Wyoming Drug Utilization Review

Opioid Dependence Medication Review

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America's opioid overdose epidemic continues to be a top public health concern.[1] Since 1999, opioid overdose deaths (prescription opioids and heroin) have quadrupled and nearly half involved prescription opioids. In 2013, healthcare providers wrote almost a quarter of a billion opioid prescriptions.[1,2] The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) categorizes opioid dependence and abuse as one diagnosis, opioid use disorder.[3] Opioid use disorder is characterized by the presence of ≥ 2 of 11 items in a 12-month period, including hazardous use, craving, social effects, and tolerance.[3] Opioid overdose and/or deaths are being prevented by medication-assisted therapy (MAT) in opioid treatment programs (OTPs) that combine medications (naltrexone, buprenorphine, methadone) with counseling.[1,4]

There is no preferred drug for MAT, as therapy choice is based on treatment goals and patient preference.[5] There are three stages of MAT; induction, stabilization, and maintenance.[5,6] The duration of each stage depends on the medication used and patient characteristics. Due to limited data on long-term effects of MAT medications, patients needing lifelong therapy should be monitored to ensure continued efficacy and safety. The dosing of MAT medications will also depend on the patient's stage of therapy.[5,6] Federal regulations restrict the use of buprenorphine and methadone for use in opioid use disorder treatment, therefore dosing for these drugs is not included.[7]

Naltrexone is a semi-synthetic μ opioid receptor antagonist that blocks the effects of opioids by occupying up to 95% of μ opioid receptors.[5,6] This can lead to the displacement of heroin or prescription opioids, precipitating withdrawal.[5] As a result, initiation begins once patients have abstained from short-acting opioids for ≥ 7 days or long-acting opioids for ≥ 10 days.[5,6] Naltrexone is available as an oral 50 mg tablet or an intramuscular, extended-release injectable, containing 380 mg of naltrexone, given once monthly.[8] While efficacious, poor adherence and large patient drop outs (20% remain on treatment at 6 months) make it an unpopular option for opioid use disorder.[9] Naltrexone does not have euphoric effects, reducing the risk for diversion and misuse.[5,6]

Naltrexone has no federal regulations restricting its use by prescribers.[7] To ensure the patient is opioid free, a test dose of 12.5-25 mg is given.[5,6] If positive for withdrawal, naltrexone should not be used. Four hours after a negative test dose on day one, 25-50 mg can be given, followed by a 50-100 mg dose on day two. During the stabilization stage, patients can continue 50-100 mg per day or begin three times weekly doses (e.g., 100 mg Monday and Wednesday, 150 mg Friday). This dose can be continued into the maintenance stage with dose adjustments made on an individualized basis.[5,6] Naltrexone is well-tolerated with the most common side effects including headache (HA), gastrointestinal upset, depression, and elevated liver function tests (LFTs).[5] Patients should be monitored for opioid withdrawal, as development may indicate subtherapeutic dosing or poor adherence. This can be overcome by increasing the dose or switching to a different medication.[5] Contraindications include patients with active opioid use or patients in withdrawal.[5,8] The concurrent use of naltrexone with other opioid antagonists (methylnaltrexone, naloxegol) should

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be avoided, as it may result in additive antagonistic effects.[5] Naltrexone can also diminish the therapeutic effect of opioid analgesics. If opioid analgesics are needed, naltrexone should be temporarily discontinued and reintroduced after an opioid free period of 7-10 days to prevent withdrawal.[5,6]

Buprenorphine is a partial μ opioid agonist with weak κ opioid antagonist activity that suppresses withdrawal, blocks illicit opioid effects, and reduces cravings.[5,6,10] This activity creates a ceiling effect where higher doses do not result in increased effect and allows for larger doses to be given with fewer adverse effects.[10] For treating opioid use disorders, buprenorphine is available as a sublingual tablet (alone or with naloxone), sublingual film with naloxone, and as a subcutaneous (SQ) implant.[8] Abuse of buprenorphine primarily involves the diversion of sublingual tablets or films that users inject.[5,6,10] If injected during opioid intoxication, buprenorphine can precipitate withdrawal, and the addition of naloxone increases this likelihood. However, if injected during withdrawal, buprenorphine can alleviate symptoms due to its partial agonist effects. The average US street value for a single buprenorphine 8 mg sublingual tablet appears to be $25/tablet, and a single 8 mg/2mg buprenorphine/naloxone sublingual film appears to be $17.25/film.[11]

It is recommended to use the buprenorphine/naloxone combination over buprenorphine to reduce the likelihood of diversion.[5,10] In 2016, the SQ implant (Probuphine®) was approved for the maintenance of opioid use disorder treatment after demonstrating an 8.8% increase in opioid abstinence at four months compared to sublingual buprenorphine.[12] The most common side effects of buprenorphine include constipation, HA, nausea and vomiting (N/V), and hypotension.[5,6,10] Due to hypotension, patients with hypovolemia, cardiovascular disease, or taking drugs causing hypotension should take precautions (blood pressure checks during initiation and titration). Elevated LFTs have been observed in patients with hepatitis C while on buprenorphine. This may be due to injected buprenorphine misuse (higher bioavailability) causing liver toxicity.[10] Baseline and periodic (every 6 months) LFT monitoring may be considered in patients at an increased risk for hepatotoxicity.[8] The main contraindication to buprenorphine is hypersensitivity to the formulation used.[8] Due to the depressant effect of buprenorphine, alcohol, sedatives, and anxiolytics should be avoided to prevent enhanced central nervous system (CNS) depression.[5,10] Buprenorphine is primarily metabolized through CYP3A4. Drugs that inhibit or induce this enzyme can alter the properties of buprenorphine, and concomitant use may require dose adjustments of buprenorphine.[5,10]

Methadone is a full μ opioid agonist that blocks opioid euphoria, reduces cravings, and suppresses withdrawal for 24-36 hours.[5,6] It is available as tablets, dispersible tablets, solutions, powders, and liquid concentrations.[8] OTP regulations require supervised administration, as unsupervised use can lead to misuse and diversion.[7] The average US street value for a single 5-10 mg methadone tablet appears to be $7.50/tablet, and a single 40 mg dispersible tablet appears to be $40/tablet.[11] Appropriate dosing is critical to reduce the risk of death or nonfatal overdose, especially during the first 2 weeks of induction.[5,6] In general, these deaths or nonfatal overdoses are due to the initial dose being too high, being increased too rapidly, or methadone interacting with other CNS depressants.[5,6]

Methadone has an extensive list of side effects that may include N/V, HA, insomnia, decreased libido, constipation, and sweating.[5,8] These side effects may diminish over time; however, constipation and sweating may persist.[8] Higher methadone doses (>100 mg/d) may be associated with QTc prolongation.[5,6] Patients with risk factors for QTc prolongation should have ECGs at baseline, 2-4 weeks after initiation, methadone doses of 30-40 mg/d, and again at 100 mg/d.[5,8] If a QTc ≥ 500 msec occurs, an immediate dose reduction is recommended, or patients should be switched to naltrexone or buprenorphine.[8] Contraindications include hypersensitivity, respiratory depression, and acute bronchial asthma and/or paralytic ileus. Caution should be used with agents that may prolong QTc, including class I or III antiarrhythmics, calcium channel blockers, and some antipsychotics and antidepressants.[8] Methadone is primarily metabolized through CYP3A4 and 2B6.[5,6] Drugs that interact with these pathways should be used with caution, as increases in methadone's serum levels may lead to unintentional overdoses and/or death.[5,6]

Healthcare providers play an important part in ending the opioid overdose epidemic by educating and/or treating patients with opioid use disorder. For more information regarding the various treatments used in

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P&T Committee Meeting Update

The P&T Committee met for its quarterly business meeting on November 9, 2017.

Highlights of this meeting include:

Trokendi XR will require prior authorization for migraine. Patients will be directed to other forms of topiramate.

The Angiotensin Receptor blockers (ARBs) will no longer require a step through an ACE Inhibitor.

PCSK9s criteria will be updated to include secondary prevention of ASCVD in patients who have not met goal with a maximum dose of a high-potency statin. Familial hypercholesterolemia will continue to be approved.

Austedo will be approved for tardive dyskinesia based on its recent approval.

Tremfya has superiority data over Humira. As such, it was recommended as a preferred agent for plaque psoriasis.

Imbruvica will be limited to indication for graft versus host disease. This will not affect its use in cancer therapy.

Haegarda, Mavyret, Bevyxxa and Benlysta will all be limited to indication. Mavyret will also have the Hepatitis C class criteria applied.

Effective January 1, 2018, Xiidra will be non-preferred to Restasis. A 12 week trial and failure of Restasis will be required prior to approval of Xiidra.

Hemophilia agents were reviewed. There is no comparative evidence in this class. The Committee requested that all patients be grandfathered should a restrictive PDL be created.

The proposed prior authorization criteria will be posted for public comment at www.uwyo.edu/DUR. Comments may be sent by email to alewis13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board, Dept. 3375, 1000 E. University Avenue, Laramie, WY 82071. Comments should be received prior to February 1, 2018.

The next P&T Committee meeting will be held Thursday, February 8, 2018 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

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MAT, the American Society of Addiction Medicine (ASAM) and CSAT provide detailed clinical and practice guidelines for opioid use disorder treatment.[5,6]

References:

1. Center for Disease Control and Prevention. Injury prevention & control: opioid overdose. George (AL): Center for Disease Control and Prevention. 2016. Available from: https://www.cdc.gov/drugoverdose/index.html. Accessed: January 27, 2017.
2. Manchikanti L, Kaye AM, Kaye AD. Current state of opioid therapy and abuse. Curr Pain Headache Rep.2016;20:34.
3. Hasin DS, O'Brien CP, Auriacombe M. DSM-5 criteria for substance use disorders: recommendations and rationale. Am J Psychiatry. 2013;170:834-851.
4. Schuckit MA. Treatment on opioid-use disorders. N Engl J Med. 2016;375:357-368.
5. Kampman K, Jarvis M. American Society of Addiction Medicine: national practice guidelines for the use of medications in the treatment of addiction involving opioid abuse. J Addict Med. 2015;9:358-367.
6. Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction in opioid treatment programs. HHS Publication No. (SMA) 12-4214. Rockville (MD): Substance Abuse and Mental Health Services Administration. 2005. Available from: http://store.samhsa.gov/shin/content/SMA12-4214/SMA12-4214.pdf. Accessed: January 27, 2017.
7. Substance Abuse and Mental Health Services Administration. Federal guidelines for opioid treatment programs. HHS Publication No. (SMA) PEP15-FEDGUIDEOTP. Rockville (MD): Substance Abuse and Mental Health Services Administration. 2015. Available from: http://store.samhsa.gov/shin/content/PEP15-FEDGUIDEOTP/PEP15-FEDGUIDEOTP.pdf. Accessed: January 27, 2017.
8. Lexi-Drugs. Lexi-Comp Online™. Hudson (OH): Lexi-Comp, Inc.; 2017. Available from: http://online.lexi.com. Accessed: January 27, 2017.
9. Bart G. Maintenance medication for opioid addiction: the foundation of recovery. J Addict Dis. 2012;31:207-225.
10. Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Treatment Improvement Protocol (TIP) Series 40. HHS Publication No. (SMA) 04-3939. Rockville (MD): Substance Abuse and Mental Health Services Administration. 2004. Available from: https://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/Bookshelf_NBK64245.pdf. Accessed: January 27, 2017.
11. StreetRx. Buprenorphine and methadone. StreetRx website. Available from: http://streetrx.com/usa. Accessed: January 27, 2017.
12. Rosenthal RN, Lofwall M, Kim S, et al. Effect of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine. JAMA. 2016;316:282.290.

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December 2017

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