

Patient Types with Buprenorphine Treatment and Difficulties in Tapering and Discontinuing Treatment

Buprenorphine is rapidly becoming the mainstay of treatment for opiate addiction and dependency. There are many studies that demonstrate its efficacy in both detox and maintenance. A major problem that has become apparent is the difficulty of tapering and discontinuing this medication. The withdrawal can be severe and long lasting, even from tiny doses. The reasons for this are not commonly understood, but can usually be explained. Knowledge of the mechanisms at work can avoid many problems and enhance clinical success, promoting successful recovery and normal life function.

With opiate addiction the Mu receptors become down regulated (less sensitive) and when the opiate is stopped the resultant under-stimulation causes a severe withdrawal syndrome. Buprenorphine is extremely effective for the treatment of opiate addiction, effectively stopping withdrawal and cravings because of its actions as a partial Mu receptor agonist (stimulator). Over time this partial Mu agonist action of buprenorphine allows the Mu receptor to move back towards normalcy. Since buprenorphine is an opioid itself (an opioid being any drug which stimulates the opioid receptors), its discontinuation can also lead to withdrawal. Although this may seem logical and straightforward, the clinical manifestations are very complex. The withdrawal may be protracted and clinically different than what we see with opiate-based Mu withdrawal. Therefore, down regulation of the Mu receptor cannot explain the whole picture

The Kappa Receptor

There is another important opiate receptor in the brain called the Kappa receptor. Unlike the Mu system, in withdrawal the Kappa system goes into overdrive. Much of the long lasting Post Acute Withdrawal Syndrome (PAWS) symptoms, such as dysphoria, body aches, anxiety, and depression may be caused by this Kappa overdrive phenomenon. PAWS can last for months, or even years, and is an important cause for relapse.

I also believe that Kappa activation may be an important cause of depression in many persons with substance abuse problems, as well as in the general population, even without the extra stimulation of opiate withdrawal. These people have a history of emotional problems, especially anxiety, anger, and emotional lability (the opposite of stability) that usually starts as a teenager or in the early 20's. (This is very similar to how bipolar disorder manifests and there is probably a large overlapping of the two groups.)

Buprenorphine is a potent, long acting Kappa blocker. Opiates are not as specific in their Kappa blocking actions as buprenorphine and most are short acting, so

the patients who benefit from this opiate action often must use frequent and ever higher doses of their opiate to get effective, consistent blocking of Kappa. This dose increase causes the Mu receptors to become less sensitive to opiates and therefore the patient requires higher and higher doses to get pain relief and stay out of withdrawal. This is known as tolerance and is the vicious cycle we so often see.

Another important factor is that since buprenorphine blocks the Kappa receptors so completely, even at low dosage, it is very likely that these receptors continue to be down regulated (less sensitive) to the normal endorphins that should cover them, even while the Mu receptors normalize.

Many of these patients started taking hydrocodone (Vicodin, Norco) or other opiate medication for legitimate pain, usually appropriately prescribed by their own physician. They find out very quickly that their depression, anxiety and lack of energy also disappears, often for the first time in their lives. I believe that much of this is due to Kappa blocking. The usual cycle then results in addiction. Many of these folks have tried SSRI's and other antidepressants in the past without success. Buprenorphine often makes them feel "normal". The Mu receptors get re-regulated in the short to medium term, but the Kappa is still a problem. Remember, many of these patients did not have a normal Kappa system prior to opiates.

Specific Patient Types

I have identified specific buprenorphine patient types that each have their own characteristics and have to be treated differently.

- 1- Many patients can taper their buprenorphine dose down to as low as 0.5 to 1 mg daily and feel fine. I believe that many of these persons are taking the drug as an antidepressant/ Kappa blocker and are not addicted to opiates anymore than other depressed patients are addicted to Prozac. They need to continue the medication to treat their depression. These are people who had emotional problems before they got addicted to opiates and who failed traditional pharmacotherapies. It is important that they receive psychotherapy and are closely observed, but they should be educated as to how buprenorphine is being used in their care. Often these patients' withdrawal is easily controlled with very low doses of buprenorphine, or the dose can be rapidly lowered. This may indicate that the predominate problem in these cases is with the Kappa system and not the Mu.
- 2- Patients who have a family history of substance abuse (including alcoholism) or a prior history themselves of substance problems are often prescribed short acting opiates, such as Vicodin and Norco (hydrocodone), or Percocet or Oxycontin (oxycodone) for legitimate

medical reasons, such as after an injury or post surgery. They often find that after their pain issue has resolved, they just cannot stop due to severe withdrawal problems. They often start using alcohol to decrease these symptoms. They may have no real psychopathology, nor abusive behaviors. They often are taking just what their doctor has prescribed. They have a physical receptor down regulation problem. They should be detoxed and then tapered; buprenorphine should be stopped quickly, if possible. This may not be easy, as these patients can quickly develop a down regulated Kappa system due to genetic vulnerability/predisposition and/or may already have developed this Kappa problem from the opiates they were using. Although buprenorphine is an excellent medication to use short term, it may be best to do the detox quickly with a rapid taper schedule, trying to avoid long-term buprenorphine exposure and Kappa down regulation.

- 3- Patients who have high opiate tolerance and/or a history of heroin or methadone use may not do well on low dose buprenorphine. I believe that they have a chronically, and possibly permanently, damaged Mu system, which may not readapt with decreasing dosages. They are also at very high risk of relapse. These patients will most likely need to be maintained on higher doses of buprenorphine, sometimes pushing the usual maximum dose of 32 mg. per day. They also need constant psychosocial support and close observation with UDS (urine drug screen) at frequent intervals. Heroin users are frequently in this group, even after shorter-term heroin use. I am not sure if this is due to the type of person who uses heroin, or if heroin itself is especially damaging to the receptors.
- 4- There are patients who have a chronically down regulated Kappa system from taking buprenorphine. These patients can be very difficult to treat. They may not have a prior history of mood problems or substance abuse. They usually require very low doses of buprenorphine to feel well. If they stop the medication, they develop a prolonged series of symptoms, which usually include various mixtures of anxiety, depression, fatigue, malaise, insomnia, or other non-specific symptoms. A strategy that I am using to taper and stop the medication is to have tiny doses compounded by a pharmacy and then to very slowly decrease the dose over time. This may allow the Kappa system to readapt to its normal state. There are other strategies that I am exploring that may help as well, but it is too early to share them.
- 5- There are legitimate pain patients, who have problems with opiate use. This can take the form of constantly increasing opiate dosage requirements, without seeing a corresponding decrease in pain and/or actual substance abuse. This problem usually develops directly under a physician's care. These people usually have a positive personal or family history of substance abuse. Many in this group have pain problems that are not sensitive to opiates, such as neuritis or fibromyalgia.
Buprenorphine was first a powerful pain medication, used in the UK and

even as an injectable pain medication In the United States (Buprenex) before being approved for use in opiate dependency. Since it is long acting, it is also a good medication for chronic pain problems. Many of my pain patients who did not do well on the usual opiates, have excellent relief with buprenorphine, often in low dosage. The Kappa blocking properties of buprenorphine have a synergistic effect in decreasing the suffering (depression and other mood disorders) in these patients as well. It is important that the abuse aspect of the problem, as well as the pain be treated with a comprehensive pain program.

This paper is meant to be a start in understanding some of the complexities that are apparent with the use of buprenorphine. It is not comprehensive and should be used as a stimulus for further discussion. We are using some new approaches, not discussed here, to deal with the pitfalls outlined above that will hopefully be useful in the treatment of these complex patients. In future papers I will describe these and elaborate on other important issues.

Please write me with any ideas or comments.

Richard Gracer, MD
Gracer Medical Group
info@gracermedicalgroup.com