**Opioids**

The term opium comes from the Greek opos meaning juice and was used in reference to the juice of the opium poppy (Papaver somniferum). Opiate is the active substance that is obtained from the opium poppy (e.g. morphine). This natural product can be chemically changed creating semisynthetic derivatives. There are also fully synthetic substances and peptides gained from other animals that cause the same effects as opiates. The umbrella term for all of these active substances is opioid and the animal peptides are called opioid peptides. The human body also produces it's own opioids (enkephalins and endorphins) which trigger feelings of happiness in positive situations.

Heroin (=Diacetylmorphine) is the most commonly consumed illegal substance. It is much more soluble in lipids than morphine, allowing a faster penetration into the brain. Once there, the diacetylmorphine is degraded to form 6-monoacetylmorphine and again to morphine. These metabolites are the active agents that cause the effects of heroine. After intravenous application, high levels of morphine reach the brain very quickly. About 1% of the population consumes heroine in Austria.

*Mechanisms of Action and Actions*

Opioids are all agonists on opioid receptors of which there are three different types known: μ, δ, and κ. These receptors are found in both the central nervous system and in peripheral organs. Their activation has many effects, including analgesia, euphoria, sedation, muscle rigidity, anxiolyse (reduction of anxiety, agitation or tension), cramps, hypothermia, miosis (excessive constriction of the pupil of the eye), respiratory depression, antitussive (suppression of coughing), antiemetic (suppression of nausea or vomiting), blood pressure reduction, bradycardia (slow heart beat), delayed emptying of the stomach, constipation, disturbances of bile flow, retention of urine, and inhibition of labor contractions (in pregnancy). After i.v. application of opioids, a feeling of warmth and euphoria is felt immediately, followed by a state of dream-like indifference. These acute effects last for three to five hours.

Regular administration of opiates leads to the development of tolerance to the drug: a decrease in the effect in spite of an unchanged dose. This pharmacodynamic tolerance reflects a decreased response of the affected organs rather than a change in the metabolism of

the substance. The tolerance is hence not the same for all effects. There is a distinct reduction in the euphoria and sedation (respiratory depression) and just a slight reduction in the peripheral effects (miosis and constipation).

*Withdrawal Symptoms*

When the long term administration of opioids is stopped suddenly, withdrawal symptoms occur. These symptoms are a reversal of the effects of opioids. They are perceived as unpleasant but are not life threatening. The duration of withdrawal depends on the duration and amount of opioids that were consumed and usually lasts for several days (with sleep disturbances over several weeks). The first subjective symptoms of withdrawal include yawning, sneezing and watery eyes, followed by agitation and a massive urge to consume opioids (called craving). Next, symptoms such as dilation of the pupils, piloerection (goose bumps), sweating, nausea, vomiting and insomnia occur, along with psychological symptoms such as anxiety and dysphoria that often trigger renewed consumption. Other symptoms of withdrawal are diarrhea, tachycardia, high blood pressure and joint and muscle pain.

Many opioid addicts repeatedly experience withdrawal symptoms either because of a lack of access or through detoxification attempts without medical observation or treatment. Through these circumstances, it is common that patients take the same dose when they relapse that they took before the period of abstinence. Because of the tolerance reduction that occurs with out regular use, this dose which was previously tolerated without problems, can lead to an overdose and acute intoxication. Hence, it is important that medical indications for detoxification be very limited when certain conditions are not present (e.g. steady motivation, only opioid consumption, continuing supervision).

*Intoxication Symptoms*

The greatest danger posed by an overdose is respiratory paralysis, which can lead to loss of consciousness, coma and death. The massive pupil constriction (pinpoint pupils) is very noticeable. Naloxone, an opioid receptor antagonist, is applied to patients with respiratory depression caused by opioid intoxication. It has no actions when opioids are not present but reverses the actions of opioids when they are present in the patient's body. The most rapid action is seen through i.v. application but patients must remain in observation over a longer period because the actions of opioids are usually longer and a second application of

Naloxone may be necessary. Withdrawal symptoms are seen in patients who are opioid dependent.

*Therapy of Opioid Dependence*

There have been some changes made to the standard therapy schema for opioid dependent patients in the past years as a result of research in this field. Addiction is a chronic, psychiatric disease, which requires long term care. In the past, short, inpatient detoxifications were common, but today the state of the art therapy is outpatient maintenance therapy. Use of detoxification should be restricted. Multi professional, interdisciplinary, long term, outpatient concepts of care (including medical, sociotherapeutic and psychotherapeutic treatment) are most effective for long-term stabilization of dependent patients.

It is important to be aware of the diversification of psychoactive medications, as it is for treatment of somatic diseases. Patients also display different levels of response to different synthetic opioids. In Austria, only oral and sublingual maintenance therapies are available, where as in some countries (such as Switzerland and Holland), controlled treatment with i.v. applied heroine is also legal.

*Substances*

1) **Methadone** is a synthetic opioid and a pure μ receptor agonist with an affinity and action comparable to that of morphine. The main difference to morphine is almost complete bioavailability by oral ingestion. Central actions are about three times faster by i.v. application. It was the first substance used to treat opioid addiction in 1965 and is the substance with the most clinical experience available today. An advantage is 1x daily dosing. Disadvantages are especially prominent after long-term use and can include excessive sweating, weight gain, apathy and depression.
2) **Morphine** is a pure μ receptor agonist with a bioavailability of only 30% by oral ingestion. Because of this and other pharmacokinetic parameters, it is not suitable for long-term maintenance therapy. There is, however, a form of slow-release morphine, which can be used as daily, oral dose. The most common side effect of this therapy is constipation. Misuse through i.v. application of tablets or capsules can also have negative effects, including embolism.
3) **Buprenorphine** is a semisynthetic opioid and both a partial agonist on μ receptors and an antagonist on κ receptors. Through the partial agonistic action on μ

receptors, it has some qualities that differ to other opioids, mainly seen in a reduced level of morphine-like action. Buprenorphine has a limited maximum action and hence a reduced addictive potential. It appears safer since the central respiratory paralysis is less like because of the ceiling effect. However, it can still be problematic, especially in combination with respiratory depressant substances (e.g. benzodiazepines). Another advantage is the delayed and weaker onset of withdrawal symptoms after the medication is abruptly stopped.

4) **LAAM** (Levoacethylmethadolhydrochloride) is also a synthetic opioid with purely agonistic actions. It can be taken orally every two days. An advantage of this therapy is the lower cost through the lower number of outpatient control visits that are necessary. However, because of its side effects on the heart, LAAM is no longer recommended by the European Monitoring Control Center for Drug Assiction (EMCCDA) since 2001.

*Maintenance Therapy*

It is important to obtain a complete medical history of patients when they first present for maintenance therapy, covering comorbid somatic and psychiatric illnesses. To increase patient compliance, it is also necessary to fully explain the treatment procedure. Verification of substance use is made via urine toxicology, tests which are also used to track and optimize the success of the therapy. Medication therapy is started when objective withdrawal symptoms are diagnosed. This happens 7-8 hours at the earliest after the last opioid use. After a set first dose, increasing amounts are given in steps, depending on the clinical signs of withdrawal exhibited by the patient. It is essential for the success of the therapy, that patients receive an adequate maintenance therapy because there is a very high rate of relapse when patients are under dosed. It is also important to avoid doses that are too high because they can cause sedation. At the beginning of the therapy, medication must be taken daily under supervision. When the patient has stabilized, he/she may be given some take-home doses in advance. If patients are no longer stabile (e.g. relapse, taking dose early and i.v. application of dose), an adjustment to another medication and/or renewed daily supervision are recommended. At the same time, it is important to treat the patient's other problems, including somatic and psychiatric problems.

*Detoxification Therapy*

This form of therapy should be used under very limited circumstances and then only as a gradual reduction of dose using synthetic opioids. Both in and outpatient settings are possible. A period of dose adjustment and saturation lasting around tree days begins the treatment. This is followed either by a fast dose reduction over 4-5 days with additional medications to reduce the withdrawal symptoms or in the form of a gradual dose reduction over months. The slow weaning is more successful, possibly because of the decreased withdrawal symptoms experienced. Treatment with Naltrexon, an opioid receptor antagonist, can be used after a withdrawal to support a patient in abstinence. However, it is often poorly accepted by patients. Caution should also be used in prescribing it because Naltrexon is toxic to the liver and 80% of i.v. drug consumers are Hepatitis C positive. Detoxification therapy seems to be recommendable in the cases of adolescents and patients with newly established addictions. Repeated withdrawal treatments are not recommended because of the danger of overdose by relapse with high craving. For a successful detoxification, it is important that patients receive sufficient treatment both medication and psychotherapeutic, along with established social structures.