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Clinical Pearl

# Treatment of Dependence on Opiate Medications

## Various therapies and treatments can help patients rehabilitate from opiate addictions and withdrawal symptoms.

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### Scope of Dependence on Opiate Medications

The National Household Survey on Drug Abuse demonstrates that 2.6 million people misuse pain relievers, including hydrocodone and oxycodone. This misuse of prescription medicines affects many people, particularly older adults, adolescents, and women. There has been a sharp increase in new users of prescription drugs for nonmedical purposes, particularly painkillers, among teenagers and young adults 12 to 17 years old (2.9 percent increase), and 18 to 25 years old (3.7 percent increase).

We have seen a 5-fold increase in the incidence of narcotic medication use for nonmedical purposes from the 1980s to the late 1990s and 2000. In 1999, approximately 4 million people were using prescription drugs nonmedically, which is about double the 2.1 million people who use heroin and cocaine.

### Signs and Symptoms of Dependence on Opiate Medications

The principle behavior manifestation of the presence of addiction is loss of control over the use of these medications, which results in excessive and continuous use in the presence or absence of pain from other sources. Addiction is a compulsion to use opiate medications that is not necessarily linked to a pain state from an identifiable cause, eg, neurological pain. Paradoxically, pain from addictive use develops because opiate medications become of central importance to one's life, despite development of adverse consequences. The pattern of addictive use becomes evident in the behavioral constellation beginning with preoccupation with acquiring followed by compulsive use and finally a pattern of relapse.

### Psychological Consequences (Chemically Induced)

- Anxiety
- Insomnia
- Depressed mood with suicidal ideation
- Fatigue
- Anhedonia
- Problems with concentration

Medical problems can be aggravated by the misuse of opiate medications, which can mask important normal pain pathways. Because addictive opiate use is not linked to a pain source, the usual signal, to refrain from behaviors that aggravate the underlying source of pain, is dulled or absent because of effects of the narcotic medications on the perception of pain. As a result, the pain source can become worse, with further destruction of tissue and increased neurological damage.

## Occupational Difficulties as a Result of Addiction

- Decreased productivity
- Increase in number of missed workdays
- Loss of employment and subsequent financial problems

Patients with drug addictions may allocate their income for drugs at the expense of required items. These patients' relationships may suffer because they are preoccupied with maintaining their addiction at the expense of their family and friends. Being "unavailable" and not invested in the relationship is common, as is physical and mental abuse. They may also lie or do illegal activities to obtain their drugs.

## Biological Mechanisms Underlying Addiction and Dependence

The major opiates include natural substances, such as opium, morphine and codeine (extracted from opium). Additional opiates include semi-synthetic and synthetic drugs produced by alteration in the chemical structure of the basic poppy products, such as semi-synthetic drugs, eg, heroin, hydromorphone (Dilaudid) and oxycodone (Oxycontin); synthetic drugs include propoxphene (Darvon), meperidine (Demerol), hydrocodone (Vicodin), and others. These opiate medications are metabolized similarly but differ in their absorption (low for heroin and high for propoxyphene) and their half-life.

All prescription opiates act primarily on the mu receptor (named after morphine) with much less action at the other receptors. The sites with mu receptors where opiates act are distributed widely in the central nervous system (CNS), including the brain and spinal cord, the peripheral nervous system, and the gastrointestinal tract. Activation of the mu receptor results in analgesia, euphoria, miosis, decreased breathing rate and muscle tone, decreased motility in the digestive tract and hormonal changes. Addiction is directly linked to the mu receptor, as it is responsible for "the rush" or "thrill" as well as the urge and drive to use more opiates (reinforcement of use).

## Physiological Responses to Intoxication

- Papillary constriction
- Hypotension
- Constipation
- Slurred speech
- Psychomotor agitation or retardation
- Respiratory depression and cardiovascular collapse (in large enough doses)

Tolerance will develop selectively to various psychological and physiological parameters with combined use over time.

## Tolerance and Dependence

Tolerance is the decreasing effect from the dose of the drug, or the need to increase the dose to maintain an effect. Intracellular changes occur, which account for tolerance and withdrawal. Tolerance develops to most addictive drugs, eg, a 20-to 100-fold increase in dosage for opiates compared to a 2-to 4-fold increase in dosage for alcohol, and can be expected as a neuroadaptation to drugs and alcohol with repetitive use and in higher doses.

## Symptoms of Withdrawal from Opiates

- Dysphoria
- Nausea
- Vomiting
- Joint pain
- Back pain

- Anxiety/Agitation
- Muscle aches
- Lacrimation
- Rhinorrhea
- Pupillary dilation
- Sweating
- Diarrhea
- Yawning
- Fever
- Insomnia
- An intense drive to use more drugs, particularly opiates

The peak period and duration of withdrawal after cessation of a drug depends on the half-life of the opiate. In general, a shorter half-life leads to shorter withdrawal. Also, the longer the duration of use of the opiate and the higher the dose, the more severe and protracted the withdrawal. For example, withdrawal from short-acting opiates such as morphine will start 6 to 8 hours after the last dose, peak in 2 to 3 days, and will generally last 5 to 7 days. Withdrawal from longer-acting opiates such as methadone will start 1 to 3 days after the last dose, peak in 7 to 10 days, and last up to 21 days. A post-acute withdrawal syndrome (p.a.w.s.) also occurs in most opiate addicts. This protracted withdrawal can last months and includes the following symptoms: insomnia, irritability, fatigue, drug craving, sweating, and dysphoria.

## Treatment of Withdrawal

Clonidine, a nonopiate alpha-2 agonist, decreases sympathetic outflow to the body. This can often reduce the symptoms of opiate withdrawal, particularly when given in an inpatient setting, by 50 percent to 75 percent, if given in adequate dosages. Generally, oral clonidine 0.1 mg qid and 0.1 mg qid as needed are given daily and a clonidine patch 0.2 mg is used weekly for 1-2 weeks. Doses should be held if the patient is too sedated or experiences orthostatic hypotension or if the blood pressure drops below 90 systolic/ 60 diastolic.

Benzodiazepines, such as diazepam, work at the GABA A receptor and are used to help with agitation, insomnia, muscle aches, and cravings. Doses are typically as follows: diazepam 5 mg qid as needed for 48 to 72 hours, although this can be given for longer periods of time, depending on the severity of the withdrawal.

Other medications used for helping with opiate withdrawal are hydroxyzine 50 mg, or trimethobenzamide 250 mg by mouth or 200 mg rectally for nausea and vomiting. Loperamide 4 mg is used for severe diarrhea. Dicyclomine 20 mg tid can be used for abdominal cramping while acetaminophen or ibuprofen are used for headaches and other pains.

Naltrexone is a mu antagonist and has been used in conjunction with the above medications for an accelerated detoxification. The advantage to this is shorter withdrawal time with less cost. Typically 12.5 mg are used the first day with an increase to 25 mg on the second day and 50 mg on day 3. Some motivated patients may also want to be on naltrexone 50 mg daily to help maintain abstinence from opiates. This seems to be especially helpful for addicted health care workers under direct supervision (someone who ensures the patient is taking the medication). Side effects of naltrexone include abdominal pain, headache, insomnia, anxiety, nausea, and vomiting. A more serious problem is potential hepatotoxicity, especially as the dose is increased above 50 mg. Liver enzymes should be monitored monthly for at least the first 6 months and every 2 to 3 months thereafter if the enzymes are normal. Naltrexone use is contraindicated in patients with severe liver disease, hepatitis, and those taking opiate agonists.

Opiate medications, such as methadone, which is a long-acting opiate, can be used for detoxification from opiate medications. They are effective in reducing symptoms of opiate withdrawal especially for intravenous opiate users and can be used instead of the above medications. Generally 15 to 20 mg of methadone is given on the first day. If the person experiences withdrawal, the dose will be increased by 10 mg increments. Once the patient no longer experiences withdrawal, the dose is decreased by 10 percent per day. However, there can be problems in withdrawing from methadone, eg, decrease in addicts' subsequent motivation to become drug free. Another challenge is that methadone can only be dispensed by FDA- and DEA-licensed clinics, which severely limits its use by most

physicians. Buprenorphine, which is a partial agonist-antagonist at the mu receptor, is also being used for opiate withdrawal and maintenance and appears to be effective. Advantages to buprenorphine are its upper limits on analgesia and respiratory depression at higher doses. It also has a milder withdrawal syndrome compared to other opiates.

## Continued Treatment

Helping opiate addicts through acute withdrawal is only the first step in sobriety. Next, patients should be referred to substance abuse treatment centers, either inpatient or outpatient depending on their drug history. Here they can gain a greater understanding of addiction, learn new coping skills, and receive help in making the personal and behavioral changes needed for recovery. This is accomplished through didactics, group, family, and individual therapies, and treatment of any comorbid medical or psychiatric conditions. Also of great importance is the patient's early involvement in a 12-step group such as Narcotics Anonymous for further support of his or her recovery. Studies show that patients' chances of remaining drug-free are much greater if they complete a treatment program and then continue in a 12-step program on a regular basis for an extended period of time.

## Prevention and Long-Term Interventions

Importantly, alcoholism and other drug addiction are accepted as contraindication to the use of opiate medications in patients with chronic, noncancer pain. However, clinicians must always consider the potential for addiction during the treatment of any patient in acute and chronic administration. In addition, those patients at risk for the development of addiction, tolerance, and dependence to opiate medications include patients with idiopathic pain (no clear etiology) and high levels of psychological distress or disability. There is general agreement that those at substantial and significant risk for the development of overuse and addiction are patients who have a prior or current history of alcohol and drug addiction. Patients should be screened for high-risk of problematic opiate use if they have any previous history of alcohol or drug misuse or addiction.

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