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INSIDE THIS ISSUE	
First Extended-Release Injectable HIV Medication	1-2
Statin-induced rhabdomyolysis: to restart or discontinue permanently?	2-3
Long-Term Benzodiazepine Use – Considerations for the Busy Practitioner:	3-7
Naloxone Prescription for Opioid Prescriptions	8

First Extended-Release Injectable HIV Medication

By: Sarah Plummer, Pharm D.

Over the years, a handful of new drug classes for HIV treatment have been developed. However, these medications are given orally at least once daily. Adherence to oral medications has been a limitation for some patients to fully suppress HIV.

In January 2021, the ViiV Healthcare announced the FDA approval of Cabenuva (cabotegravir, rilpivirine) the first and only complete long-acting injectable regimen for HIV treatment. This innovative treatment allows virologically suppressed (HIV-1 RNA less than 50 copies per mL) adults living with HIV without prior treatment failure or resistance to cabotegravir or rilpivirine to maintain viral suppression with 12 dosing days per year.

Cabenuva is provided as a co-pack with two injectable medicines cabotegravir an integrase strand transfer inhibitor (INSTI) and rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI). It is dosed once monthly, as an option to

replace the current antiretroviral (ARV) regimen. Before receiving the first injection of Cabenuva, patients need to take 1 Vocabria (cabotegravir) tablet and 1 Edurant (rilpivirine) tablet once a day for one month to ensure medications are well-tolerated.

The approval of Cabenuva is based to two clinical trials, ATLAS and FLAIR, which included more than 1100 patients from 16 countries. In both studies, the most common adverse reactions observed in >2% were injection site reactions, pyrexia, fatigue, headache, musculoskeletal pain, nausea, sleep disorders, dizziness, and rash. Serious adverse events occurred in 4% (24/591) of patients taking Cabenuva and 3% (17/591) of adverse events led to withdrawal.

The approval of this new, long-acting injectable treatment is likely to improve adherence with the HIV regimen and lower the risk of spread. Like some other HIV treatment regimens, a patient assistance program is available for those who qualify.

<u>Reference:</u>

Cabenuva Package Insert. Accessed 3/19/21. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212888s000lbl.pdf

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Statin-induced rhabdomyolysis: to restart or discontinue permanently?

By: Casey Fitzpatrick, PharmD, BCPS

Rhabdomyolysis (often called rhabdo) is a medical condition characterized by the breakdown of damaged muscle resulting in the release of muscle cell contents into systemic circulation.[1] Manifestations of this condition can range from an asymptomatic elevation of serum muscle enzymes to extremely high enzyme levels resulting in life-threatening electrolyte abnormalities and acute renal failure.[2] The "classic triad" of clinical symptoms in moderate-to-severe cases are: muscle pain, muscle weakness, and brown or "tea-colored" urine. Rhabdomyolysis is most often associated with severe or intense exercise but there are multiple other potential causes including medications such as statins.

Statins, or HMG-CoA reductase inhibitors, are a group of medications commonly used in the treatment of hypercholesterolemia and mixed hyperlipidemia. Statins can have adverse effects on skeletal muscles which range from slight myalgia to severe rhabdomyolysis. The exact mechanism of how statins contribute to myalgia and rhabdomyolysis is not clear; risk factors that may predispose a person to develop statin-induced rhabdomyolysis includes frailty or low body mass index, older age, female sex, hypothyroidism, hypertension, polypharmacy, and alcohol or drug abuse.[3]

The decision whether to restart statin therapy in patients who developed rhabdomyolysis remains controversial. The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management

of Blood Cholesterol states "Patients who experience rhabdomyolysis with statin therapy may need to discontinue statin use indefinitely, although reversible causes should be sought."[4] A study by Zhang, et al. found that patients who continued receiving statin therapy after an adverse event saw a 10-20% lower incidence of both cardiovascular events and death from any cause.[5] With uncertainty surrounding this medication-induced condition, the decision to restart or discontinue statin therapy permanently following a diagnosis of rhabdomyolysis should be individualized and be based on the anticipated risks and benefits.

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Long-Term Benzodiazepine Use – Considerations for the Busy Practitioner:

By: Craig Kimble, PharmD, MBA, MS, BCACP, TTS

Introduction:

We have all heard the reports that long-term use of benzodiazepines (BZDs) produces complications especially when patients try to stop taking them. But what exactly are those complications, when is it appropriate to intervene, and what are the latest recommendations to prevent them? This article will summarize the latest information surrounding BZD use, withdrawal, considerations, and management. It is not intended to be comprehensive and address all aspects of care but rather to be a high-level review.

Adverse Events and Complications of BZDs:

Long-term use of BZDs can increase the risk of several serious adverse effects. These include impaired cognitive functioning, complications with mobility, impaired driving ability, and increased number of falls. Discontinuation of long-term BZD use can also result in withdrawal symptoms, increased risk of accidental overdose especially when combined with other central nervous system depressants, persistence of BZD-related adverse effects, physical dependence, and other BZD related use disorders.[1,2]

Concerns related to patient safety are behind many of the recommendations around BZD use. Several guidelines and expert consensus statements have cautioned against the chronic use of BZDs, especially in older and at-risk populations (see tables 1 for geriatric populations and table 2 for special population considerations). Though BZD remain a first-line treatment for acute alcohol withdrawal and may be used as acute anticonvulsants, they should generally be avoided for anxiety disorders, panic disorder, and insomnia. Other effective treatment options with superior safety profiles should be used when possible for these conditions. If a BZD is used, providers should consider limiting its use to 2-4 weeks if possible.[3]

Table 1: Excerpt from 2019 American Geriatrics Society Beers Criteria for potentially Inappropriate Medication Use in Older Adults, Criteria, and Discussion Related to Benzodiazepines[3]

Benzodiazepine	Rationale	Recommendation	Quality/ Strength of recommendation
Short/ Intermediate Acting	-Older adults have increased sensitivity to BZDs and decreased metabolism of long-acting agents. In general, all BZDs increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults. -May be appropriate for seizure disorders, rapid eye movement, sleep behavior disorder, BZD withdrawal, ethanol withdrawal, severe GAD, and periprocedural anesthesia.	Avoid	Moderate/Strong
Alprazolam			
Estazolam			
Lorazepam			
Oxazepam			
Temazepam			
Triazolam			
Long Acting			
Chlordiazepoxide			
Clonazepam			
Clorazepate			
Diazepam			
Flurazepam			
Quazepam			

Table 2: Populations with Special Considerations for Long-Term Benzodiazepine Use

Populations at Risk for Complications from Long-Term Benzodiazepine Use	Complication	Current Recommendations
Geriatric population	Increases risk of falls May have sleep problems	Taper off benzodiazepines if possible Consider tapering from shorter-acting agent due to the possibility of decreased metabolism in older adults. (See table 1)
Patients prescribed concurrent opioids	Added sedative effects and Increases risk of overdose and death especially if history of substance use disorder	Taper off benzodiazepine if possible; If used for institutional withdrawal treatment, consider more rapid taper over 2-3 weeks.
Patients with unstable psychiatric illness - generalized anxiety disorder (GAD)	May worsen symptoms; may reduce effectiveness of evidence-based psychotherapy; increase chance of harm	Limit use. Taper off benzodiazepines if possible; generally reserved for patients that continue to have severe symptoms of anxiety despite trials of other appropriate treatments.
Post-Traumatic Stress Disorder (PTSD)	May worsen symptoms and of depression	Taper off benzodiazepines if possible. Guidelines recommend against use as primary treatment for PTSD.
Medical comorbidities such as obesity, sleep-disordered breathing, COPD, traumatic brain injury, and hepatic or renal dysfunction.	Increased risk of respiratory depression.	• Taper off benzodiazepines if possible. • Most BZDs are metabolized primarily by CYP-mediated oxidation. If liver impairment, BZDs may have prolonged duration. • Consider using lorazepam (best evidence), oxazepam, and temazepam as they are mostly metabolized by conjugation if concerns of liver impairment. • Most do not need to be adjusted in renal impairment. Avoid lorazepam in renal failure
Pregnancy	Concerns with cleft lip/palate and	• Recommend patients taper of BZDS in pregnancy.

	urogenital and neurological malformations.	• A more rapid taper over 1 month can be done if tolerated. • May cause withdrawal symptoms in newborns. • Risk-Benefit discussion should occur with physician; Previously category D or X.
Breastfeeding	Crosses into breast milk resulting in adverse event in babies (prolonged effect, sedation, depression, "floppy baby syndrome").	• If necessary, use an agent with a shorter half-life. Infants may not have developed the mechanism to metabolize BZDs effectively.
Harm reduction	Minimize patient adverse events	• If complete discontinuation not possible, taper to lowest possible dose. • Encourage PRN and intermittent use as infrequently as possible.

Benzodiazepine Tapering

It should be noted, if a patient uses a benzodiazepine for longer than 8 weeks, clinicians should consider tapering it versus an abrupt stop to prevent withdrawal. Withdrawal symptoms include anxiety, depersonalization, depression, hypersensitivity to sensory stimuli, perceptual distortions, and weight/or appetite changes. During withdrawal, the patients preexisting symptoms may also worsen for a prolonged period.[5] Withdrawal symptoms may occur in a short-term (5-28 days) or protracted (6-12 months) phase after stopping benzodiazepines.

For most patients, a gradual taper over several months can be implemented to discontinue benzodiazepine therapy. Goals include decreasing withdrawal effects and management of rebound symptoms as well as recurrence of underlying symptoms that were being managed by the benzodiazepine. The general rule is that once a taper is started, it is okay to lengthen the taper but do not go back up on the dose. In general, for outpatient benzodiazepine tapers, the dose should be reduced by approximately 25% every week. As the end of the taper nears, this may need to be decreased further to 25% every 2 weeks if the patient is experiencing rebound or withdrawal symptoms. Consider longer tapers if patient has apprehension about the taper process or with those taking high doses for many years. In those cases, consider tapering 10-25% every 2-4 weeks and continue this process up to 6 months, as necessary.

Adjunctive Medication with BZDs

Many prescribers have used adjunctive medications to minimize withdrawal symptoms with BZDs. While there may be some small benefit to using aids such as hydroxyzine, carbamazepine, and pregabalin, there currently is no strong recommendation to use additional medications to aid in BZD tapering and withdrawal symptoms and use is based off limited data. The addition of psychotherapy when tapering BZDs however does have significant evidence and can lead to increased successful tapers and future abstinence rates. Cognitive behavioral therapy for anxiety and insomnia have been shown to be beneficial in discontinuing BZD therapy in patients not already receiving specialty mental health services.

Barriers to Tapering

There are a number of real and perceived barriers to effectively tapering BZDs. Barriers to tapering include fear of return of symptoms or fear of withdrawal effects. They also include the patient's sense of safety because of long-term use without adverse effects. Ensure a slow taper to minimize withdrawal symptoms, counsel that anxiety and insomnia do occur but diminish over time but if persistent may require other treatment or psychotherapy. Prescribers should highlight the negative outcomes that can occur to the patient including falls, cognitive impairment, balance problems, etc. and that tapering off these medications can help avoid those.

Final Thoughts:

Prescribers have used BZDs in a variety of conditions for more than 50 years. As we have learned about these drugs from clinical experience, it has become more apparent of their effects on cognition in older adults, side effects, and misuse / dependence potential. We have also come to realize the real danger for overdose and death when combined with other sedating medications, particularly opioids. There is a value to avoiding BZD use and attempting to use safer treatment methods when possible. In general, it is best to avoid use in patients with risk factors for adverse outcomes when possible including current, recent, or recurrent substance misuse or abuse, current opioid use, older adults, diagnosis of sleep apnea, COPD, or other indicated high-risk individuals. However, if needed for acute use, try to minimize use and taper as appropriate. Prescribers may also consider treatment agreements. It is okay to stay the duration of the taper but do not increase the dose once the taper is stated. Keep supplies of medication at 7-14 days during tapers. In addition, please consider an appropriate taper when candidate patients are identified.

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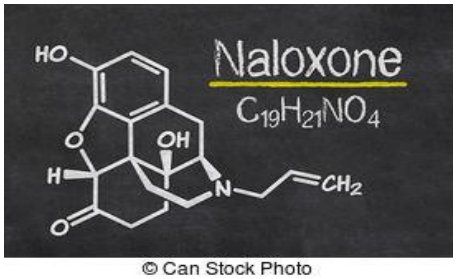
Naloxone Prescription for Opioid Prescriptions



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By: Robert Stanton, M.B.A., Pharm D., BCPS

Naloxone has played a critical role in reducing opioid-related deaths. This includes opioid use for legitimate purposes. Beginning this year, the Medicaid Drug Utilization Review process will review patients on opioid dosages of 50 morphine milligram equivalent per day and higher, especially those who have a history of overdose or substance use disorder, or concurrent benzodiazepine therapy who do not have a concurrent naloxone prescription. If such Medicaid patients do not have a concurrent naloxone prescription, a reminder letter suggesting a naloxone prescription will be issued. The CDC, in their 2016 guideline for prescribing opioids for chronic pain, recommend concurrent naloxone prescription to the patient or family members.[1] The CDC guideline also emphasizes the increased risk if concurrent benzodiazepine therapy is being prescribed with opioid dosages of 50 MME per day or higher. Similarly, the FDA began requiring Black Box Warnings for opioids and benzodiazepine labeling relating to increased risks and deaths from combined use.[2] Recently in 2019, the FDA also issued an alert and a new warning for the gabapentinoids, gabapentin (Neurontin, Gralise), enacarbil (Horizant) and pregabalin (Lyrica), warning of the risk of respiratory depression.[3] The FDA alert emphasizes that the concurrent use of gabapentinoids and opioids can lead to death.[3]

The preferred naloxone dosage form for Medicaid patients is naloxone nasal spray.

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