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The Role of Buprenorphine and Methadone in Opioid Use Disorder Harm Reduction

Daniel Leavins
Lakeview Health, leavins_dd@lynchburg.edu

Opioid Use Disorder: The Role of Buprenorphine and Methadone

Daniel Leavins PA-C

University of Lynchburg

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Opioid use disorder is a chronic medical condition affecting more than 2 million Americans in 2016 resulting in more than 42,000 opioid overdose deaths.[1,2] Life expectancy has decreased in the last decade due to unintentional deaths related to overdoses. The accessibility of treatment for opioid use disorder has reached less than 20% of Americans in need creating wide disparities for medical treatment. [2] Emergency rooms throughout the country are managing more than 1000 patients per day based on the dramatic rise in using illicit opioids.[3] Street drugs including heroin are routinely laced with synthetic carfentanil and fentanyl.[2] Clinicians have the daily task to differentiate appropriate, medically necessary opioid prescriptions for legitimate pain management versus misuse and abuse.[4] Advances in the pharmacological management of opioid use disorder have created opportunity to expand treatment in rural areas using buprenorphine products.[5] Opioid use disorder must be part of a long-term management strategy to decrease morbidity and mortality from devastating medical consequences such as endocarditis, hepatitis, sepsis, HIV and drug overdose.[6]

Etiology

The etiology of substance use disorder is related to the dysregulated processing of natural reward pathways and hijacking of brain reward.[7] Patients experiencing substance use disorder present with diminished subjective reward responsiveness and reduction of natural rewards in the brain. Opioid use disorder will result in attenuated dopaminergic neurotransmission in responding to the natural reward system.[8]

The American Psychiatric Association (APA) has reclassified opioid dependence and abuse to better delineate the spectrum of opioid use disorder classification. The older designated opioid terms were replaced with opioid use disorder mild, moderate or severe.[9] The clinical distinction has aided to distinguish severity of disease and treatment implications.[9] Addiction is a chronic relapsing disease of the brain involving compulsive behavior despite ongoing negative consequences to behavior.[9]

Patient Presentation

The patient with opioid use disorder will often present with characteristic behaviors.[9] They are often obsessive and impatient to obtain specific opioids and often call after hours to a clinician for refills. The drug seeking behavior can manifest as missing scheduled appointments and calling at last minute for an emergency appointment request. A patient may also request multiple medication adjuncts such as Neurontin, Soma or benzodiazepine as many can present with polysubstance use disorder. Fabricating stories are common typically describing somatic pain complaints without a clear diagnosis. The patient can also endear themselves to the clinician and staff for favorable narcotic prescribing agenda. Multiple allergies are commonly listed by drug-seeking behaviors to corral clinician to prescribe a specific narcotic. A patient may also use another patient's diagnostic studies using computer software to give the illusion of a documented medical issue justifying opioids.

Physical Exam/Psychiatric History

The physical examination is completed as a component of treating substance use disorder. The clinician must ensure physical examination is properly documented in the patient medical record before starting any new prescriptions for substance use disorder.[10] Tobacco use is included in medical history and counseling for cessation treatment availability.

A detailed psychiatric history must be conducted before starting any treatment for opioid use disorder. A patient may need a consultation with a psychiatrist for psychiatric comorbidities surrounding opioid use disorder.[10] A query should be conducted on any other use of poly substances affecting treatment plan moving forward.

Laboratory Workup

The typical lab tests ordered are metabolic panel, complete blood count, liver panel study, hepatitis panel, HIV, syphilis, tuberculosis skin testing and sexually transmitted disease urine screen.[10] A urine drug screen is sent for quantitative analysis for 12- panel drugs of abuse.[10] All females of childbearing age must be provided with a urine pregnancy test and queried for current contraception method used.[10]

Diagnosis

The *Diagnostic and Statistical Manual for Mental Disorders*, Fifth Edition (DSM-5) has defined opioid use disorder as the problematic pattern of opioid use leading to clinically significant impairment or distress or manifested by at least two of the following, occurring within a 12 month period:[11]

- Opioids are often taken in larger amounts or over a longer period of time than was intended.
- A persistent desire or unsuccessful efforts to cut down or control opioid use.
- A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
- Craving, or a strong desire or urge to use opioids.
- Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
- Continued opiate use despite having a persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
- Important social, occupational, or recreational activities are given up or reduced because of opioid use.
- Recurrent opioid use in situations in which it is physically hazardous.
- Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by the substance.
- Tolerance.
- Withdrawal.

Opioid use disorder is classified by severity from mild, moderate, or severe.

- Mild: 2 to 3 symptoms
- Moderate: 4 to 5 symptoms
- Severe: 6 or more symptoms[11(p541)]

Treatment/Management

The clinician prescribing buprenorphine and methadone in outpatient setting continues to evolve after the Drug Addiction Act of 2000 provided accessibility to create alternate treatment pathway other than methadone.[12] Initially, the oral formulation of buprenorphine was authorized per qualified doctors completing x waiver training. Buprenorphine and methadone have been shown to effectively treat opioid use disorder and improve sustained abstinence.[13] Research studies have found patients most likely had health insurance utilizing buprenorphine, whereas uninsured patients were more apt to seek state-funded methadone programs.[13]

The profile of medication-assisted treatment is discussed as part of individual care with patient consultation (table 1).[4] The drug methadone is a full opiate agonist creating increased euphoria and respiratory depression at increasing dose schedule.[14,15] The rate of respiratory depression and overdose is higher with methadone due to full agonist effect.[15] Buprenorphine products have a respiratory depression ceiling effect leading to greatly reduced the degree of respiratory demise.[15] The unique chemical structure of buprenorphine has both agonist and antagonist effect on the opioid receptor sites.[15] Additionally, the buprenorphine-naloxone

combination products have abuse-deterrent for intravenous use and diversion. Naloxone was created as a rapid-acting formulation treating opioid overdose providing life-saving full blockade to the receptor sites .[15] Methadone can be responsible for creating a long QT syndrome affecting the re-polarization of the cardiac rhythm.[16] The elongated QT interval can lead to life-threatening cardiac abnormalities such as torsade's de pointes leading to potential seizures, syncope and cardiac death.[16]

The medication buprenorphine can be prescribed by a qualified provider upon completing government approved training and receiving an x waiver from the Drug Enforcement Administration (DEA).[17] Primary care providers are uniquely situated for expansion of medication-assisted treatment for harm reduction.[17]

Pregnancy and opioid use disorder have special considerations for maternal-infant leading to complications including low birth weight and early premature delivery.[10] Methadone has most studied research involving pregnancy and represents the standard for treating opiate use disorder. Research has shown treatment with methadone or buprenorphine outcomes to mother and developing fetus similar.[18]

The financial component of buprenorphine and methadone requires consideration before starting any medication maintenance program. The cost of medication is one component of a treatment strategy. The patient must also consider travel distance to a clinic or doctor, insurance coverage and potential requirements for counselor cost outside of treatment. The availability of insurance or entitlements will typically be more desirable for patients seeking treatment.

Methadone maintenance therapy costs average $4,600 yearly with improved rates of retention compared to buprenorphine.[19] Buprenorphine maintenance therapy has an average yearly cost of $4,100 providing lower dollar cost for medication. Total cost should also include the office visit, drug, therapy interactions, and medication administration.[19] A primary care clinic would likely be a less expensive alternative to obtain buprenorphine maintenance. However, the cost will vary dramatically from a region and individual medical practices. Methadone dispensing must follow under guidelines of a certified drug treatment program also known as a methadone clinic.[19]

Formulations of sublingual buprenorphine available are Suboxone film offered in 2/0.5 mg, 4/1 mg, 8/2 mg, and 12/3 mg respectively.[20] Buprenorphine tablets are available in the generic formulation in doses of 2/0.5mg and 8/2mg.[20] Each of the above formulations can be prescribed for home use for the patient.[20] Methadone is available in oral tablet form 5mg, 10mg, and disintegrating 40 mg tablet.[10] Oral methadone preparations currently available are 5mg per 5 ml, 10 mg per 5 ml and 10mg per ml.[10]

The first starting dose recommended for methadone range is 10-30 mg, and reevaluation after 3-4 hours and a second can be administered if not exceeding 10 mg on the first day if withdrawal continues.[10] Federal guidelines mandate initial methadone dose cannot exceed 30 mg.[10] Typically patients will dose an average range from 60 to 120mg daily for maintenance based on adjustments.[10] A dose increase of 5-10 milligrams increments is given incrementally every seven days to avoid potentially adverse side effects.[10] Methadone has no lifetime limits for the treatment of opioid use disorder. Methadone must be administered in approved methadone office or clinic meeting state and federal guidelines.

Buprenorphine should be prescribed in the medical office setting. The patient should be demonstrating mild-to-moderate opioid withdrawal before the first dose to reduce the possibility of precipitated withdrawal.[10] Induction should start at 2-4 mg and increased in increments of 2-4 mg.[10] Clinical prescribers should observe patients in the office setting during the induction phase. The Food and Drug Administration approved dosing to a limit of 24 mg daily.[2]

Buprenorphine subdermal has gained traction recently as an alternative delivery system for daily dosing for six months.[21]

Naltrexone is a full opioid antagonist used for treating opioid use disorder. Naltrexone will block the opioid agonist effects on mu receptors.[6] The medication is prescribed in 50mg oral dose schedule on a daily basis. Injectable extended-release naltrexone (Vivitrol) 380 mg intramuscular is prescribed monthly to manage opioid use disorder.[22]

Finally, the medical community has been slow to embrace the utilization of buprenorphine-naloxone products for medication-assisted treatment. Stakeholders must continue to educate and support clinicians involved in outpatient treatment utilizing buprenorphine for medication-assisted treatment .[23]

Patient education

The patient should be involved in deciding on the best treatment options available based on preference, previous treatment and setting before choosing buprenorphine, methadone or naltrexone medication management.[10] The patient and family should be involved in counseling and support groups.[10] The psychosocial situation and co-occurring disorders are also part of the planning and discussion for an appropriate opioid treatment program. Primary care offices will need to refer patients for methadone in an approved clinic setting.[10]

Follow-up

The clinicians should have access to the Prescription Drug Monitoring Program (PDMP) for monitoring of potential diversion and other potentially harmful prescribed medications.[10] Patients should be randomly given urine drug screens in the office setting.[10] Medications should be brought to the office for pill count randomly for early signs of possible diversion or misuse. The primary care physician may ultimately refer to an addiction specialist or inpatient addiction treatment for patient violating office opioid agreement. Advanced practice providers (APPs) have been granted prescribing privileges for buprenorphine, although the lower rate of participation (table 2).[24]

Conclusion

Medicated -Assisted Treatment (MAT) has continued to be underutilized in the United States. APPs have recently obtained the ability to apply for x waiver for prescribing buprenorphine products for opioid use disorder after completing 24 hours site approved training.[24] The Drug Enforcement Agency is responsible for providing special identification number included in prescribed buprenorphine prescriptions upon waiver completion requirements.[24] APPs are positioned to participate in solutions for opioid epidemic currently experienced in the United States. Buprenorphine, naltrexone, and methadone products are well-study medications for safely treating opioid use disorder along with counseling .[10]

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Table 1

Methadone	**Buprenorphine**
Full mu agonist	Partial mu agonist
Titratable withdrawal relief	Limited withdrawal relief in long-term opiate users.
Limited availability, lower cost	Widely available but high-cost
Greater retention in treatment	Less retention in treatment
Higher diversion risk	Lower diversion risk
More frequent supervised administration	Patient self-administration typical
More effective in co-occurring opiate and cocaine dependence	Less effective in co-occurring opiate and cocaine dependence
High monitoring, frequent urine drug screens	Less monitoring required

Table 2

Counts of DATA–Waivered Practitioners, as of June 4, 2018