Abstract. Addiction is a hindrance in the long term treatment of complex regional pain syndrome (CRPS) because addiction in itself aggravates CRPS, causes stress in the sympathetic nervous system resulting in more severe sympathetic dysfunction, and results in perpetual presence of rebound (withdrawal) pain.

Descriptors. addiction, competition, destruction, complex regional pain syndrome (CRPS), rebound phenomenon, tolerance, withdrawal pain.

INTRODUCTION

The problem of addiction as outlined in this article, will show how it directly affects the sympathetic nervous system by causing stress (with resultant severe pain, sweating, tremor, etc.) and aggravating complex regional pain syndrome (CRPS).

On the other hand, the use of pain medication in long term pain narcotic patients should be limited to the non-addicting type of pain medications (such as Stadol or Ultram) or at least to the less addicting pain medications such as Stadol, Nubain or Buprenorphine (Buprenex). In the meantime, it should be understood that one cannot keep the patient on any narcotic for ever. Simultaneously, the use of antidepressant medications should be increased until the analgesic effect of the antidepressant makes it unnecessary for the patient to take long term doses of strong medications.

THE FOUR PRINCIPLES OF ADDICTION

To be able to understand the principles of narcotic use as well as the reason for non-addicting nature of the infusion pump, one has to understand the principles of addiction.

It is true that any pain medication or tranquilizer even though non-addicting may be abused. This abuse is usually in a small number of patients who try to accelerate the frequency and dosage of the medication to get pleasure out of it.

The following is a useful guide to help understand the four principles of addiction.

COMPETITION

The first principle of addiction is Competition. Competition refers to the fact that if the brain is naturally providing chemicals to relieve pain, or anxiety, or to provide good rest and sleep, the extraneous intake of similar chemicals in the form of medications will compete with the brain's own natural chemicals such as endorphines and
endogenous benzodiazepines (endo BZs). If the patient takes Morphine by mouth, through a skin patch, or by injection at the usual doses of 60-100mg a day, then the brain will cease the formation of the natural endorphines. This is only to protect the human body so that the combination of natural endorphines and the strong narcotics does not cause a deep coma, arrest of breathing, and death.

On the other hand, if the pain medication is taken that does not compete with endorphines and is not complimentary or similar to the endorphines, then the body will continue forming endorphines without disruption.

In the first case when the brain does not form its own endorphines, 4-6 hours after the intake of Morphine the body is left with no protective effect of pain medication. As a result, the withdrawal (rebound) pain develops.

In the second case, when the brain does not stop the formation of endorphines there are no withdrawal effect and no rebound pain.

If the patient has taken Morphine for an acute condition such as a recent trauma, heart attack, or surgical procedure and if after the original trauma has cleared up, and if the dosage of Morphine is continued, then the patient will have a perpetual pain due to the withdrawal effect of the strong addicting narcotics. What makes the narcotic addicting is the fact that it competes and forces the arrest of secretion of the body's natural endorphines.

**REBOUND PHENOMENON**

The second principle of addiction is Rebound Phenomenon. The rebound phenomenon has been discussed in detail in principle number one.

The rebound phenomenon (withdrawal) pain is quite different from the original pain of the disease that requires pain medication. The disease may be nothing but a fracture of the ankle. The pain in this situation is quite excruciating and limited to the ankle. On the other hand, the rebound phenomenon (withdrawal) is due to the use of strong addicting narcotics which causes pain all over the body in the form of headache, neck pain, low back pain, joint pain and extremity pain. It is a non-specific continuous pain and has nothing to do with the pain due to the original focalized injury. Long after the disease has been fixed and cured, the patient will continue to have rebound (withdrawal) pain which will continue indefinitely.

**TOLERANCE**

The third principle of addiction is Tolerance. This refers to the fact that as the rebound pain becomes more disabling and severe due too long standing use of addicting narcotics, the brain learns to tolerate larger doses of narcotics and to control the vicious circle of the rebound pain adding to the original pain. As a result, the patient demands more and more of the pain medication, and even after taking large doses of pain medications, they still have a very poor and irregular sleep pattern.
DESTRUCTION

The fourth principle of addiction is Destruction. Destruction refers to certain chemicals that destroy the cells and generators of biogenic amines and hormones in the brain and as a result reduces the amount of endorphines and endo BZ’s. The best example is alcohol which by its destructive effect paralyzes the formation of the above-mentioned chemicals. Alcohol is a strong analgesic and anesthetic. However, once its immediate effect is gone, then the pain recurs in the form of severe rebound. In this regard it is practically identical to all the other narcotics. In addition, the alcohol destroys other chemicals that are effective in controlling the pain(for example antidepressants).

However, in the case of abuse of non-addicting narcotics or benzodiazepines (BZs) sudden discontinuation of the non-addicting medications will not cause the severe withdrawal and the stressful symptoms and signs of the rebound. These consist of excessive sweating, rapid heartbeat, rise in the blood pressure, tremor, and severe anxiety and practically psychotic reaction. Such a withdrawal phenomenon is limited to the withdrawal from addicting medications.

In the case of application of an infusion pump, none of the above four principles of addiction are involved. The dosage of medication given to the patient is so small (a dosage of one day is given in prescription form in one month). This does not compete and stop the formation of endorphines. There is no withdrawal phenomenon (no rebound symptoms) because of the strict drip irrigation form of application of medication. There is no tolerance because of the fact that the patient has no control over the intake of medication, and the body is not being exposed to the rebound phenomenon.

The infusion pump is not given to facilitate the intake of an addicting medication. It is given to prevent the above-mentioned four principles of addiction and tends not to cause problems of withdrawal and tolerance. The dosage of medicine is too small to stop the formation of other biogenic amines, endorphines, endo BZs, and other hormones in the brain.

In our experience, the use of Stadol or Buprenorphine (Buprenex), both are Morphine agonist-antagonist analgesics, and are not even controlled drugs. Both medications are quite helpful in facilitating the discontinuation of addictive narcotics (1).

With the use of such medications as Ultram, Stadol, Nubain, and Buprenex these medications will help enhance the pain relief and drowsiness in the presence of endorphines or other non-narcotics. Yet, when these medications are given along with other narcotics which are addicting, the combination is so strong that it causes nausea, vomiting, excessive drowsiness, and even breathing problems.

OPIATES

The use of opioids play a major role in control of pain and inflammation in peripheral and central nervous system(2). The endogenous ligands-opioid peptides(endorphins) are expressed by resident immune cells in peripheral tissues (2). Depriving the patient of proper pain medication can aggravate the immune system dysfunction. The selection of proper opiates for treatment of CRPS is quite critical. Both opioid agonists and mixed Morphine agonist-antagonists have been used for treatment of pain in such patients(1).

Opiates are considered effective in treatment of neuropathic pain(3). However, due to the complexity and multiple origins of the pain in CRPS, in some patients the opioid agonists are not as effective(1,4).
Long term use of opioid agonists has the potential of tolerance and dependence, impairment of physical function, depression, and lack of improvement in physical function (1,5-8). Yet, 83% of pain specialists have been reported in 1992 to maintain chronic non-cancer pain patients on these medications(9). This percentage has grown higher since then: of 824 patients in our study, only 36 (4.3%) had not received long term opioid therapy(1).

Contrary to the common concept, large doses of opiates disrupt the natural sleep pattern. The nocturnal sleep pattern is interrupted every few hours and the patient is tired and sleepy in the day time. The use of proper antidepressants and adherence to the above mentioned therapeutic window helps correct this problem (1).

**MORPHINE**

Long term use of Morphine suppresses many specific functions of the immune system(10). Both acute and chronic application of Morphine strongly suppress the T-cell and B-cell immune functions(11). Morphine may interfere with the development of antibody - antigen immune function(12). Due to the fact that many cells and organs related to the immune system have shown opiate receptors, Morphine has the potential of directly affecting and altering many immune processes (2,13). Morphine may affect and suppress noxious stimulus-evoked fos protein-like immunoreactivity (10). Morphine and other similar opioid agonists bind to opioid receptors in limbic system (temporal lobe), affecting memory and mood(1,14).

**BUPRENORPHINE**

Buprenorphine, an opiate agonist-antagonist, is a strong analgesic without causing dysphoria, or dependence, (15-17). Sublingual Buprenorphine has been used successfully for detoxification from Cocaine, Heroin and Methadone dependence(15-17). Buprenorphine is a Class V narcotic in contrast to Morphine, Methadone or Fentanyl, which are Class II. Within the proper therapeutic window, Buprenorphine (2-6mg/day) and Butorphanol (up to 14 mg/day), act as opioid antagonists by occupying only mu and delta receptors. In higher than therapeutic doses, they fill the Kappa receptors as well, changing said drugs to pure opioid agonists and resulting in problems of rebound and tolerance (1,18,19).

Within 2-6mg per day, Buprenorphine occupies mu and delta opioid receptors, but the kappa receptor is not occupied and is capable of receiving endorphins. When all three opioid receptors are occupied, endorphines cannot bind to them. Consequently, endorphin formation is ceased, leading to dependence and tolerance (1,20).

Researchers from Harvard and others have found Buprenorphine to act as an antidepressant leading to “...clinically striking improvement in both subjective and objective measures of depression”(1,21-23). This is in contrast to the common depressive effect of opioid agonists.

**ANTICONVULSANTS**

Anticonvulsant treatment is helpful in CRPS for two types of symptoms(24,25): (i) Spinal cord sensitization leading to myoclonic and akinetic attacks, and (ii) in patients who suffer from ephaptic - or neuroma - type of nerve damage characterized by stabbing, electric shock, or jerking type of pain secondary to damage to the nerve fibers (26). In such cases, anticonvulsants, especially Tegretol (nongeneric), Valproic Acid, Gabapentin, and Klonopin (nongeneric), are quite effective(25,27,28-32). The ephaptic, causalgic CRPS II is best managed with combination of an effective anticonvulsant, antidepressant, and analgesics(1).
The use of Clonazepam is effective in control of myoclonic jerks (30). Decades of experience with Klonopin and Tegretol in neurology have taught the lesson that brand Klonopin and Tegretol are superior to their generic forms (Clonazepam and Carbamazepine) in controlling epileptic seizures. The American Academy of Neurology has recommended that generic antiepileptic drugs not be prescribed. Gabapentin (Neurontin) which is an adjunctive anticonvulsant, provides relief for burning type of neuropathic pain. Similar to Tegretol, Gabapentin is also neuroleptic (29). Carbamazepine, similar to Mexiletin, is an effective sodium channel blocker (33,34). It is far better tolerated than Mexiletin (1).

**ANTIDEPRESSANTS**

Antidepressants possess pure analgesic properties (35). An example is Doxepin (Zonalon) topical cream which is an excellent topical analgesic for neuropathic pain. The analgesic effect of tricyclics is reversed by Naloxone (36). The analgesic property makes the therapeutic use of antidepressants essential for treatment of neuropathic pain (1,35).

Certain antidepressants such as tricyclics and Trazodone, increase the synaptic serotonin and norepinephrine (nor ep) concentrations (24). This balanced phenomenon provides effective analgesia, natural sleep, and antidepressant effect (36). Trazodone provides analgesic effect in less than 24 hours in contrast with five to seven days for the same effective result with tricyclics (24). Trazodone does not cause weight gain when compared to amitriptyline (1).

Of the tricyclics, Amitriptyline has been the most widely used analgesic, but it has strong anticholinergic and sedative side effects, and may cause paranoid and manic symptoms (37,38). More importantly, it has a tendency to cause weight gain. In our study of 824 CRPS patients, 612 had already been tried on Amitriptyline (1). In the first year, these patients gained an average of over 7kg, and, in the following year, an additional 3.6kg. Trial of Desipramine or Trazodone did not cause any significant weight gain. Weight gain in a CRPS patient who already has difficulty with ambulation is quite harmful (1).

**CONCLUSION**

The stress of severe pain and the stress of rebound pain are two major aggravators of CRPS. With the above-mentioned methods, one should eliminate such distress.

No CRPS patient will have a day of rest or any improvement unless their pain is effectively suppressed with the help of strong pain medications, nerve blocks, and large enough doses of antidepressants.

It is foolish to ask the patient to simply "live with the pain" and not to take strong pain medications. However, the most effective strong pain medication is a proper antidepressant.
References:


