

Medication-Assisted Treatment of Opioid Use Disorder

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Addiction is a chronic progressive brain disease in which the afflicted individual has lost control of a substance or behavior that produces a high, a sense of well-being and euphoria. The addicted person, to whatever substance or behavior it might be, becomes obsessed with whatever it is that they are doing or using to experience this euphoria, and sooner or later enters a stage of compulsive use. Once they have gotten to this point there is no return to sociable drinking, drug use, gambling, or whatever it is that they have become addicted to. Without treatment, periods of abstinence are inevitably followed by relapse into the addictive behavior.

In the case of substance abuse, whether it is to alcohol, opiates, or other drugs, the initial stage of treatment typically involves detoxification from the substance. This allows for a controlled withdrawal and prevention of the severe physical illness which goes along with abrupt discontinuation of the addictive substance. All recovery efforts after detox essentially fall into the category of relapse prevention. Results with the treatment of alcoholism have been encouraging. Many alcoholics after detox follow up with either AA, counseling, or some combination of both, often with good success. Some of these people never return to drinking. Experience has shown that following detoxification and a good professional treatment program, as many as 30% of people will maintain total abstinence for the rest of their lives. Of those who relapse, as many as 50% eventually achieve total abstinence. The factors that go into whether people do or do not succeed are many, and include the availability of supportive family and friends, the recognition that addiction is a disease that they indeed do have, willingness to follow a prescribed recovery plan, attention to treatment of medical and psychiatric coexisting disorders, and concern about consequences such as losing family, job, or being incarcerated. One of the greatest motivators is the sense that the addict has of not being able to tolerate what they have become or what they are doing any longer. We call that hitting bottom, and when it happens, it is a profound emotional and spiritual experience.

As challenging as the treatment of alcoholism is, the treatment of opioid (narcotic) addiction is exponentially more difficult. At the time that I saw my first middle-class suburban college student heroin addict in the mid 1990's, we didn't have much in the way of tools to assist patients to maintain abstinence from opioids once they were detoxified. Even if she had accepted inpatient treatment, her chances of relapse were very high following such treatment.

This was the state of things back then. Addiction treatment was based on a recovery model developed by the Alcoholics Anonymous fellowship in the late 1930's. This model has had dramatic success with millions of people in recovery from alcoholism and other addictions over the years. It continues to grow and be successful, and the 12-step approach that it developed remains the backbone of addiction recovery. Some heroin addicts have successfully utilized the AA program, but most have seen themselves as different enough from alcoholics to not stay with the program. Unfortunately, many of the AA members are not comfortable with addicts attending the AA meetings. In response to these concerns, Narcotics Anonymous was founded over 50 years ago, and it has also enjoyed considerable success in helping people with recovery. The other treatment resource that was available to me back in the mid-1990's was the 28 day structured treatment model that had been developed in Minnesota in the 1950's. This was a model which included education, individual and group therapy, family education and therapy, and introduction to the program and philosophy of Alcoholics Anonymous and related fellowships.

In my experience, if detox is all that is offered to a heroin addict, the chances of staying away from heroin are less than 2% in any given recovery effort. And this does not improve dramatically if you follow up detoxification with a 28 day structured treatment program. Broadly speaking, there are 2 aspects to relapse with heroin or any opioid addiction. The first has to do with the acute withdrawal syndrome, a condition which feels like the flu multiplied by a factor of at least 100. This physical illness is greatly feared by every opioid addict. Even more of a problem, is the post-acute withdrawal syndrome which lasts for several weeks to several months after detoxification. During the post-acute withdrawal phase the addict frequently is depressed, lacks energy, feels unmotivated, has a limited capacity to experience pleasure, and sleeps poorly. These feelings persist because of chemical changes that have taken place in the brain, caused by the repetitive use of heroin or other opioid drug. Addicts in this situation are obsessed with the thought that all they have to do is get one dose of heroin or oxycodone or whatever it is that they normally use, and that they will feel normal again. This is half true. The half that is true is that they will feel much better. The half that is not true is the part about using just one dose. As soon as that dose is used, the compulsion to repeat using kicks in with full force and the addict will not be able to stop using. Early in the natural history of opiate addiction, the addict is no longer looking to get high, but rather, just to get by. It is a terrible, life-destroying trap.

Inherent in understanding addiction is the awareness that it is a chronic relapsing illness. In the case of opioid addiction in particular, the onset of a relapse can be a fatal event. This is because one of the characteristics of opioids is that they induce tolerance. Tolerance is a phenomenon in which the brain adjusts to the repeated use of the drug, so that it requires more and more drug to produce the same effect. After some time, the addict is using a dose of drug which would be fatal to a person who has not developed tolerance. Loss of tolerance occurs quickly when people are detoxified. All too often, when addicts relapse, they use an amount of drug that they have been accustomed to in the past, not realizing that it is entirely too much of a dose in their detoxified state. So

a great many relapses are fatal events, and often occur in an addict who has just been released from detox or from jail. Likewise, after several weeks or months of not using, an addict is equally vulnerable to a fatal accidental overdose because of the loss of tolerance. Another reason for fatal overdoses has to do with the potency of the heroin itself. Not only is the heroin available in a much more concentrated form than it used to be years ago, but the illicit drug manufacturers are often adding fentanyl to the product. Fentanyl is much more potent than heroin and can be manufactured very cheaply. The addict who buys the drug has no way of knowing what he or she is really buying, and frequently will not live to regret his or her mistake.

Most alcoholics feel much better once they have gone a few days or weeks without drinking, and this adds to the motivation to stay sober. They don't go through a post-acute withdrawal syndrome. Many do experience recurrent obsession and compulsion to use, and do relapse, but the percentages are much different. So while the 12-step recovery program of Narcotics Anonymous has been life-saving for a great many people, the vast majority of people who are referred either don't go or don't stay with the program because their compulsion to use overwhelms them. We have needed something more to offer these people.

Back in the 1950s the idea of medication-assisted treatment arose, and was developed at the Rockefeller University by doctors Dole and Nyswander with the use of methadone. The idea of using methadone for relapse prevention is that as a long acting opioid drug, the addict can take methadone and go 24 hours without going into acute withdrawal. Their opioid receptors are occupied by the medication, allowing the patient to feel reasonably normal. The idea was that if the addict could get a dose of methadone in the morning, he or she could then go to work, be productive, have a family, pay taxes, and live a reasonably normal life. They could become productive members of society instead of a burden on society.

Methadone is a synthetic drug which means that it is not derived from the opium poppy. It was developed in the 1930's in Germany. It is addictive, but with its long duration of action, in a supervised setting, it can be life-changing. Methadone is also subject to abuse, and the system that was set up in which it is administered to patients is highly regulated. The first experimental methadone clinic was set up in 1962 in New York City. In the USA we still have methadone treatment available and by 2012 over 300,000 patients were enrolled in clinics across the country. Methadone is a drug with its own set of problems, not the least of which is that the patients have to go to a federally licensed methadone clinic every day to be dosed. Over time they can get take-home privileges. For some people it has been excellent, and for other people it has just been another stage of their illness that they have gone through. Methadone certainly has its detractors, and there are good reasons for being concerned about the use and the effects of methadone, but for some people it is still the best treatment that we can offer, and some people do very well on it.

In the 1960's buprenorphine was synthesized in the laboratory. Buprenorphine is a drug which is derived from thebaine, an opium alkaloid. It is derived from the poppy plant. It

has some unique properties which differentiate it from most other opioid drugs. One of these is that like methadone, it has a very long duration of action. What this means at the level of the brain is that once it attaches to the receptor site it lets go very slowly. What is more unique to the drug is that it is what we call a partial agonist. A partial agonist is a drug that under certain conditions will attach to the receptor site and activate it, and under other conditions it will attach to the receptor site and block it. And it can do both at the same time. Almost all of the commonly used opioid drugs are full agonists, which means that the drug molecule attaches to the receptor site and activates it. It turns out that as a partial agonist, if used as prescribed, buprenorphine is much safer than full agonist drugs, and does not cause a "high." Another useful characteristic of buprenorphine is that, like methadone, it blocks the high caused by other opioids to a significant degree. Therefore, patients who are using buprenorphine are not only not likely to crave getting high, but if they do use an opioid they learn that the high is blocked.

Buprenorphine was first introduced into the United States as an injectable drug for the treatment of moderate to moderately severe acute pain. The brand of this medication was Buprenex, and it has been available for use in treating patients since the 1980's. In the mid-1990's when we started seeing more heroin and prescription drug (oxycodone, hydrocodone, morphine, etc.) addiction, several doctors started using Buprenex for opioid detoxification. The effectiveness of this medication was astounding compared to anything that we had available up until that point. As the opioid epidemic gained steam in the late 90's, efforts were made to bring buprenorphine to market for relapse prevention as an alternative to methadone. Buprenorphine was seen as much safer than methadone, one of the chief advantages being that it was considered to be safe enough to be administered in an office-based practice rather than at a methadone clinic. Obviously, an injectable form such as we had was inappropriate for medication-assisted treatment of addiction beyond detox. So efforts were made to develop a tablet for oral administration. It turned out that the best way to administer buprenorphine was to let it dissolve under the tongue (sublingual) and be absorbed through the lining of the mouth, rather than to have it swallowed as a tablet.

Authorizing the availability of office-based medication-assisted treatment with buprenorphine required an act of Congress. In 1920 the United States Supreme Court interpreted the Harrison Act of 1914 in such a way that it made it illegal for a physician to prescribe a narcotic to a drug addict for the purpose of treating the narcotic addiction. For this reason, it took an act of Congress to get methadone approved. Another act of Congress was required to get buprenorphine approved for office-based addiction treatment. The law, called DATA 2000, was not written specifically for buprenorphine, but rather authorized that any Schedule 3 or higher medication could be approved by the FDA for office-based treatment of addiction.

The Drug Enforcement Administration is authorized by Congress to categorize potentially dangerous or abusable drugs into one of 5 schedules, depending upon the level of potential dangerousness and consideration of medical usefulness of each medication. Schedule 1 drugs are considered either to be so dangerous or to have such

little medical usefulness as to not be legal to prescribe or even to have in one's possession. Schedule 2 drugs are considered to be the most dangerous of the medically useful drugs and are the most strictly regulated. With each succeeding higher schedule, numbers 3 through 5, the medications are considered to be less and less dangerous. Most opioid drugs, including methadone, are Schedule 2, so the DATA 2000 law does not apply to them. However, since buprenorphine, as a partial agonist, is seen to be a less dangerous drug, with much less abuse potential, it has been rated by the Drug Enforcement Administration as Schedule 3. In 2002 the FDA approved Suboxone and Subutex as drugs that could be prescribed for the office-based treatment of opiate addiction. The original idea of Subutex was that it be used for detoxification. Subutex is buprenorphine with no accompanying drug. Suboxone is buprenorphine plus another drug, naloxone. The idea of including naloxone was that if this product was injected, the naloxone would act as a blocking agent and make the overall experience disagreeable at best to the addict. If the Suboxone is used under the tongue as directed, the naloxone has no effect whatsoever. It's a nice little piece of medication engineering.

Doctors require a special waiver to prescribe buprenorphine for medication-assisted therapy, which they obtain by taking additional training. Sublingual buprenorphine became available at the pharmacies and I started prescribing it in January of 2003. Since that time over 3 million people in the USA have been prescribed some form of buprenorphine for the detoxification and relapse prevention of opioid addiction. It has made me a much better doctor.

Because the first and the only buprenorphine containing drugs for several years were Suboxone and Subutex, these names became the vernacular by which buprenorphine has been referred. It's like calling facial tissue Kleenex or like referring to all gelatin-based flavored desserts as Jell-O.. Other companies have also come out with buprenorphine-based products for the treatment of addiction. These are Zubsolv, Bunavail, and we now have generic versions of Suboxone and Subutex tablets. Brand-name Subutex and Suboxone tablets are no longer manufactured. The only product currently branded by the name Suboxone is a sublingual film. They all work well, and every product has its potential advantages and disadvantages, which I won't go into here. We also now have 2 buprenorphine-based products marketed for the treatment of chronic pain in this country. Buprenorphine, by itself, does not cure drug addiction. What it can do is return a sense of normalcy to the addict's life, so that they can go through a process of learning how to deal with life on life's terms. They can experience a normal range of feelings and learn how to manage their feelings without reverting to use of drugs. They can remain abstinent for a long enough time to recover from their compulsion to use opioids.

Another drug used in the treatment of opioid addiction is naltrexone. Unlike buprenorphine, naltrexone does not activate the opioid receptor at all. Rather, as a full antagonist, it blocks it completely. Patients taking naltrexone are unable to experience any effect if they take an opioid drug. Naltrexone is available as an oral tablet for daily administration, or in a monthly injection, called Vivitrol. Like buprenorphine, naltrexone

is only successfully used as part of a comprehensive plan of counseling and support group attendance. It can be used after opioid detox, and also is useful for the first 6-12 months after buprenorphine has been discontinued.

In my practice I expect my patients to stay on the medication a minimum of one year, and I find most patients are not ready to discontinue it until 2 or more years into their recovery. While this may seem extreme to many people, I think it is important to recognize that opioid addiction is a chronic brain disease. Discontinuing drug abuse is only the beginning of a long process that involves brain healing as well as learning how to live again. Or in the case of the hundreds of thousands or more of teenagers who are becoming addicted to opiates, we are really looking at them learning how to live for the first time.

One of the great obstacles to success in coming to grips with our opioid epidemic and treating patients successfully is the ignorance that is prevalent in our society about this disease. Accompanying this ignorance is a moralistic sense that not only are addicts bad people, but doctors who treat addicts (or pain patients) with medications are equally bad people. There is also in what my opinion is an excessive concern about abuse of buprenorphine. There is no question that this occurs. Some patients who get prescriptions either overtake the medication or more often, sell it and obtain other drugs. The responsibility of the prescribing physician is to monitor his or her patient carefully, and most doctors who treat addictions are very conscientious in this regard. The buprenorphine that finds its way into "the streets" usually is bought by addicts who either can't find heroin and want to keep themselves from being sick, or want a break from their heroin addiction but don't want to go and see a prescribing physician for whatever reason. Many addicts have no access to a prescribing physician. There are people who will abuse the drug, primarily the generic Subutex tablet (buprenorphine without the accompanying naloxone) either by grinding it up and using it by nasal insufflation ("snorting"), or by intravenous injection. Admittedly, this is a problem. My estimate is that less than 3% of the prescribed buprenorphine is abused in such a manner. While acknowledging that this is a problem, by itself it is not a reason to limit the use of buprenorphine for its legitimate purpose. This medication has been life-saving for a great many people. It has kept a great many thousands of people alive and out of jail. It has prevented the tragedies that have afflicted so many families. It frustrates me when I'm seeing a young adult, and their parent comes in and the very first question they have is "When can we stop the Suboxone?" If we were treating diabetes their first question wouldn't be "When can we stop the insulin?" People think that we are just trading one drug for another, but this is not the case. Patients do not get "high" on buprenorphine. It restores the normal chemical balance in the brain that has been disrupted by the use of opioids. So the patient is able to feel normal, and get on with rebuilding their lives instead of relapsing over and over. And, when the time is right, they can be tapered off the buprenorphine successfully.

Many people don't realize that ever since 2009 the incidence of overdose deaths in this country has exceeded the incidence of motor vehicle accident deaths. Most of these overdose deaths have involved opioids. And what has shocked the middle class in this

country, is that opioid addiction is no longer confined to the inner cities where they don't have to notice it. It has affected the life by now of virtually everyone that I know. It's hard to find a family that either hasn't been directly affected by opioid addiction or who is close with families who have been affected. Every medical treatment that we have has potential problems. I haven't heard a clamor for eliminating the use of chemotherapy for cancer patients because it can cause serious and even fatal side effects. As physicians and as a society we manage our treatment and our resources in the best way that we can, recognizing that there will be some level of collateral damage in any action that we either take or don't take.

In summary, addiction is a chronic, relapsing brain disease which is potentially fatal. Persons with this disease can be successfully treated if they want help. In the case of opioid addiction, medication-assisted treatment has become the standard of care for most patients, and has saved many thousands of patients from death or despair.