (MI).[4-6] Furthermore, the FDA issued a safety announcement in 2011 stating that stimulant products and atomoxetine should not be used in patients with serious heart problems, or in those for whom an increase in blood pressure (BP) or heart rate (HR) would be problematic.[7] Debate remains regarding the safety of stimulants in the cardiovascular patient population. Specifically, the use of stimulants in patients with a history of or susceptibility to arrhythmias has not been studied. In an effort to elucidate risk, interpretation of current evidence surrounding stimulant and stimulant-like drugs is offered.



CNS stimulants exert their action on the brainstem ascending arousal system and cortex, blocking the reuptake of norepinephrine and dopamine into the presynaptic neuron and increasing their release into the extraneuronal space. An increase in circulating catecholamines can activate cardiovascular beta-1 adrenoreceptors resulting in increased inotropy and heart rate, while activation of alpha-adrenoreceptors causes vasoconstriction and a rise in blood pressure. Studies have indicated small but statistically significant increases in BP (1-6 mmHg) and HR (2-5 bpm) with short-term stimulant use, as well as similar findings with once-daily methylphenidate for up to one year of use.[8-11]

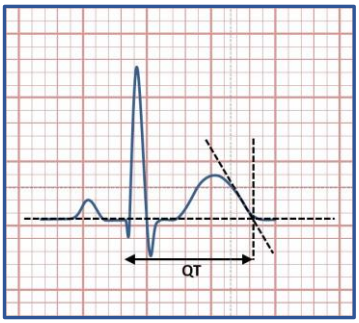
ADHD Drugs in Adults, *continued*

The nonstimulant medication atomoxetine is a selective norepinephrine reuptake inhibitor (SNRI) indicated for ADHD. Atomoxetine appears to be free of effects on other noradrenergic receptors and neurotransmitter systems.[12] Nonetheless, it has been shown to have similar increases in BP and HR with short term use compared to stimulants.[13-17] The aforementioned studies excluded subjects with clinically significant chronic medical conditions or did not offer description of comorbidities such as cardiovascular disease. In addition, the studies were not powered to determine risk of clinical cardiovascular events due to inadequate sample size or follow-up duration.

The observed effects of stimulants on BP and HR would be expected to increase cardiovascular risk. Schelleman et al. found a 1.8-fold increase in risk of sudden death or ventricular arrhythmia in adult patients who initiated methylphenidate therapy.[17] Methylphenidate dosage was inversely associated with risk, suggesting that the association may not be directly causal. Limitations of this study include unmeasured confounding variables due to the nonrandomized design, that methylphenidate users (n=43,999) were more likely to have preexisting cardiovascular disease than nonusers (n=175,955), and limited duration of follow-up with a median of 60 days. Even so, the findings are of concern and should not be disregarded.

Conversely, a retrospective population-based study of more than 150,000 adults with prescriptions for methylphenidate, amphetamine, or atomoxetine matched to non-users demonstrated a lack of association between stimulant use and incidence of MI, sudden cardiac death (SCD), and stroke.[15] Individuals with cardiovascular disease were included and potential confounding variables were adjusted for in the analysis. However, the study had several limitations, and the authors did indicate that a modestly elevated risk could not be ruled out given the limited power and lack of a complete data set of risk factors. A similar study found no evidence of increased risk of serious cardiovascular events in adult initiators of amphetamines or atomoxetine but could not rule out modest elevated risk due to limitations of unmeasured confounders and lack of stratified analyses.[16-17]

Potential for QT Prolongation



In analyzing safety of drug use in arrhythmia patients, potential for QT prolongation and risk of torsades de pointes (TdP) should be considered. Trials have found no statistically or clinically significant changes in QT intervals over short- and long-term treatment with methylphenidate and amphetamine drugs.[10-12,18]

Alternatively, there is evidence that atomoxetine may prolong the QT interval. Scherer et al. demonstrated that atomoxetine inhibits cardiac hERG potassium channel currents which, in turn, can cause action potential prolongation and increase risk of development of acquired long-QT syndrome.[19] When studied in healthy CYP2D6 poor metabolizers, atomoxetine was not associated with a clinically significant change in corrected QT (QTc) which is similar to findings of a pooled analysis to determine cardiovascular safety of atomoxetine.[20,13] However, there are few published reports of atomoxetine-induced life-threatening long QT syndrome.[21,22] CredibleMeds® is a nationally-recognized site that classifies potential QT prolonging drugs according to risk.

As a result of recent literature and case reports of atomoxetine, it was recently added to the category of drugs that have possible risk of TdP. Methylphenidate and amphetamine-containing drugs are recommended to be avoided in patients with congenital long QT syndrome.

ADHD Drugs in Adults, *continued*

Modafinil and Armodafinil

Modafinil and its R-enantiomer, armodafinil, are novel nonamphetamine psychostimulants indicated for improved wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or shift-work disorder (SWD). Both medications have similar wake-promoting actions to sympathomimetic stimulant agents yet differ in pharmacological profile and are thought to have lower potential for abuse and adverse cardiovascular events. Nonetheless, package labels have similar cardiovascular warnings to the stimulant drugs. Exclusive to modafinil and armodafinil is the warning against use in patients with history of left ventricular hypertrophy or in those with mitral valve prolapse who have experienced mitral valve prolapse with previous CNS stimulant use. This recommendation is based on minimal evidence of three patients of such history with observed adverse events of ischemic T-wave changes, dyspnea and palpitations in clinical studies.[23,24]

Conclusion

Although the cardiovascular impact of stimulant use is minimal in healthy populations, with minor elevations in HR and BP concern remains regarding use in patients with preexisting cardiovascular conditions. The adrenergic activation caused by stimulants and stimulant-like drugs may have a larger impact on autonomic regulation in patients with compromised cardiovascular function. Even modest elevations in HR and BP may exacerbate preexisting cardiovascular conditions, particularly arrhythmias.

Studies to date evaluating cardiovascular safety of stimulant drugs have several limitations that may confound outcomes. Data have been retrospective and limited to less than two years, thus longer-term safety and cumulative effect of stimulants are unknown. Due to lack of inclusion of patients with history of cardiovascular disease, particularly arrhythmias, results should not be extrapolated to such populations. Furthermore, study outliers and case reports indicate the possibility of greater cardiovascular risk than observed, especially in vulnerable populations.

Until further evidence of safety is demonstrated by large-scale, long-term, standardized trials, the avoidance of stimulant use in arrhythmia patients is prudent. Assessment of clinical benefits and risks should be made on an individualized basis when therapy is warranted. If initiated, caution must be exercised as detailed in regulatory warnings, with monitoring of cardiovascular parameters and use limited to short durations and lowest effective doses.

Rx Review: Health First Colorado's Medication Therapy Management Program

Since 2007, the Health First Colorado Rx Review program has been helping members who take multiple medications ensure that their pharmacotherapy regimens are safe and effective.

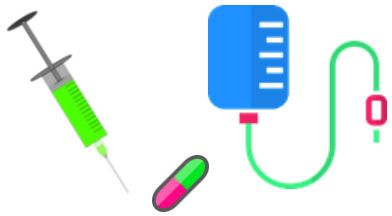
Members centrally identified in various cohorts are invited by mail to participate in a comprehensive medication review by telephone. The goal of this initiative is to help members better understand the medications they use, minimize the impact of drug interactions and side effects, and suggest ways to improve adherence to therapy.

Rx Review consultations for our members are conducted by pharmacist interns and pharmacists at the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences. Member participation is voluntary, and this service is provided at no cost to invited patients and their providers.

For more information about the Rx Review program, contact the Pharmacy Liaison at 303-866-3588.

Physician Administered Drugs (PAD)

by Rachele Poissant, PharmD, HCPF PAD Pharmacist



Health First Colorado will be implementing a new utilization management (UM) Program for the fee-for-service, physician-administered drug (PAD) benefit. **Starting January 18, 2022**, a select number of PADs will be subject to prior authorization (PA) requirements.

Keystone Peer Review Organization (Kepro) will offer training sessions for providers in the coming months. Additional information will be sent via email, newsletters, monthly provider bulletins, as well as on the https://hcpf.colorado.gov/physician-administered-drugs and https://hcpf.colorado.gov/par web pages.

After implementation, providers will need to submit a PA request to the UM vendor, Kepro, for any member receiving any PADs listed in the table below. Providers must also ensure that an approved PA is on file prior to PAD administration. There must be an approved PA on file for each of the PADs requiring a PA that a member receives. Completed PA requests will be reviewed and responded to within 24 hours of receipt. All PAD PA procedures and clinical criteria are on **Appendix Y: Physician Administered Drug Medical Benefit Prior Authorization Procedures and Criteria** available at https://hcpf.colorado.gov/billing-manuals.

- PA questions or concerns may be directed to Kepro
  Phone 1-720-689-6340, Fax 1-800-922-3508
  Provider Issues Email: COproviderissue@kepro.com
  Provider Training Registration Email: COproviderregistration@kepro.com

- Claims questions or concerns may be directed to the Department's fiscal agent
  Gainwell Technologies (formerly DXC Technology) at 1-844-235- 2387

- All other PAD benefit questions or concerns may be directed to HCPF_PAD@state.co.us

Drug Class	HCPCS	Drug Name
Bone Resorption Inhibitor Agents	J0897	Prolia
		Xgeva
Botulinum Toxin Agents	J0585	Botox
	J0586	Dysport
	J0587	Myobloc
	J0588	Xeomin
Immune Globulin Agents	J1459	Privigen
	J1556	Bivigam
	J1557	Gammaplex
	J1561	Gammaked
		Gamunex
		Gamunex-C
	J1566	Gammagard S/D
	J1568	Octagam 5%, 10%
	J1569	Gammagard Liquid
	J1572	Flebogamma DIF
	J1599	Asceniv
		Panzyga
Drugs in Other Classes	J0172	Aduhelm
	J3380	Entyvio
	J0517	Fasenra
	J2182	Nucala
	J2350	Ocrevus
	J1745	Remicade
	J1300	Soliris
	J2323	Tysabri
	J2357	Xolair

DUR Board Member Spotlight

by Ryan Tran
PharmD Candidate,
DUR Intern

Patricia Lanius, BSPharm, MHA

Patricia Lanius is the Pharmacy Operations Manager of the Ambulatory Care Pharmacy Services at the University of Colorado Hospital on the Anschutz Medical Campus. Her role focuses on leveraging technology and operational workflow to optimize each patient's experience at different transition points in their health care journey.

Ms. Lanius attended the University of Pittsburgh where she received her Bachelor of Pharmacy degree. Before coming to Colorado her work experience focused mainly on the acute care of patients. In addition, Ms. Lanius has received her Master of Healthcare Administration degree from CSU Global.

Ms. Lanius became interested in ambulatory care and outpatient settings as she realized how much time patients spend in those areas and how great an impact those settings can have on patients' overall sustained health. Her work experience in ambulatory settings includes leadership positions in home infusion and outpatient pharmacy in health systems, including Community Health Services/Safety Net organizations to support a collaborative approach to care.

Aside from pharmacy, Ms. Lanius loves the outdoors. She revels in the different beauties Colorado has to offer and she can be found anywhere there is a body of water or a patch of flowers. She also enjoys gardening, needlework, and baking.

Overall, Ms. Lanius loves the state of Colorado and wants to give back to it by offering an operational point of view as the board works together to optimize patient care for all Health First Colorado members.

November 2021 DUR Board PDL Drug Classes

- Hepatitis C Virus Treatments
- HIV Treatments
- Pulmonary Hypertension Therapies
- Newer Generation Antidepressants
- Antiemetics
- *H. Pylori* Treatments
- Targeted Immune Modulators
- Respiratory Agents
- Non-Steroidal Anti-Inflammatory Drugs
- Antibiotics, Inhaled
- Anti-herpetic Agents
- Oral Fluoroquinolones
- Triptans and Other Migraine Agents
- Antipsoriatics
- Topical Immunomodulators
- Topical Steroids
- Pancreatic Enzymes
- Proton Pump Inhibitors
- Non-Biologic Ulcerative Colitis Agents
- Immune Globulins
- Newer Generation Antihistamines
- Antihistamine/Decongestant Combinations
- Intranasal Rhinitis Agents
- Leukotriene Modifiers

HCPF Pharmacy Resources Page
https://www.colorado.gov/hcpf/ pharmacy-resources#PDL

January 1, 2022
Colorado Preferred Drug List (PDL)
https://hcpf.colorado.gov/sites/hcpf/files/01-01-22%20PDL.pdf

Are you sure your patients who use opioids have **NALOXONE** available for an **overdose emergency**?

Welcome, Dr. Shaban

Dr. Kamleh Shaban is the new child and adolescent psychiatry consultant for the Department.

As part of Health First Colorado's DUR program, a child and adolescent psychiatrist is available for provider-to-provider telephone consultations to assist in the management of complex cases involving Colorado Medicaid members. These consultations are provided at no charge to you or your patient.

Thank you to **Dr. L. Charolette (Charlie) Lippolis** for her years of service in this capacity.

DUR Board Member Spotlight

by Thao Anh Mai
PharmD Candidate,
DUR Intern

Liza Claus, PharmD, BCACP

Dr. Liza Claus is a clinical pharmacy specialist at the A.F. Williams Family Medicine Center, Assistant Professor at the University of Colorado School of Pharmacy, and Program Coordinator of CU's PGY2 Ambulatory Care Residency.

Dr. Claus is originally from Portageville, Missouri, and obtained her PharmD from the University of Missouri-Kansas City. She completed a Community Pharmacy PGY1 and an Ambulatory Care/Family Medicine PGY2 at the University of Mississippi and the University of Colorado Denver, respectively.

At A.F. Williams Family Medicine Center, Dr. Claus provides chronic disease state management for many Medicaid patients as well as targeted Medicaid outreach for eligible patients. Since becoming a Colorado DUR Board Member in 2018, her clinical responsibilities have informed her dedication to patient advocacy and access. Dr. Claus aspires to identify and continually improve access to care for Medicaid patients, making sure there is alignment between evidence-based medicine and therapeutic options that Medicaid patients have access to. While at clinic, Dr. Claus has the opportunity to see how her patients are positively affected by the DUR Program—an experience that she describes as deeply rewarding.

Outside of work, Dr. Claus enjoys spending time with her husband and 22-month-old son—whether it is traveling, spending the day at the lake, or cheering on the St. Louis Cardinals.

The Colorado Evidence-Based Drug Utilization Review (CO-DUR) Program

The Colorado Evidence-Based DUR (CO-DUR) Program is located at the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences in Aurora. The purpose of this program is to provide research analytics and clinical pharmacy support to Health First Colorado, Colorado's Medicaid Program.

Established in 2012, the CO-DUR team is responsible for supporting a diverse range of services in collaboration with the Department's Pharmacy Office. Some of these activities include:

- Development of robust quarterly research modules and ad hoc analyses on a broad range of clinical topics
- Preparation and development of draft drug utilization criteria in advance of quarterly DUR Board meetings
- Preparation of DUR Board meeting agendas, minutes and other documents
- Publication of Winter and Summer DUR Newsletters

CO-DURx | Skaggs School of Pharmacy and Pharmaceutical Sciences
The University of Colorado Evidence-Based Drug Utilization Review Program

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Another important component of the CO-DUR team's collaboration with the Department is to prepare and distribute letters to providers by mail as part of the retrospective Drug Utilization Review (RDUR) program. These letters alert providers to potentially significant pharmacotherapy issues involving individual Colorado Medicaid members and create opportunities for prescribers to make medication therapy adjustments when warranted.

This collaborative RDUR program is educational in nature, and it allows providers to incorporate drug utilization information for individual Medicaid members into the regular assessment of drug therapy requirements.

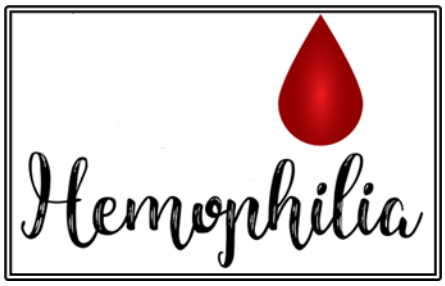
Some RDUR communications represent situations in which a member has received medications from more than one prescriber.

Module Summary: Hemophilia and Associated Treatment Among Health First Colorado Members

Background

Hemophilia is caused by genetic mutations that lead to the lack of functional blood clotting proteins — factor VIII (FVIII) in type A, and factor IX (FIX) in type B. Since the 1970s, pharmacotherapy has evolved from administration of naturally derived standard half-life factor replacement to use of bypass therapy for patients with high-titer inhibitors (5%–30% of severe hemophilia A and 1%–5% of hemophilia B), and in 2014 to the use of recombinant extended half-life factor products. In 2018, a novel, non-factor, bypassing agent entered onto the market. Hemlibra® (emicizumab) is an antibody-based treatment for hemophilia A which bridges factors IXa and X, allowing the coagulation cascade to continue without factor VIII. Hemlibra was initially approved for use with factor Inhibitors for hemophilia A on November 16, 2017, then for hemophilia A without factor VIII inhibitors on October 4, 2018, and finally for breakthrough therapy designation for hemophilia A without inhibitors on April 16, 2018. While these newer therapies have improved hemophilia care, they come at a high cost.[1-3]

Leveraging Medicaid data from 2005-2020, Hernandez et al. found that total Medicaid spending in hemophilia pharmaceuticals tripled from 2005 to 2019, from $521 million in 2005 to $1.57 billion in 2019. Across the study period, annual spending more than doubled for factor VIII (from $330 million in 2005 to $779 million in 2019) and more than quadrupled for factor IX (from $52 million in 2005 to $238 million in 2019). In 2019, only 1 year after Hemlibra approval, factor VIII represented $778,592,692 of $1,569,746,508 (50%) of total Medicaid spending on hemophilia pharmaceuticals; factor IX represented $237,846,173 (15%); bypassing agents represented $262,242,517 (17%); and Hemlibra represented $291,065,124 (19%).[4]

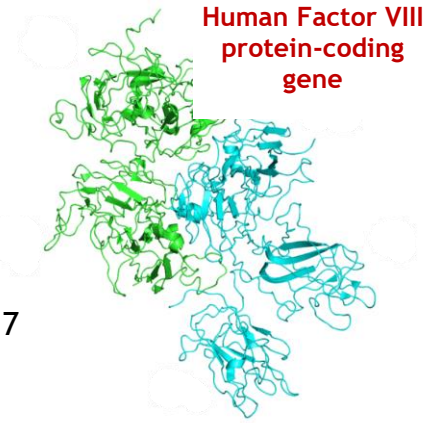


In terms of utilization, the investigators found that before 2015, a steady increase existed in the use of standard half-life recombinant factor, which dominated the market. After the entry of extended half-life recombinant factor in the third quarter of 2014, the use of standard half-life recombinant factor decreased from 142,087,494 units to 48,161,021 units (a 66% decrease) for factor VIII and from 24,724,386 units to 10,682,603 units (a 57% decrease) for factor IX.

After the entry of extended half-life factor in the US market, total units decreased from 175,019,342 units to 103,771,307 units (a 41% decrease) for factor VIII but remained constant for factor IX. From 2017 to 2019, the use of bypassing agents decreased from 11,634,758 units to 3,558,170 units (a 69% decrease).[4] The investigators concluded that hemophilia is now "one of the most expensive medical conditions to manage."[4]

As this class of drugs are currently unmanaged on the Health First Colorado Preferred Drug List, our DUR team conducted an analysis using pharmacy and medical claims to describe the demographics of members with hemophilia (Type A, B, or both) and their treatment utilization stratified by hemophilia type. We describe health care utilization between members with hemophilia Type A using Hemlibra and members not using Hemlibra.

Findings


Human Factor VIII protein-coding gene

Within our analysis, we identified 273 members with a hemophilia type A diagnosis, 57 members with a hemophilia type B diagnosis, and <30 members with both diagnoses during the study period (January 1, 2018 – March 31, 2021). The majority of patients with hemophilia type A were male (55%) ranging in age from 0-35 years (54%); for hemophilia type B, the majority were female (51%) with 40% being between the ages of 0-17 years; and for both hemophilia type A and B, the majority were male (90%) between the ages of 0-17 years (50%).

Among members with hemophilia type A, Advate® was the most commonly prescribed Factor XIII product (19.4%), with 28.9% of members with hemophilia type A receiving a Factor XIII product overall. Benefix® was the most commonly prescribed Factor IX product among members with hemophilia type B (21.1%), with 33.3% of these members receiving a Factor IX product overall. Factor IX products were commonly prescribed for members with both hemophilia type A and type B (68.2%). Hemlibra® was prescribed for 11.7% of members with hemophilia type A, and by 13.6% of members with both hemophilia type A and type B. Amicar® was more commonly prescribed for members with both hemophilia type A and type B (13.6%) than for members with only type A (8.8%) or only type B (1.75%).

Switching from one hemophilia treatment to another was most common among members with both hemophilia type A and type B; 36% of these members had at least one medication switch, while 17% of members with hemophilia type A had at least one switch and only 3% of members with hemophilia type B had at least one switch. Clinically, this is common and may be reflective of specific factor availability and number of weight-based units needed. It is important to highlight that units will vary not only between, but among, brand name products.

In terms of healthcare utilization, we identified 247 members with a Type A hemophilia diagnosis (with or without type B) and at least six months of follow-up after their earliest hemophilia diagnosis. Fewer members who filled Hemlibra had at least one inpatient stay (3.8%) compared to members who had not filled Hemlibra (24%). Approximately 20% of the members filled a Factor VIII product during the six-month follow-up.

Our mission is to improve health care equity, access and outcomes for the people we serve while saving Coloradans money on health care and driving value for Colorado.
https://hcpf.colorado.gov

Are you interested in observing a virtual Colorado DUR Board Meeting?

Board meetings are held once a quarter in:

- FEBRUARY
- MAY
- AUGUST
- NOVEMBER

Meeting dates, times, agendas and minutes are posted on the DUR Board web page at https://hcpf.colorado.gov/drug-utilization-review-board. Zoom meeting information for public attendees is posted on the same web page a few days prior to each meeting.

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Module Summary: Hemophilia and Associated Treatment Among Health First Colorado Members

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Images

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