

Oxycontin, Percodan, Methadone & All Those Other Nasty Opioids: Or Are They?

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TRUE OR FALSE?

1. Oxycotin is the most addictive opioid .
True _____ False _____
2. Opium, demeral and hydrocodone (Novahistex DH) all share the common characteristic of being a pain masker and a cough suppressant.
True _____ False _____
3. Codeine and morphine come from the same source.
True _____ False _____
4. Dilaudid is a better pain masker than morphine.
True _____ False _____
5. Percodan and Percocet are related to CNS depressants.
True _____ False _____
6. Methadone is a by-product of World War II.
True _____ False _____
7. Methadone has minimal side effects if used regularly.
True _____ False _____
8. Morphine is legally classified as a narcotic.
True _____ False _____
9. Narcan can reverse the effects of an opioid overdose.
True _____ False _____
10. Withdrawal from oxycotin is life threatening.
True _____ False _____

PRINCIPLES OF PHARMACOLOGY

The Basics

- The Brain
- Electrical and Chemical Transfer
- Neurotransmitters

Pharmacokinetics

- Absorption
- Administration
- Distribution
- Metabolism
- Elimination
- Half-Life

Pharmacodynamics

- Methods to Enhance the message
- Tolerance

OPIOIDS

These drugs are also referred to as narcotics, opiates (opium derivatives), narcotic analgesics, and opioid analgesics, though opioids is the most inclusive term. Opioids are found in nature and occur in both a synthetic and semi-synthetic form. The use of opium is described in the writings of the Sumerians as early as 4000 BCE. The ancient Greeks knew about the uses of poppy juice, or opion, and described the occurrence of tolerance and dependence. During the Middle Ages, the plant was used by Arab physicians for sedation, analgesia, and relief of dysentery. Arab traders are thought to have introduced this psychoactive drug to the Far East at that time.

Opium from the Asian poppy *papaver somniferum* is eaten or smoked. While many opioids are injected intravenously, and this is the popular perception of the way to administer this substance, they may also be sniffed, smoked, taken orally, or rectally, across mucous membrane. Opioid analgesics can be classified with CNS depressants as both slow CNS functioning. However, along with their disinhibiting characteristics, opioids also remove the emotional reaction to pain. They do not eliminate pain, rather, they mask it and assist people in dealing with the psychological component of pain. Opioids also slow down the gastrointestinal tract and act as cough suppressants as one of their primary effects is depression of the medulla oblongata which is responsible for controlling cardiac, respiratory, and vasomotor centres. Opioids are metabolized mainly in the liver, although heroin is converted rapidly to mono-acetyl morphine and hence to morphine in the blood and in the brain. Excretion occurs largely via the kidneys, although some metabolites are excreted in the faeces. Elimination is usually a matter of a few hours, although a few members of this family of drugs are metabolized and excreted much more slowly, notably methadone.

Opioids are used in medicine to relieve acute pain suffered as a result of disease, surgery, or injury, in the treatment of some forms of acute heart failure, and in the control of moderate to severe cough control or diarrhea. They are of great value in the control of pain in the later stages of terminal illnesses such as cancer, where dependence is no longer an issue. Opium customarily produces an exaggerated feeling of well being, a release from anxiety. To this time, attempts to separate the analgesic effects from euphoria-producing effects have been largely unsuccessful (Ternes & O'Brien, 1990).

Short-term effects of opioids are:

- relief from pain;
- a state of contentment, detachment, and freedom from distressing emotion;
- euphoria;
- respiratory depression;
- suppression of cough;
- nausea or vomiting;
- suppression of diarrhea; and,
- dry mouth.

In comparison with other psychoactive agents opioids are relatively benign. The most harmful long-term implication of opioid use is often the lifestyle users maintain. Abscesses, cellulitis, liver disease, HIV, hepatitis, and possible brain damage may also result from infections associated with unsterile injection techniques. Pulmonary complications, including various types of pneumonia, may also result from the unhealthy lifestyle as well as the depressant effect of opioids on respiration. Emboli composed of small-undissolved particles or air bubbles may block small blood vessels in the lungs, brain, heart, or other organs. With chronic use weight loss, reduction in sex hormone levels, and suppression of the immune system leading to frequent infections, are common.

With continuous use, tolerance develops within days to many effects of opioids including respiratory depression, analgesia, sedation, nausea, and enhancement of mood. If administration is intermittent, however, little change in drug sensitivity is observed. However, regular users do become both psychologically and physically dependent upon opioids. Opioids with their powerful mood-enhancing and anxiety-relieving effects have a high psychological dependence liability. Patterns of purposeful drug-seeking behaviour are difficult to break, and the relapse rate is significant. Withdrawal from opioids, which may begin as early as a few hours after the last administration, produces uneasiness, yawning, tears, diarrhea, abdominal cramps, goosebumps, and a runny nose. These symptoms are accompanied by a craving for the drug. The most marked withdrawal indications peak between 48 and 72 hours after the last dose and subside over a week to ten days though some bodily functions do not return to normal levels for as long as six months. Sudden withdrawal by heavily dependent users who are in poor health has occasionally been fatal. However, withdrawal is much less dangerous to life than are alcohol, barbiturate and non-barbiturate sedative hypnotic induced withdrawal syndromes. Overall, the symptoms are similar to an extremely severe and exceedingly painful case of the flu. With opioids, overdose is a much greater concern than withdrawal. An overdose of opioids is indicated by the combination of coma, depressed respiration and pinpoint pupils. Death almost always results from respiratory depression within a few hours of administration, although late complications such as pneumonia, pulmonary edema, or shock may also be fatal. Opioids are controlled under the Federal Narcotic Control Act. The Act permits individual physicians, dentists, pharmacists, and veterinarians, as well as hospitals, to keep supplies of certain opioids. However, unlawful possession of an opioid, including cultivation of the opium poppy, may result in a maximum prison sentence of seven years. The maximum penalty for trafficking or possessing opioid for the purpose of trafficking is life imprisonment. Importing or exporting opioids without authorization also carries a maximum penalty of life in prison.

One method of categorizing opioids is by placing them into one of the following groups:

- a) Natural opioids (alkaloids) derived from opium or dried poppy juice:
 - i) Morphine
 - ii) Codeine (methyl morphine)
 - iii) Opium (Pantopan)

b) Semi-synthetic, chemically modified versions of codeine or morphine that are more potent than the natural form of the drug:

- i) Heroin
- ii) Hydromorphone (Dilaudid)

c) Synthetic drugs produced to mimic the effects of natural opioids with only minimal structural similarities to opium:

- i) Meperidine (Demerol)
- ii) Hydrocodone (Novahistex DH)
- iii) Propoxyphene (Darvon)
- iv) Methadone

plus: antagonists, drugs that counteract the effects of opioids:

- i) Pentazocine (Talwin)
- ii) Naloxone (Narcan)
- iii) Naltrexone (Revia).

a. Natural Opioids

i. Morphine

Morphine is a natural substance derived from the opium poppy. It is used clinically for pain management especially with continuous dull pain and is considered the prototypical narcotic analgesic (Ternes & O'Brien, 1990). Discovered in 1803 it has the second greatest dependency potential after heroin (see also Table 3.4). Most commonly injected, it can also be smoked, inhaled, or swallowed. As morphine is not as lipid soluble as heroin, codeine, or methadone, onset of action is not as prompt. Drowsiness and mental clouding occur at doses higher than those required for pain relief. Lethargy and impaired concentration and cognition are reported. On the streets it is referred to as "M" or "Morph".

ii. Codeine (methyilmorphine)

Like morphine, codeine is derived from the opium poppy. It is a drug of relatively low potency used in cough syrups, and in preparations containing non-opioid pain suppressants such as ASA. It is partially subject to non-medical use because of its ready availability. In Canada it can be bought without a prescription. Discovered in 1832 codeine is often used by opioid-dependent persons when more potent drugs are unavailable. Dependence, tolerance, and withdrawal are similar to that experienced by a morphine abuser, though much less intense. Seizures are possible with high doses of codeine. It is known as "school boy" to illicit users.

iii. Opium

Opium is a crude resinous preparation obtained from the unripened seed pods of the opium poppy. It has an unpleasant odour and bitter taste that frequently produces nausea when consumed. Morphine

comprises approximately 6% - 12% of the bulk of crude opium, and codeine 0.5% - 1.5%. Most of the majority of the plant consists of a variety of substances with little psychoactive properties.

Opium is smoked because of its euphoric properties, while clinically it can be used to treat diarrhea and dysentery. Opium as an analgesic in clinical medicine has largely been replaced by naturally occurring, semi-synthetic, and wholly synthetic substitutes such as morphine, hydromorphone, and meperidine. Nonetheless, a highly purified form of opium marketed as Pantopan is still occasionally used in situations where a person cannot tolerate morphine. Dependence and tolerance are much lower and less marked with opium than with morphine.

b. Semi-Synthetic Opioids

i. **Heroin (diacetyl-morphine or diamorphine)**

Heroin, first produced in 1898, is a powerful semi-synthetic opioid analgesic created by modifying morphine. It is rapidly metabolized to its intermediate product monoacetyl-morphine and then to morphine in the blood and then onto the central nervous system. Through the widening of blood vessels heroin provides a feeling of warmth, euphoria, described as an orgasmic-like high along with a feeling of detachment from life. Although it has only ever been used by a very small percentage of persons and regularly ranks among the drugs least used by Canadians, it remains widely publicized due to the lucrative drug trade and the continuing controversy over its medical use. Heroin is a highly effective pain masker and it has been approved on a limited basis for the management of severe pain associated with terminal illness. Physical effects may include restlessness, vomiting, nausea, fatigue, dry mouth, and a warm, heavy feeling throughout the body. Other physical effects are constipation, increased urination, contraction of the pupils, itchy skin, and slowed breathing. In larger doses users have their pupils contract to pinpoints; the skin becomes cold, moist and bluish; breathing become slowed or even stopped, thereby causing death. Long-term effects can include pulmonary complications, constipation, menstrual irregularities in women, and reduction in reproductive hormone levels for both men and women.

Tolerance to heroin develops rapidly with regular use and both physical and psychological dependence occurs. Overdose is generally due to users injecting pure or minimally cut heroin rather than the typical dose which tends to be diluted with substances such as sugar, baking soda, or baby powder. Withdrawal symptoms usually appear four to five hours after the last dose and can be quite severe. They often last seven to ten days and include severe anxiety, insomnia, increased perspiration, chills, shivering, and tremors. However, as previously stated, while highly unpleasant, withdrawal is much less life threatening than withdrawal from heavy use of alcohol, barbiturates or non-barbiturate sedative hypnotics. Heroin is used primarily by intravenous injection though it can also be smoked, inhaled, swallowed, and administered by skin-popping. On the streets heroin is referred to as "dust, H, scag, junk, horse or smack". The price for heroin in 1999 in urban areas of Canada ranged from \$30.00 to \$50.00 per "hit" or from \$250.00 to \$300.00 per gram.

ii. Hydromorphone (Dilaudid)

Synthesized in 1936 hydromorphone is a morphine derivative. It is a potent analgesic used to mask severe pain and to suppress the cough reflex. It can be administered both orally and intravenously though the latter tends to produce pain and tissue irritation when the drug is used chronically. Dilaudid produces less nausea, vomiting, and drowsiness than morphine, but more intense respiratory depression. This drug has a pain masking potential seven to eight times that of morphine. Tolerance and physical dependence develop with withdrawal symptoms similar to that of a severe flu. Psychological features of withdrawal are depression, anxiety, insomnia, loss of appetite, combined with periods of agitation. A smaller amount of hydromorphone is required to produce an overdose when compared with other opioids. In double-blind experiments, situations when neither user nor experimenter being aware of what substance is being administered, the effects of hydromorphone could not be distinguished from heroin. Its street names are "juice" and "dillies".

iii. Oxycodone (Percodan)

Oxycodone, first produced in 1938, is created by modifying codeine. Oxycodone is used to treat moderate to severe pain. It has powerful mood-enhancing, analgesic and sedative effects. It is available alone, or in combination with non-opioid analgesics such as ASA (Percodan) or acetaminophen (Percocet). Administration is exclusively oral. Oxycodone also produces a powerful physical dependence in users because of its potent effects.

c) Synthetic Drugs

i. Meperidine (Demerol)

One of the earliest synthesized opioids, meperidine was first made available in Germany in 1939. It is effective as a short-acting oral analgesic. It can also produce central nervous system excitement at high doses manifested by muscle twitches, tremor, and agitation. It is widely used in clinical settings, though with chronic administration, metabolites can accumulate and give rise to toxic reactions. Meperidine produces both physical and psychological dependence similar to that of morphine, though tolerance is slower in developing. Withdrawal begins in three hours, peaks in eight to twelve hours, and ends in four to five days. There is little nausea, vomiting and diarrhea, but muscle twitching, restlessness and anxiety are much worse than with morphine.

ii. Hydrocodone (Novahistex DH)

Hydrocodone, synthesized in 1955, is more potent than codeine. It is used mainly as a cough suppressant, an antitussive, and in combination with antihistamines. High doses can produce euphoria and sedation. Dependence to hydrocodone is greater than that to codeine with tolerance also occurring much more rapidly. The severity of the withdrawal reaction ranges between that produced by codeine and that of morphine.

iii. Propoxyphene (Davron)

Propoxyphene is a mild analgesic used to relieve mild to moderate pain as an alternative to codeine.

Synthesized in 1955, dependency, tolerance and withdrawal are similar to that produced by codeine. Davron has one-half to two-thirds the potency of codeine when administered orally. It is sold alone or in combination with ASA and is consistently among the top ten most prescribed substances in North America. Abuse is minimal as high doses produce dizziness, skin rashes, skin irritation and if injected, toxic psychosis is a risk.

iv. Methadone

Methadone is a long-acting analgesic with properties similar to those of morphine first synthesized by the Germans during World War II as an alternative to opium-based analgesics. It is unlike morphine in that it is highly effective when administered orally, and as it is excreted slowly, being effective for up to 24 hours. As it produces morphine-like actions and cross-tolerance and does not produce a "high" for opioid users when given orally, methadone is used primarily as substitution therapy for opioid-dependent individuals. However, tolerance and withdrawal do occur in methadone users, though its development is much slower than with other opioids. Without other forms of intervention, chronic users eventually become both psychologically and physically dependent upon methadone. Ternes and O'Brien (1990) claim that a street heroin user can be placed on methadone and then weaned off within ten days yet there are Canadians who have been receiving methadone for upwards to twenty years. Methadone's side effects include weight gain, constipation, numbness in extremities and for some, hallucinations (Brecher, 1972).

d) Antagonists

i. Pentazocine (Talwin)

Pentazocine, synthesized in 1962, is a weak opioid antagonist with moderate analgesic properties. More accurately classified as an agonist-antagonist. Other substances in this category include buprenorphine, butorphanol, meptazinol, and nalbuphine. Pentazocine was created to relieve pain without producing a dependence or leading to abuse, as does use of other narcotic analgesics. Tolerance can develop though it is slower than with most opioids. Talwin has no cross-tolerance with any other opioid. Withdrawal effects include abdominal cramps, chills, hypothermia, vomiting, and a craving for the drug. Unfortunately, when combined with the antihistamine Tripeleminamine hydrochloride, such as Benzoxal, and injected, a heroin-like effect is produced. This combination is referred to as "T's and Blues". Combining Talwin with Ritalin produces a similar effect: "T's and Reds". Attempts have been made to prevent this mixing by adding naloxone (see below) to create Talwin Nx but this has not appeared to have completely stopped the practice.

ii. Naloxone (Narcan)

Unlike pentazocine, naloxone is a pure antagonist with no pain relief properties. Naloxone has several therapeutic uses. It will reverse the opioid-induced respiratory depression that is commonly observed in cases of overdose but will not antagonize the respiratory depression caused by high doses of other psychoactive drugs. Naloxone begins working within thirty seconds of administration. It is also used in the control of seizures induced by meperidine or propoxyphene. When Naloxone is

administered to an opioid-free individual, there is little or no discernible effect, other than occasional mild dysphoria. Side-effects are limited to gastrointestinal symptoms.

iii. Naltrexone (Revia)

Naltrexone is an antagonist with properties similar to those of naloxone but with a much longer duration of action. As with naloxone, even after prolonged use discontinuation does not produce withdrawal, respiratory depression, gross behavioural effects, or euphoria. Naltrexone suppresses the effects of heroin. This also allows it to be used in a similar capacity with heroin users as antabuse or temposil is use with alcohol dependent persons, as a protective drug. While some clinical trials have demonstrated the positive value of naltrexone as a protective drug others have shown that it is not totally effective in this function (Schechter, 1990). Recently, naltrexone has received much publicity and taken on a new life as an anti-alcohol craving drug and has been also touted for use with persons who have impulse control disorders such as gambling and kleptomania (Litten & Allen, 1998).

Clinical Features of Various Opioids

Drug	Clinical Dosage (Milligrams)		Duration of Onset (Minutes)		Dependency Liability
	Injection	Oral	Injection	Oral	
Morphine	10	60	30 - 60	90 - 120	high
Codeine		32-65		90 - 120	moderate
Heroin	5	60	30 - 60	90 - 120	high
Dilaudid	1.5	7.5	30 - 60	90 - 120	high
Percodan		30		30 - 60	high
Meperidine	75	300	30 - 60	60 - 120	high
Methadone		20		60 - 120	high
Talwin	60	180	30 - 60	90 - 120	low

Source: Fehr(1987); Ternes and O'Brien(1990)

Duration of Various Opioids Compared with Morphine

Drug		Duration
Hydromorphone	(Dilaudid)	slightly shorter
Meperidine	(Demerol)	shorter
Methadone	(Dolophine)	same
Oxymorphone	(Numorphan)	slightly shorter
Pentazocine	(Talwin)	shorter

Source: Krogh, 1995