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Opiates and Opioids

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Information: Use of Opiates and Opioids

In the U.S. there is seldom a day that passes without numerous deaths from illegally-acquired and/or prescription opiate/opioid overdose. Prescription opiates/opioids kill twice as many people as heroin and cocaine combined. Some studies suggest that about 75% of people with a dependence on heroin began with prescription painkillers.

Prescription opiate/opioid abuse has contributed to heroin addiction and overdoses. For the past few decades, overprescribing physicians have been the primary factor. Persons evolve from opioid prescription medication to street heroin…why? Many states attribute this to for-profit pain clinics (nicknamed "pill mills") that prescribe large quantities of painkillers to people who don't need them medically (Centers for Disease Control and Prevention (CDC)).

In response to this prescription-induced "opioid crisis," the CDC issued new and stricter opioid prescription guidelines in 2016. These guidelines were updated in 2022 as it was recognized that opioids could be prescribed responsibly to those without other pain control options.

The prescribing of opioids by pain clinics and qualified physicians is now more closely monitored. In addition to the 2022 CDC guidelines, many states have implemented their own standards for opioid prescription. Still, difficulties remain. The number of opioid-related and opioid overdose deaths continue to be problematic. The current ready availability of illegally produced, cheap, and highly potent opioids, particularly fentanyl smuggled into the U.S., are a major factor.

Opiates and Opioids

Although the term *opiate* is often used as a synonym for *opioid*, the term *opiate* is properly limited to the natural alkaloids found in the resin of the opium poppy (morphine, codeine), while *opioid* refers to the opiates as well as the semi-synthetic (heroin) and synthetic (fentanyl) classes of substances. Opioids are sometimes called *narcotics* due to their ability to produce stupor and sleep.

Opioids are a class of medications used mostly to control pain. They are the most effective pain medications currently available. Examples of frequently used opioid medications are morphine, fentanyl, and oxycodone. As a class, opioids have a high potential for dependence and addiction. In most cases, the body adapts to having the drug present in the body, which is called tolerance.

This process occurs when the neuroreceptors in the brain become desensitized to the drug, which results in a reduction of its effect in the body.

There are a number of general classes of opioids:

Natural (Morphine)
Semi-synthetic (Oxycodone)
Synthetic (Methadone)
Endogenous (Endorphins)

Opium

Opium is the naturally occurring latex of from the *Papaver somniferum* poppy plant. Opium is chemically complex and contains numerous chemical compounds, including morphine and codeine. Best estimates are that opium is comprised of between 10-16% morphine, while codeine makes up about 2%. The use of opium by humans has been traced to over 5000 years BCE. *Laudanum*, a tincture of opium historically comprised of all the alkaloids of opium dissolved in ethanol remains available by prescription (in a modified formulation) in the U.S. and several other countries.

Morphine

Morphine is the original opiate drug. Morphine has been the clinical standard for pain control for many years. It is a narcotic drug used to treat moderate and severe pain. It derives its name from Morpheus, the Greek God of Dreams.

Heroin

Heroin (diacetylmorphine) was first synthesized in 1874. When acetic anhydride is added to morphine in the proper chemical environment, heroin is produced. This makes heroin a semi-synthetic opioid drug.

Heroin is used medically in several European countries under the name Diamorphine (also used in heroin-maintenance programs). Heroin is more potent and addictive than morphine. It has the ability to travel directly to the brain where it shuts down frontal lobe thinking and produces a sense of euphoria. Heroin is a Schedule I drug in the U.S and therefore is not used medically.

Historically, and prior to a full understanding of its addictive qualities, heroin was used by doctors in the U.S. to treat many medical conditions. It was also available for purchase without a prescription as an over-the-counter medication. At the time, heroin was thought to be a safe and non-addictive treatment for numerous medical conditions, including morphine and cocaine addiction.

Heroin is a prodrug of morphine. It is metabolized into morphine in the body. The effects of street heroin normally last from 3 to 4 hours. A “speedball” involves the simultaneous use of heroin and cocaine.

Codeine

Codeine, (3-methylmorphine) a natural opiate, is available as single ingredient or as a component of many medications. Codeine is derived from the poppy plant and has been used for years as an analgesic, anti-coughing and anti-diarrheal medication. In the body, the liver converts a portion of codeine into morphine. Codeine has a similar abuse potential as morphine and should be taken only as prescribed. Approximately 5-10% of codeine will be converted to morphine in the body.

Oxycodone

Oxycodone (1917) is a semi-synthetic opioid medication (synthesized from the opiate thebaine). It is one of the most widely used opioids and is often used in combination with other medications to create new formulations. It can be combined with ibuprofen (Combunox), acetaminophen (Percocet), or aspirin (Percodan) to create a synergistic effect. The most popular formulation is simply oxycodone, sold as brand name OxyContin. The recommended starting dose of oxycodone for pain control is 10 milligrams (mg) taken every 12 hours.

Oxymorphone

Oxymorphone (Opana) has about twice the strength of oxycodone. It was first synthesized in 1914. Both oxymorphone and oxycodone were first synthesized in Germany.

Hydrocodone

Hydrocodone is a semi-synthetic opioid pain medication (synthesized from codeine). Vicodin and Lortab are brand names of hydrocodone plus acetaminophen. Acetaminophen increases the effect of hydrocodone. Abuse of the drug is high because frequent use of hydrocodone will lead to tolerance. Hydrocodone was first synthesized in1920 in Germany.

Hydromorphone

Hydromorphone is a semi-synthetic derivative of morphine frequently used to treat chronic pain and several other conditions. It is produced under the brand name Dilaudid among others. Hydromorphone, used in combination with other drugs (including midazolam) has been used as a lethal injection. The state of Ohio used a combination of hydromorphone and midazolam to execute Dennis McGuire in January 16, 2014.

Meperidine

Meperidine (Demerol) is a synthetic opioid first manufactured in 1939. It is a used for short-term treatment of moderate to severe pain. Long-term use of meperidine is contraindicated due to the undesirable effects of its toxic metabolite *norpethidine*.

Methadone

Methadone (synthetic opioid) was developed in Germany in 1937 and introduced into the United States in 1947 (Dolophine). It is a Schedule II drug in the U.S. Methadone was widely used by the German army during WWII. Current applications are analgesic and addiction maintenance.

Tramadol

Tramadol is a synthetic opioid sold under various brand names including Ultram and Conzip. It was patented in 1972 by the German drug company Grünenthal. Tramadol is used to treat mild to severe acute and chronic pain. Tramadol is considered by some to be an atypical opioid as it inhibits norepinephrine and serotonin re-uptake. The efficacy of tramadol largely depends upon it being converted to *O*-desmethyltramadol in the liver, making oral administration more effective than injection.

Fentanyl

Fentanyl is produced under the brand name Duragesic and many others. Fentanyl is a synthetic opioid that has become the most commonly prescribed pain medication in the United States. It can be used as a transdermal patch, a chewable tablet, or lollipop (Actiq). The abuse potential of fentanyl is high and should only be used under the care of a qualified physician. Illegally manufactured and distributed fentanyl is a major contributor to fatal and nonfatal overdoses of opioids in the U.S.

Nitazenes

The pool of people at risk of overdose from a new type of super-strength synthetic opioid is widening. Once linked to contaminated batches of heroin, nitazenes are increasingly being found in counterfeit medicines, including benzodiazepines and oxycodone. Nitazenes have also been found in “club drugs” like ecstasy. In such cases, persons thinking they are ingesting a “safe” dose of their club drug may be consuming a lethal dose of one of the several formulations of nitazenes.

Nitazenes are a form of synthetic opioid first developed in the 1950s as analgesics, but were found to be so potent they were never approved or marketed as medicine. Since 2019, they have re-emerged within illegal drug supplies in the United States, UK and other European countries.

Manufactured in a laboratory and relatively cheap to make, nitazenes can range from tens to many hundreds of times more potent than morphine. While nitazenes are structurally unrelated to other opioids, they also bind with the mu-opioid receptor, relieving pain and evoking feelings of euphoria followed by drowsiness. Like morphine and heroin, nitazenes also suppress the respiratory system, which can result in death, but the effects of nitazenes are seen at much lower doses.

There is evidence that most of the compounds that comprise the nitazenes, including isotonitazene (street name ISO), protonitazene, metonitazene and etonitazene, are manufactured in China. (quoted/adapted from Wilkinson, E., (2024). *Everything you need to know about nitazenes.* https://www.pharmaceutical-journal.com). There is also evidence that China supplies the chemical precursors for the synthesis of nitazenes to the drug cartels in Mexico. The Mexican drug cartels then synthesize nitazenes, often disguise them or add them to counterfeit drugs, and smuggle them into the U.S.

The U.S. Drug Enforcement Agency has classified many of the current formulations of nitazenes as Schedule 1 drugs under the Controlled Substances Act, meaning they have no medical use and have a high risk of abuse (quoted from Christopher P. Holstege, Professor of Emergency Medicine and Pediatrics, University of Virginia, https://www.theconversation.com).

Relative Drug Potency compared to Morphine

Morphine 1
Meperidine 0.1 (Demerol)
Heroin 1.5 - 3
Hydromorphone 10 (Dilaudid)
Alfentanil 10–25
Fentanyl 75–125 (Duragesic)
Remifentanil 250
Sufentanil 500–1000 (maximum potency for use in humans)
Etorphine 1000–3000 (legally available for veterinary use only)
Carfentanil 10,000 (legally available for veterinary use only)

Your Brain on Opiates

Opiate abuse causes major, long-lasting chemical changes in the brain. When an opiate is injected or taken in pill form, it travels to the brain's opiate receptors and releases endorphins - chemicals that produce happy, positive feelings and reduce pain - producing a "reward response" that causes the brain to crave more of the drug.

The healthy brain produces natural endorphins on its own. After prolonged use, opiates create a flood of artificial endorphins in the brain that signals the brain to stop producing the natural kind, leading to intense cravings and physical dependence. This type of use changes the way the brain functions and produces the opposite effects of those that first draw most people to use opiates.

Over time, the only way for the user to feel normal and avoid feeling sick and depressed from the loss of natural endorphins is by using higher and higher doses of the drug or graduating to a more dangerous drug (e.g., prescription drug users begin injecting heroin). Getting high is no longer about feeling the euphoria from the drug but simply trying to function. This process in the brain is the primary reason why opiates are so addictive.

If the opiate addict stops using the drug, severe withdrawal symptoms such as anxiety, suicidal thoughts, depression, nausea, diarrhea, heart palpitations and restlessness can occur almost immediately. In most cases, withdrawal lasts 2-4 days, though withdrawal from heroin can last from 1-2 weeks (Opiatesrx.com).

Narcan and Revia

Opioid effects (adverse or otherwise) can be reversed with an opioid antagonist such as naloxone (Narcan) and naltrexone (Revia). Naloxone binds to opioid receptors with higher affinity than most opioid agonists. Naloxone attenuates and/or reverses opioid-agonist effects. It displaces the opioid but does not activate the receptor.

Narcan is now routinely carried by paramedics, police officers, and other first responders. The administration of Narcan by first responders to those that have overdosed on opioids has been credited with saving many lives.

The elimination half-life of naloxone can be shorter than that of the opioid itself, so repeat dosing or continuous infusion may be required when naloxone is used to treat acute opioid overdose.

Buprenorphine and Suboxone

Buprenorphine (Butrans) is a partial opioid receptor agonist. Buprenorphine binds to opioid receptors and triggers a partial response. Buprenorphine is used to treat chronic moderate to severe pain. It is often administered via a transdermal skin patch, referred to as the “B-patch”. The B-patch is long-acting and is not used for treatment of acute pain. Buprenorphine is sometimes used in conjunction with other opioids. *Suboxone* is a combination drug that contains buprenorphine and naloxone. Suboxone is used primarily to treat opioid addiction.

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