Buprenorphine and Opioid Use Disorder Management with Dr. Neal Christopher

Emmanuelle Issa, Neal Christopher, DO, David Puder, MD

Dr. Neal Christopher and Dr. David Puder do not have any conflicts of interest.

We are joined again by Dr. Neal Christopher, who is currently the Vice Chair and Associate Medical Director of Arrowhead Regional Medical Center and the Psychiatry and Addiction Consultant for the San Bernardino County Department of Public Health. Dr. Christopher has previously appeared on the Psychiatry and Psychotherapy Podcast in episode 063, "Interviewing Well For Psychiatry Residency & Beyond," and episode 103, "Acceptance and Commitment Therapy with Dr. Steven Hayes."

In this week's episode, Dr. Puder and Dr. Christopher discuss the recent elimination of the X-Waiver and what it means for providers, the mechanism and efficacy of buprenorphine, and practical tips for prescribing buprenorphine and supporting patients on their road to recovery from opioid use disorder.

This episode continues our podcast series on addiction, designed to meet the one-time, 8-hour training requirement introduced by the Consolidated Appropriations Act of 2023. This mandate applies to all providers registered with the Drug Enforcement Administration (DEA), and our series primarily focuses on the treatment and management of patients with substance use disorders.

Here are other episodes that contribute towards the training requirement:

Episode 183: Xylazine, Methamphetamines, Bath Salts, and Spice with Dr. Cummings (1 CME unit)
Episode 182: Opioid Use Disorder with Dr. Cummings (1 CME unit)
Episode 181: Alcohol Use Disorder with Dr. Cummings (1 CME unit)
Episode 044: Marijuana and Mental Health (0.5 CME units)
Episode 064: Does Cannabis Use Increase Schizophrenia and Psychosis? (0.75 CME units)
Episode 066: Fentanyl: The Next Phase in the Opiate Epidemic (0.75 CME units)
Episode 030: Ketamine and Psychedelics with Dr. Michael Cummings (0.75 CME units)

All these episodes, along with future releases, are included in our yearly subscription. For registration or additional information about this course, please visit: https://www.psychiatrypodcast.com/cme-program.

We appreciate your dedication to enhancing patient care and tackling the substantial challenges associated with addiction and detoxification.

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Federal Legislation Regarding Controlled Substances

In 1970, the Controlled Substances Act established five schedules of controlled substances and required that healthcare providers who wished to prescribe these narcotic medications for maintenance or detoxification treatment annually obtain a license from the Drug Enforcement Administration (Preuss et al., 2023). Each provider's unique license number allowed for controlled substance prescriptions to be linked to them, which caused healthcare providers to be apprehensive about prescribing these medications.

The Drug Addiction Treatment Act of 2000 (DATA 2000) amended the Controlled Substances Act and allowed providers to prescribe buprenorphine and other Food and Drug Administration (FDA)-approved controlled drugs in schedules III, IV, and V for treatment of opioid dependence in office-based settings if certain conditions were met (*Model Policy on DATA 2000*, n.d.). This amendment increased access to treatment by eliminating the requirement that patients only receive opioid agonist treatment in Opioid Treatment Programs, which were sometimes restricted to being referred to as "methadone clinics."

The DATA 2000 specified the following requirements that providers prescribing buprenorphine are required to follow: they must be licensed in the state, must have a valid DEA controlled substances registration and identification number, must follow federal and state regulations concerning controlled substances, and must hold a current waiver (*H.R.2634*, 2000). The DATA 2000 also limited the number of patients a healthcare provider was allowed to treat unless they filed an application with the DEA to extend the waivered capacity. The provider must also demonstrate the ability to recognize when to offer or refer patients to counseling and other supplemental services.

Elimination of the X-Waiver

In 2021, the Mainstreaming Addiction Treatment (MAT) Act removed the requirement that healthcare providers were required to obtain a specific DEA waiver in order to prescribe certain controlled substances (*H.R.1384*, 2021). It also instructed the Substance Abuse and Mental Health Services Administration (SAMHSA) to organize a national campaign to educate providers about substance use disorder and encourage them to incorporate maintenance and detoxification treatment into their practices. This act empowered healthcare providers to treat opioid use disorder (OUD) by allowing providers that held a standard controlled substance license to prescribe buprenorphine to their patients (Dydyk et al., 2023).

In December of 2022, the MAT Act eliminated the DATA-Waiver (X-Waiver) program (Dydyk et al., 2023). In an effort to increase access to OUD treatment, the Consolidated Appropriations Act of 2023 (the Omnibus bill) removed the federal requirement for a special waiver to

prescribe controlled substances (*Waiver Elimination (MAT Act)*, 2023). SAMHSA now encourages that all providers registered with the DEA with Schedule III authority prescribe buprenorphine to treat OUD in their own practice if permitted by applicable state law. Additionally, there is no longer a limitation to the number of patients with OUD that a provider can treat.

Current DEA Training Requirement

The Consolidated Appropriations Act of 2023 enacted a new one-time, 8-hour training requirement for all providers registered with the DEA. The deadline to complete this is the date of the provider's next scheduled DEA registration submission on or after June 27, 2023, whether it be an initial registration or a registration renewal. This is only a one-time training requirement and will not affect future registration renewals (*DEA Training Requirement,* 2023).

There are several options to fulfill this requirement:

1. You automatically satisfy this training if you are board certified in either addiction medicine from the American Board of Preventive Medicine, the American Osteopathic Association, or previously from the American Board of Addiction Medicine, or else in addiction psychiatry from the American Board of Psychiatry and Neurology.

2. You automatically satisfy this training if you graduated in good standing from a medical, physician assistant, advanced practice nursing, or dental school in the US within five years of June 27, 2023 and successfully completed a comprehensive curriculum including a minimum of eight hours of training on treating and managing patients with opioid or other substance use disorders. The training must include the appropriate clinical use of all medications approved by the FDA for substance use disorder treatment or safe pharmacologic management of dental pain and screening. It must also contain education on brief intervention and referral for appropriate treatment of patients with or at risk of developing opioid and other substance use disorders.

3. You can satisfy this training by completing a total of 8 hours of training on treatment and management of patients with opioid or other substance use disorders.

See this announcement letter addressed to DEA-registered healthcare providers for more information on the new training requirement:
https://www.deadiversion.usdoj.gov/pubs/docs/MATE_Training_Letter_Final.pdf

Buprenorphine: Mechanism of Action, Pharmacodynamics, and Pharmacokinetics

Buprenorphine is a synthetic opioid that is FDA-approved for the treatment of acute pain, chronic pain, and opioid use disorder (Kumar et al., 2023). It acts as a delta-receptor agonist, a kappa-receptor antagonist, and most importantly, a partial mu-receptor agonist. Its partial

agonism properties can be described to patients as “a key that fits very tightly into a lock that remains there for a long time but doesn’t open the door all the way.” Fentanyl, a very strong mu-receptor agonist, can be described as “a key that completely opens the door” and naloxone, a mu-receptor antagonist, can be referred to as “a key that slams the door shut”. Buprenorphine is very effective in OUD treatment because it is used as an agonist substitute for stronger full agonists like fentanyl and heroin. It occupies the mu-receptor with a higher binding affinity than other opioids but doesn’t fully activate the downstream pathway like stronger opioids do. As a partial agonist, buprenorphine has a ceiling effect: it will begin to antagonize itself as it reaches a certain concentration, which makes it much harder to overdose and experience respiratory depression.

Buprenorphine has slow dissociation kinetics, which allows its own withdrawal symptoms to be milder and not as uncomfortable for the patient (Kumar et al., 2023). However, if taken too soon after the use of another opioid like fentanyl or heroin, buprenorphine will bind with a greater affinity to the mu-receptors and displace the stronger opioids, which will precipitate a very severe iatrogenic withdrawal that is miserable for patients. Patients often describe the withdrawal experience as “feeling like you’re dying.” Symptoms include flu-like symptoms such as fever and chills, diarrhea, muscle cramps, depression, etc. This very unpleasant experience may reduce a patient’s desire to continue with treatment, so timing is key and will be discussed below.

Buprenorphine has poor bioavailability when administered orally due the liver and intestines breaking down most of the drug (Kumar et al., 2023). Therefore, the preferred route of administration is sublingually, which avoids the first-pass effect and allows absorption to occur quickly. Buprenorphine has a slow onset of action and reaches its peak effect 3 to 4 hours after administration with an average half life of about 38 hours. The cytochrome CYP34A enzymes break down buprenorphine to its active metabolite, norbuprenorphine, which has weak intrinsic activity. The inhibition of these enzymes by certain drugs (i.e. antifungals, macrolide antibiotics, HIV protease inhibitors) will cause increased levels of buprenorphine while the activation of these enzymes by other drugs (i.e. carbamazepine, topiramate, phenytoin, barbiturates) will decrease buprenorphine levels. Thus, the dosage needs to be adjusted based on other medications the patient may be taking. About 80% of buprenorphine and its active metabolite are excreted in the feces while 20% is excreted by the kidneys.

Buprenorphine is widely available combined with naloxone in sublingual film and sublingual tablet forms. Naloxone is commonly known as the opioid overdose rescue medication due to its strong competitive opioid antagonistic effect and its high affinity for the mu-receptor that allows for a very rapid reversal of overdose symptoms (Jordan & Morrisonponce, 2023). Due to naloxone’s inability to be absorbed orally, buprenorphine has the predominant effect when the sublingual film or tablet is taken. If the combination is taken in IV form, naloxone is absorbed and its strong antagonistic effect prevents the high that excess buprenorphine can cause. Additionally, the naloxone component can even precipitate instant withdrawal, which can significantly discourage and dissuade the patient from abusing the combination drug again in

the future (Kumar et al., 2023). On the other hand, patients who worry about experiencing withdrawal and cravings find comfort in the fact that when taken sublingually as prescribed, buprenorphine/naloxone will stave off cravings without precipitating withdrawal.

The following is a list of possible adverse effects that may be experienced with buprenorphine treatment: constipation, nausea, vomiting, dizziness, orthostatic hypotension, drowsiness, headache, memory loss, sweating, dry mouth, miosis, sexual side effects, and urinary retention. More serious adverse effects to be aware of are hypotension, central nervous system depression, QT prolongation, and a lowered seizure threshold.

https://americanaddictioncenters.org/suboxone

Practical Tips for Buprenorphine Administration in Clinic

The Substance Abuse and Mental Health Services Administration (SAMHSA) has created the following very helpful resources for practitioners who are looking into prescribing buprenorphine:

> Buprenorphine Quick Start Guide:
> https://www.samhsa.gov/sites/default/files/quick-start-guide.pdf
> Buprenorphine Quick Start Pocket Guide:
> https://www.samhsa.gov/sites/default/files/quick-start-pocket.pdf

One of the most commonly used formulations of buprenorphine used to treat OUD is Suboxone, which combines buprenorphine and naloxone in a fixed 4 to 1 ratio and is most commonly administered as a sublingual film. (The first number corresponds to the buprenorphine dose and the second number corresponds to the naloxone dose: i.e., 8 mg/2 mg means 8 mg buprenorphine with 2 mg naloxone.) Sublingual films have the lowest potential for misuse since there is no risk of a patient crushing a pill to snort or inject it.

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Induction Therapy in Clinic

If a patient has been using heroin and/or fentanyl but has recently moved from contemplation to action and is ready to begin treatment, induction therapy with Suboxone can be initiated (Kumar et al., 2023). If the patient has been using short-acting opioids like heroin or oxycodone, treatment should be started 6 to 12 hours after last use. If the patient is using a long-acting opioid like morphine or oxycodone extended-release formulations, treatment should be initiated at least 24 hours or longer after last use. If the patient is using a fentanyl patch, treatment must be started at least 48 to 72 hours after last use.

Providers can use the following Clinical Opiate Withdrawal Scale (COWS) calculator to quantify the severity of opioid withdrawal symptoms. Induction therapy may be initiated if the patient has a COWS score of 12 or greater:
https://www.mdcalc.com/calc/1985/cows-score-opiate-withdrawal

According to the SAMHSA Buprenorphine Quick Start Guide and the Alberta College of Family Physicians induction flow diagram below, the initial buprenorphine dose should be 2 to 4 mg for most patients. If a patient is on high doses of opioids, an additional 2 to 4 mg of buprenorphine can be added on the same day. After the first dose, the healthcare provider should monitor the patient over the next hour to assess whether the withdrawal symptoms have resolved. The COWS calculator can be used to determine the presence and severity of withdrawal symptoms. If the patient is feeling significantly worse, they might be experiencing a possible precipitated withdrawal. The induction process should be stopped and symptoms should be treated. The patient should be rescheduled to attempt induction 24 hours later. If severe withdrawal symptoms are not precipitated, an additional 2 to 4 mg dose can be administered and the patient should be monitored for 2 to 4 hours. If withdrawal symptoms are still not completely alleviated, this process can be repeated up to a maximum of 12 mg on the first day. Once withdrawal symptoms are relieved, the patient can be sent home with 2-4 tablets of 2 mg buprenorphine to complete the induction treatment at home. A follow-up appointment should be scheduled in the next 2 to 7 days. The patient should be instructed and encouraged not to use any opioids at home in the meantime.

Alternatively, a patient might be referred to follow up with a healthcare provider in the outpatient setting after going through a bridge program during a stay at an emergency department (ED). Emergency physicians often start patients with OUD on induction therapy with buprenorphine and monitor them during their ED stay. They are then discharged with enough medication to make it to their first outpatient follow-up appointment, where a provider takes over treatment and titrates dosage according to withdrawal symptoms. A study published in the Journal of the American Medical Association (JAMA) showed that high-dose buprenorphine treatment greater than 12 mg and up to 28 mg is a safe and effective method of induction with no increased incidence of precipitated withdrawal, oversedation, respiratory depression, or other adverse effects secondary to buprenorphine (Herring et al., 2021). For most patients using either fentanyl or IV heroin, 16 mg given as the 8-2mg sublingual film BID is

becoming a proven approach to both initiate and bridge patients from the ED into outpatient care.

Maintenance Therapy

According to SAMHSA and the Alberta College of Family Physicians, the dose of buprenorphine can be gradually increased with respect to the patient's level of withdrawal symptoms. If withdrawal symptoms are experienced before that day's dose of buprenorphine, the dose can be increased by a maximum of 4 mg each day. While most patients respond well to 8 to 12 mg per day, the maximum total dose recommended in one day is 24 mg.

Providers should be aware that patients with OUD hide the truth due to the stigma of substance use. However, providers should aim to develop strong relationships where patients feel like they can have honest discussions and tell the truths that they would have otherwise lied about. Providers should not default to deception every time, especially at the beginning of treatment. An inherent mistrust in the patient builds a relationship on a shaky foundation and only increases the risk of relapse and future deception. If a patient reports that their dose of buprenorphine is too low, it may be because they are taking a medication that induces metabolism of buprenorphine or it may be because it truly is too low and needs to be titrated up. Providers should not be afraid to increase the dose because it will keep patients compliant with treatment in the long run.

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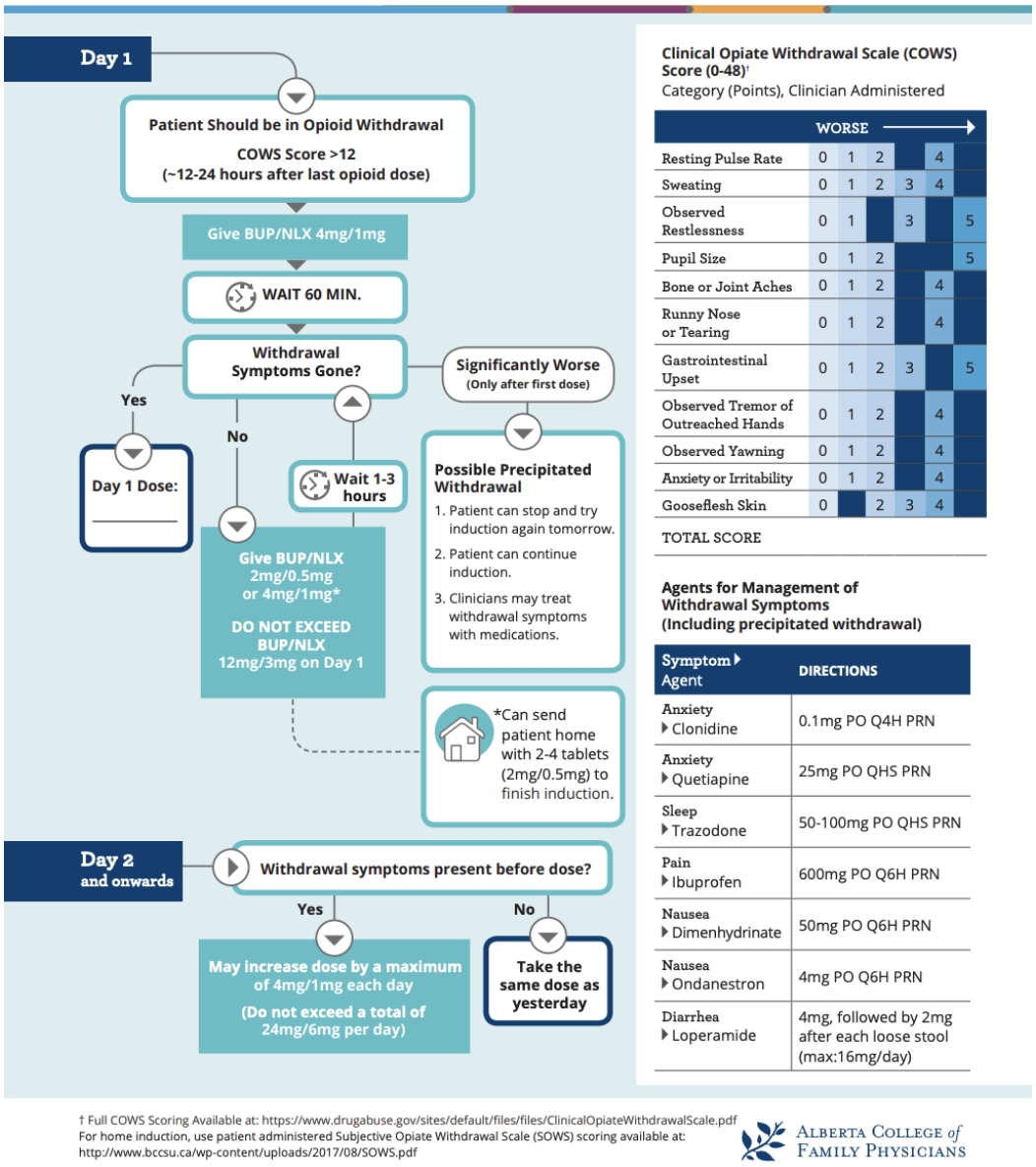

Alberta College of Family Physicians
https://www.cfpc.ca/CFPC/media/Resources/Continuing-Professional-Development/PEER-Design-Final.pdf

Please refer to this StatPearls article on buprenorphine for more information on how to prescribe buprenorphine for special patient populations including elderly, pregnant, breastfeeding, HIV positive, hepatitis positive, and chronic pain patients: https://www.ncbi.nlm.nih.gov/books/NBK459126/

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Relapse Management

Relapse is an inherent aspect of opioid use disorder (OUD), demonstrating the chronic nature of this condition. Understanding the pathophysiological impact of OUD on the brain is crucial; it underlines the inability of patients to refrain, evolving from a voluntary action to a compulsive disorder, signifying the loss of choice over time. The treatment journey is progressive, aiming at brain healing and restoring the patient's ability to say no. Providers should approach relapses without blame or shame, focusing on positive advancements, however incremental they may be, and continuously advancing treatment strategies. A nonjudgmental and supportive approach is essential, emphasizing the importance of maintaining progress and supporting any positive steps taken.

To augment relapse management, providers should embrace a comprehensive approach, incorporating family therapy to build a supportive and understanding environment, and initiating peer support systems to offer shared experiences and mutual understanding. A proactive and personalized relapse prevention plan, focusing on individual triggers and effective coping mechanisms, should be integrated meticulously. Furthermore, the fortification of psychological defenses through resilience building, stress management, and individual and group counseling is pivotal. Continuous education and empowerment are fundamental to enhancing treatment adherence and fostering a sense of control and self-efficacy in managing OUD. These strategies are vital to crafting a resilient support framework, aiming to minimize relapse risks and bolster sustained recovery and well-being.

Education on harm reduction is crucial, such as promoting safer usage practices for those not ready to cease opioid use. It can be a lifesaving interim step, allowing individuals the opportunity to pursue treatment when they are ready. It is paramount to provide a supportive, empathetic, and nonjudgmental environment, allowing patients to be open about relapses without fear of reprimand, thus aiding the progression to recovery.

Discontinuing Buprenorphine Therapy

The question of discontinuing use of buprenorphine may come up with patients who have been on maintenance therapy for longer periods of time. There are many reasons patients desire to stop taking buprenorphine. In some cases, it might be due to adverse effects like constipation, which is why it is important for healthcare providers to inquire about potential side effects like bowel movement frequency on a regular basis. These adverse symptoms can be treated directly, like prescribing stool softeners for constipation, or reducing the dose if patients complain about drowsiness. It is pertinent that providers be proactive in inquiring about how the patient is tolerating the medication to assure that they do not stop buprenorphine due to adverse effects that can be treated. There is no medical reason to discontinue treatment if the patient is not experiencing interactions with other medications or unbearable adverse effects.

In other cases, discontinuing use of buprenorphine is brought up due to pressure being applied by loved ones. Family and friends can sometimes view buprenorphine as "replacing an addiction with another addiction." To combat this common myth, providers can discuss the progress that the patient has made with his or her family members and friends by pointing out that buprenorphine has taken away their loved one's cravings and has helped him or her to stop using illicit drugs. Providers can inform families and friends that staying on buprenorphine will significantly decrease the risk that their loved one will relapse and overdose.

Although it is recommended that patients stay on buprenorphine for a minimum of 6 months and ideally 2 years with no illicit drug use and no cravings, patients commonly stop treatment within a few weeks or months. The best way to prevent a relapse of OUD is to maintain patients on buprenorphine. A study published in the American Journal of Psychiatry showed that patients who were retained on buprenorphine for 15 to 18 months had significantly decreased incidence of emergency department visits, inpatient hospitalizations, and filling opioid prescriptions in the 6 months after treatment discontinuation (Williams et al., 2020). However, risk of ED visits, hospitalizations, and overdose were high following discontinuation of buprenorphine regardless of treatment duration. Patients with treatment duration of more than 15 months before discontinuation showed better adverse event outcomes but still had high incidences of adverse outcomes. It is important that providers inform patients of these possibilities including a significantly higher risk of relapse and strongly encourage them to continue buprenorphine.

Therefore, anytime a patient stops opioid maintenance treatment there is risk of relapse. However, if a patient desires to stop buprenorphine treatment and has not had any cravings or illicit drug use for about 5 years, providers can partner with them to gradually taper the dose and ultimately trial discontinuation of buprenorphine. Providers can start by suggesting a taper regimen at a rate of 1 to 2 mg every 1 to 2 weeks or every month. If patients insist on tapering faster, the dose can be decreased every other day or decreased by 2 mg per week. Clonidine can be prescribed to treat peripheral withdrawal symptoms and loperamide can be taken for diarrhea.

Non-Pharmaceutical Interventions for Opioid Use Disorder Management

It is helpful for the patient to be connected with sources of support outside of the medical office, such as individual therapy, group therapy, and Narcotics Anonymous support groups where they can be connected with a sponsor. However, healthcare providers have the power to help patients at a level that goes beyond pharmacologic interventions. While medications like buprenorphine should never be withheld in favor of trying non-pharmaceutical interventions first, simple steps such as practicing psychotherapy skills and motivational interviewing can go a long way. During the initial addiction medicine evaluation, providers can work on enhancing patient motivations for change, uncovering patient values, and identifying cognitive distortions

and barriers. Treatment approaches should match patients' needs and they should be offered treatments they are willing to receive. Providers should reduce shame as much as possible because shame-induced treatment only pushes patients further into addiction. If continuing use is planned or likely to occur, then harm reduction principles should be taught.

Motivational interviewing and acceptance and commitment therapy are very effective tools and help to build strong positive relationships between providers and their patients. Please refer to episode 103 of this podcast, also featuring Dr. Neal Christopher, to learn more about acceptance and commitment therapy: Episode 103: Acceptance and Commitment Therapy with Dr. Steven Hayes

Conclusion

In summary, all providers registered with the DEA with Schedule III authority can now prescribe buprenorphine to treat OUD in their own practice with no limitation to the number of patients if permitted by applicable state law. To register with the DEA, providers must complete a one-time, 8-hour training requirement if they do not automatically satisfy one of the other two requirements discussed above.

Buprenorphine is a synthetic opioid that is FDA-approved for the treatment of OUD. It has many pharmacokinetic and pharmacodynamic properties that make it very effective for treating OUD. One of the most commonly used formulations of buprenorphine is Suboxone, which is a sublingual film that combines buprenorphine and naloxone and therefore reduces the risk of misuse and overdose.

Healthcare providers can learn how to initiate buprenorphine induction therapy in their clinics, as well as provide maintenance therapy. The risk of relapse and many other adverse outcomes of opioid misuse are almost completely eliminated with maintenance of an appropriate dose. At this time, it appears that the risk of relapse is greater with discontinuation than compared to remaining on maintenance treatment regardless of time frame. Many patients will choose to discontinue at some point and providers should assist with safe tapering and referral.

It is important that providers manage relapse in a nonjudgmental and supportive way and learn how to incorporate non-pharmaceutical interventions such as acceptance and commitment therapy into their practice.

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