DISCLOSURES

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The Individualized Treatment of Opioid Use Disorder

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COMMENTARY

The treatment of opioid use disorder (OUD) has progressed substantially over the past 50 years. We now have an excellent arsenal of therapies to combat this chronic but deadly disease. OUD, like other substance use disorders, can be successfully managed, but there is no cure. Relapse is always a threat. Like other chronic diseases, the clinical progression of substance use disorders, including OUD, can be best characterized by periods of exacerbation and periods of remission, but the patient is never disease-free. It is not uncommon for a simple trip to the dentist or the emergency department to precipitate a full-blown exacerbation of drug-seeking behavior. Just a few hydrocodone or alprazolam tablets from a legal prescription can quickly escalate to a life-threatening relapse.

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Patients in recovery should consider themselves “allergic” to self-administered controlled substances. When controlled substances are used, they should be administered under strict supervision and surveillance of an addiction medicine specialist or addiction psychiatrist.

Use disorders are not a substance-specific disease. Patients may transition through the abuse of many different substances throughout the course of the disease process. Many patients may start with heavy alcohol use then find that their alcohol consumption decreases as they move into opioids as their drug of choice. Patients may go through a methamphetamine phase and then a heroin phase; drug use is often determined by drug availability. Recovery from OUD can be sabotaged by benzodiazepines or other dopamine-releasing chemicals, even when prescribed by well-meaning clinicians who fail to consider a substance use disorder as part of the patient’s medical history.

In 1965, Dole et al. proposed a chronic disease model of opioid addiction and showed that outcomes could be improved by the use of a long-acting synthetic opioid called methadone under closely supervised administration.¹ Dole postulated that patients with dependence were dopamine resistant, much like a type 2 diabetic is insulin resistant. As a result of this dopamine resistance, patients with addiction live in a chronically dysphoric state without drugs. Dole hypothesized that if this were true, then dopamine supplementation might create more normal behavior and function as opposed to dopamine restriction.

For over 50 years, Dole's hypothesis has held up to scientific rigor. Multiple studies have confirmed that medication-assisted treatment, when combined with psychosocial counseling, improves mortality and morbidity.²⁻⁴ Methadone, administered under close supervision as part of a comprehensive and integrated program, provides desirable outcomes for not only the individual but also provides a public health benefit by reducing the transmission of infectious disease and violent crime.^{5,6}

Today, we have strong evidence supporting the use of 3 basic medication approaches to the treatment of OUD. The first is full agonist therapy in the form of methadone. The second is partial agonist therapy in the form of buprenorphine, and the third is antagonist therapy in the form of naltrexone.

It is essential to understand that there is not a "one size fits all" approach to treating the complex disease of addiction. Peer support groups such as Alcoholics Anonymous and Narcotics Anonymous may work well for some, while others may respond better to individualized, private counseling. Some patients will respond best to naltrexone, while others may require treatment with buprenorphine or methadone. Over the course of the disease, the optimal treatment medication may even change. Patients may need to stabilize on methadone or buprenorphine then move to antagonist therapy with naltrexone. The process may reverse itself, requiring the patient to go back to methadone or buprenorphine after a period of stabilized care on antagonist therapy or complete abstinence from all medication. No single drug class approved by the U.S. Food and Drug Administration (FDA) and used in the treatment of OUD is the best option for all patients. It is vital that doctors and patients have access to methadone, naltrexone, and buprenorphine in order to use the right medication for the right patient at the right time.

We have established that there are 3 FDA-approved medication classes with proven efficacy in the treatment of OUD and that no one has a universal benefit over the other in all situations, but the conversation does not end there. Within each class of medication assistance, delivery systems can make all the difference. If you doubt this, ask any cigarette smoker why a nicotine patch is such a poor substitute for a cigarette.

Within each class of medication assistance, delivery systems can make all the difference. If you doubt this, ask any cigarette smoker why a nicotine patch is such a poor substitute for a cigarette.

Methadone clinics tend to use liquid methadone to prevent "tablet cheeking," the practice of hiding tablets or capsules in the mouth to be shared, sold, or traded on the street later. Liquid preparations may also allow for greater flexibility in dosing compared with pills.

Side effects of buprenorphine therapy can be managed by changing the delivery system. Bunavail (buprenorphine and naloxone buccal film), with its patented delivery system known as "BEMA (BioErodible MucoAdhesive) technology," has demonstrated a 68% reduction in constipation compared with the gold standard delivery system of Suboxone (buprenorphine and naloxone) sublingual film by reducing the amount of swallowed buprenorphine.⁷

The buprenorphine and naloxone film product also creates less oral mucosal irritation and allows for more discreet dosing. A phase I trial of another delivery system, Zubsolv (buprenorphine and naloxone) sublingual tablets, showed a more tolerable taste and faster absorption than other buprenorphine products.⁸

Diversion is the illegal activity of selling, sharing, or trading prescription medication with unintended recipients. We do not know exactly how extensive the problem of buprenorphine diversion is, but evidence exists that the practice is quite common. In 2016, the U.S. National Household Survey on Drug Use and Health reported that 11.5 million Americans misused a prescription pain reliever, and the most common source was from a friend or relative.⁹

Accidental exposures from improper storage is also a concern. Data from the National Poison Data System between 2007 and 2016 revealed more than 11,000 reports of accidental or unintentional ingestion of buprenorphine, prompting a call to poison control centers, among children and adolescents aged ≤ 19 years.¹⁰ Of the 11,000, more than 85% of those exposed to buprenorphine were under 6 years of age.

Another concern associated with self-administered buprenorphine therapy in the outpatient setting is drug holidays. Patients may use buprenorphine during the work week then discontinue the treatment to use recreational full agonist opioids, such as heroin, on the weekend.

In the case of transmucosal administration of buprenorphine, variation in plasma concentrations between doses may lead to vulnerabilities even with proper patient adherence to their treatment regimens.

Sustained-release injectable buprenorphine (Sublocade) and a buprenorphine implant (Probuphine) offer solutions to the challenges of diversion, accidental pediatric poisoning, and drug holidays, while also offering sustained plasma concentrations. The buprenorphine implants offer sustained plasma concentrations for up to 6 months without the need for

self-administration.¹¹ Limitations of the buprenorphine implant include the availability of only a single dose-size, which is a relatively low dose for the treatment of OUD. Cost and the requirement of an office-based surgical procedure for insertion and removal may also be problematic.

The buprenorphine injection virtually eliminates the risks of diversion and accidental pediatric exposure, while reducing the risk for drug holidays and helping to improve patient adherence.¹² This monthly buprenorphine injection is available in 2 doses (300 mg and 100 mg), and it ensures mu receptor blockade during its duration of action.

With the use of these 2 buprenorphine products for treatment of OUD, many physicians are concerned about adherence to oversight efforts such as drug testing and office visits, as well as participation in psychosocial counseling. There is much more involved in the treatment of OUD than simply prescribing buprenorphine. Buprenorphine therapy is intended to be used as part of a comprehensive treatment program, which includes counseling, drug testing, and regular interaction between the patient and the care team. Most OUDs can be managed in the outpatient setting but doing so requires oversight. When patient plasma concentrations are at therapeutic levels, patients may underestimate the need for comprehensive care. In the case of transmucosal delivery of buprenorphine, care providers may have more control over the frequency of visits due to the requirements for daily dosing that can be somewhat governed by the amount of medication dispensed by the prescription.

Substance use disorders, including OUD, are complex diseases that involve the management of biochemical and environmental factors. This requires a complex combination of medication and psychosocial counseling. In the medical management aspect of OUD, there is no “one size fits all” approach. There is not a perfect medication or delivery system that fits the needs of every patient. Each drug and delivery system has its own unique set of advantages and disadvantages. The more tools that we have in the toolkit, the better the addiction medicine profession can combat this public health juggernaut that has proven to be one of the most challenging scourges of the 21st century.

DISCLOSURES

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