https://madeforthismoment.asahq.org/pain-management/opioid-treatment/what-are-opioids/

What Are Opioids

Stay safe by knowing about the potential side effects of prescription opioids and how they can be properly used to manage pain.

What are opioids?

Opioids, sometimes called narcotics, are medications prescribed by doctors to treat persistent or severe pain. They are used by people with chronic headaches and backaches, by patients recovering from surgery or experiencing severe pain associated with cancer, and by adults and children who have gotten hurt playing sports or who have been seriously injured in falls, auto accidents, or other incidents.

How do opioids work?

Opioids attach to proteins called opioid receptors on nerve cells in the brain, spinal cord, gut, and other parts of the body. When this happens, the opioids block pain messages sent from the body through the spinal cord to the brain. While they can effectively relieve pain, opioids carry some risks and can be highly addictive. The risk of addiction is especially high when opioids are used to manage chronic pain over a long period of time.

While they can effectively relieve pain, opioids carry some risks and can be highly addictive.

What are the potential side effects?

Side effects of opioids include:

- Sleepiness
- Constipation
- Nausea

Opioids can also cause more serious side effects that can be life-threatening. The following might be symptoms of an opioid overdose and should be reported to a doctor immediately:

- Shallow breathing
- Slowed heart rate
- Loss of consciousness

In addition, if you suddenly stop taking opioids, you can sometimes experience symptoms such as jittery nerves or insomnia.

Addiction is also possible. Opioids can make your brain and body believe the drug is necessary for survival. As you learn to tolerate the dose you've been prescribed, you may find that you need even more medication to relieve the pain — sometimes resulting in addiction. More than 2 million

Americans misuse opioids, according to the National Institute on Drug Abuse, and every day more than 90 Americans die by opioid overdose.

Are there different types of opioids?

Yes. There are many types of prescribed opioids that are known by several names, including:

- Codeine
- Fentanyl
- Hydrocodone
- Oxycodone
- Oxymorphone
- Morphine

These medications are often sold under brand names such as OxyContin, Percocet, Palladone, and Vicodin.

The different types of opioids are prescribed by doctors in different strengths and administered in various forms, depending on the patient, the situation, and the type and level of pain.

Heroin is an illegal and highly addictive form of opioid with no sanctioned medical use.

View generational differences on opioid use (PDF)

How are opioids taken?

Many opioids are taken in pill form, but they can also be taken as lozenges or lollipops. Some are administered through a vein, by injection or through an IV, and others can be delivered through a patch placed on the skin or with a suppository.

How can you safely use opioids to manage pain?

Opioids can be part of an effective pain management plan, but to help avoid side effects and risk of addiction, **you should use them only under a physician's supervision**.

Anesthesiologists — medical doctors who specialize in anesthesia, pain management, and critical care medicine — have extensive training and experience in prescribing opioid and non-opioid pain medications. If you need help managing pain, an anesthesiologist can work with you to make sure your pain is under control while minimizing side effects and the risk of addiction.

5 Questions to Ask Your Doctor When Prescribed Opioids

If you are prescribed opioids, follow these safety tips:

- **Talk to your physician or anesthesiologist.** Make sure you have considered all alternative pain-relieving medications that don't carry an addiction risk. If opioids remain the best option, ask how to minimize the risks and side effects. Provide information on your medical conditions — and if you have taken opioids in the past, tell your physician how they affected you. Also tell your physician if you have a history of addiction to drugs or alcohol; people predisposed to alcohol abuse may be more susceptible to misusing opioids.
- **Watch out for side effects.** Some side effects of opioids may be mild, such as sleepiness and constipation, while others, including shallow breathing, slowed heart rate, and loss of consciousness, can be serious and may be signs of an overdose. Ask your physician what you should be aware of and what you can do to prevent potential problems. If you experience possible symptoms of an overdose, contact your doctor or call 911.
- **Take opioids only as directed.** Follow your physician's directions, and read the prescription label. If you take other medications, ask your physician whether it is also safe to take opioids.
- **Prepare for surgery.** If you are taking opioids and preparing for surgery, talk with your surgeon, the anesthesiologist, and other physicians who are treating you. Chronic use of opioids increases your risk of complications from surgery and can lengthen your hospital stay. Your medical care team can help you safely manage your pain before surgery.

Also ask your physician about other pain management alternatives, including:

- **Combination therapy.** Opioids by themselves may not always fully control your pain. Combining opioids with other medications or nonmedication treatments, while under the care of a physician, can improve your pain management and result in your needing a lower dosage of opioids.
- **Nondrug therapies.** Many people find relief with alternative therapies, such as biofeedback, meditation, massage, and acupuncture. You may also get relief with interventional therapies such as nerve blocks, or surgical procedures in which the nerves causing the pain are cut. An anesthesiologist or other pain medicine specialist can help you find what works best for you.
- **Injections or implants.** If you are having muscle spasms or nerve pain, an injection of local anesthetics or other medications can help short-circuit your pain. If you have chronic pain

in your back, arms, or legs, a pain medicine specialist might suggest spinal cord stimulation, in which a device is implanted in your back and blocks pain by delivering electric pulses to your nerves and spinal cord.

https://medlineplus.gov/opioidsandopioidusedisorderoud.html

Opioids and Opioid Use Disorder (OUD)

What are opioids?

Opioids, sometimes called narcotics, are a type of drug. They include strong prescription pain relievers such as oxycodone, hydrocodone, fentanyl, and tramadol. The illegal drug heroin is also an opioid. Some opioids are made from the opium plant, and others are synthetic (man-made).

A health care provider may give you a prescription opioid to reduce pain after you have had a major injury or surgery. You may get them if you have severe pain from health conditions like cancer. Some providers prescribe them for chronic pain.

What are the side effects and risks of opioids?

Opioids can cause side effects such as drowsiness, mental fog, nausea, and constipation. They may also cause slowed breathing, which can lead to overdose deaths. If someone has signs of an overdose, call 911. These signs may include:

- Very small pupils of the eyes
- Falling asleep or loss of consciousness
- Slow, shallow breathing
- Choking or gurgling sounds
- Vomiting
- Limp body
- Pale, blue, or cold skin
- Faint heartbeat
- Purple lips and fingernails

When using opioids, there is also a risk of opioid use disorder (OUD).

What is opioid use disorder (OUD)?

Opioid use disorder (OUD) means that you have a problematic pattern of using opioids. The pattern causes a lot of distress and impairment (meaning that it causes problems in and interferes with your daily life). Instead of OUD, sometimes people use the terms "opioid dependence" and "opioid addiction." Dependence means feeling withdrawal symptoms when not taking the drug. Addiction is a chronic brain disease that causes a person to compulsively seek out drugs, even though they cause harm.

The risk of OUD is higher if you misuse the medicines. Misuse can include taking more than your prescribed dose or taking it more often, using it to get high, or taking someone else's opioids.

Opioid use disorder and overdoses are serious public health problems in the United States. As more people misuse opioids, more women are misusing opioids during pregnancy. This can lead to health risks for the mother and baby. The baby may be born with neonatal abstinence syndrome (NAS). NAS is a group of withdrawal symptoms that a baby has after being exposed to drugs during pregnancy.

Another problem with increased opioid misuse is that it can also lead to more heroin use. There are some people who switch from prescription opioids to heroin because heroin may be cheaper and easier to get.

How are opioid use disorder (OUD) and opioid overdose treated?

There are effective medicines to treat OUD. Using medicines to treat OUD is called medications for opioid use disorder (MOUD). MOUD can help you stop using the drug, get through withdrawal, and cope with cravings. It is often combined with behavioral therapy and counseling. Having support from family and friends can also help.

There is also a medicine called naloxone which can treat opioid overdoses. It can reverse the effects of the overdose and prevent death if it is given quickly.

How can I prevent problems when taking prescription opioids?

To prevent problems with prescription opioids, be sure to follow your doctor's instructions when taking them. Do not share your medicines with anyone else. Contact your doctor if you have any concerns about taking the medicines.

NIH: National Institute on Drug Abuse

TAKING OPIOIDS FOR PAIN?
Some Hard Questions You Should Ask

More than 300 million opioid prescriptions are written annually—often for postoperative pain or chronic pain in the back or legs. Opioids can help ease moderate and severe short-term pain. But long term they come with big risks, such as addiction and overdose, and they can negatively impact quality of life.

The American Society of Anesthesiologists suggests you ask yourself and your physician some tough questions.

WHY WAS I PRESCRIBED OPIOIDS?

- Were opioids prescribed to me automatically?
- Are there other effective pain management options?
- If opioids are the best option to treat my moderate to severe pain, how long should I take them?

ARE OPIOIDS AFFECTING MY QUALITY OF LIFE?

Am I suffering from common opioid side effects, such as severe constipation, mental fogginess, nausea, or depression?

WHAT ARE MY CONCERNS ABOUT TAKING OPIOIDS—OR STOPPING THEM?

- Will people judge me because I'm taking opioids?
- Can I become addicted or even overdose? (Ask your physician about naloxone, which reverses the effects of an overdose.)
- Will I be able to manage my pain if I stop taking opioids?

ARE THERE OTHER PAIN MANAGEMENT OPTIONS?

Could I be helped by alternative treatments such as:

- Injections or nerve blocks
- Electrical stimulation or spinal cord stimulation
- Physical therapy, ultrasound, or massage
- Acupuncture
- Biofeedback, meditation, deep breathing, or relaxation
- Surgical procedures

WHAT TYPE OF PHYSICIAN CAN BEST HELP ME MANAGE MY PAIN?

Could a physician who specializes in pain best help me? (These specialists have four years of medical school and additional specialty training, such as anesthesiology, followed by another year of training to become an expert in treating pain.)

For more information about physician anesthesiologists, including those who manage pain, visit asahq.org/madeforthismoment.

American Society of Anesthesiologists | Made for This Moment

Questions to Ask If Taking Opioids

Were you just prescribed opioids? Have you been taking them for a while? Find out what you should ask your doctor - and yourself - about your use of this medication.

Download

How should you stop taking prescribed opioids?

Patients who suddenly stop taking opioids can sometimes experience symptoms such as jittery nerves or insomnia, so it's important to work with your anesthesiologist or another doctor to taper, or wean yourself off of, and ultimately stop the medication.

Your anesthesiologist can:

- Individualize your tapering plan to minimize symptoms of opioid withdrawal.
- Monitor your withdrawal symptoms.
- Adjust the rate and duration of the tapering based on your response.
- Guide you to additional sources of support.

It is important to know what to expect when you start cutting back on the medication. Opioid withdrawal symptoms can, but don't always, include some of the following:

- Drug cravings
- Anxiety
- Insomnia
- Abdominal pain
- Vomiting
- Diarrhea
- Tremors (shaking)

These symptoms can be minimized through measures such as a slow reduction in dosage, consultation with the appropriate specialists, and psychological support for anxiety.

Courtesy of the California Society of Anesthesiologists

What are some of the benefits of stopping opioids?

While withdrawal symptoms can be difficult to endure, they can be managed effectively with positive results, especially with the assistance of a specialist like an anesthesiologist. According to the Centers for Disease Control and Prevention, most people have improved function without worsening pain after stopping opioid use. Some patients have even experienced improved pain relief after weaning off the medicine, even though pain might briefly get worse at first. Additionally, alternative therapies with fewer risks and side effects may be effective in managing pain.

Because opioids mask pain, removing them can also give the pain management specialist a better understanding of the nature and level of your discomfort. With that understanding, the physician can better assess which alternative treatments could be effective for you.

Anesthesiologists are the most highly skilled medical experts in anesthesia care, pain management, and critical care medicine, with the education and training that can mean the difference between life and death.

https://my.clevelandclinic.org/health/drugs/21127-opioids

Opioids

Opioids (sometimes called narcotics) are a class of drugs healthcare providers prescribe to manage moderate to severe pain. They also sometimes prescribe opioids for chronic coughing and diarrhea. Opioids have high addiction potential, so it's important to talk with your provider about their risks and benefits before taking them.

What are opioids?

Opioids (sometimes called narcotics) are a class of drugs that are chemicals — natural or synthetic — that interact with nerve cells that have the potential to reduce pain. Healthcare providers typically prescribe opioids to manage moderate to severe pain.

However, opioids can become addictive because they not only dull pain, but also produce a sense of euphoria. This, combined with tolerance build (needing to increase doses to produce the same

effect) can lead to opioid use disorder. Because of this, providers have modified their prescribing practices to reduce the length and strength of opioids to try to prevent addiction.

What is the difference between opiates and opioids?

Opiates are derived from the naturally occurring poppy plant (*Papaver somniferum*) that creates the active ingredient in the drugs. Common opiates include opium, heroin, morphine and codeine.

An opioid is a substance that can be derived from the poppy plant, be synthetic or be semi-synthetic, meaning the active ingredients are created chemically in a lab. Common opioids include morphine, oxycodone, Oxycontin®, hydrocodone, fentanyl and others.

All opiates are opioids, but not all opioids are opiates. But opioids and opiates have the same effects on your body because they have similar molecules and they both have high addiction potential.

What are opioids approved for?

Prescription opioids are approved for managing moderate to severe pain. This can include:

- Some types of acute pain (sudden and short-term).
- Cancer-related pain.
- Post-surgical pain.
- Vascular pain, such as acute sickle-cell crisis.

The U.S. Food and Drug Administration (FDA) has also approved the use of some opioids to treat intense coughing and chronic diarrhea. Loperamide is an opioid healthcare providers use to treat diarrhea and irritable bowel syndrome (IBS). Opioids such as codeine and dextromethorphan are useful as cough suppressants.

How do opioids work?

"Opioid" is an umbrella term that represents all compounds that bind to opioid receptors. Opioid receptors are found throughout your central and peripheral nervous systems, as well as in your gastrointestinal (GI) tract. These receptors regulate many body functions, including:

- Pain.
- Mood.
- Stress.
- Reward.
- Gastrointestinal functions.
- Breathing (respiration).

Once activated, opioid receptors initiate a cascade of chemical reactions that ultimately modulate the transmission of pain signals. Opioids also cause neurons that produce dopamine,

the neurotransmitter that plays a role in how we feel pleasure, to fire more frequently. This creates feelings of euphoria (intense happiness).

Some opioids are used to stop diarrhea by slowing gastric motility — the process by which food travels through your digestive tract via a series of muscular contractions. This allows more time for absorption of the food in your system.

What are the types of opioids?

There are over 100 different types of prescription opioids. The most commonly prescribed opioids and some of the most common brand names include:

- Hydrocodone (Vicodin®).
- Oxycodone (Oxycontin, Percocet®).
- Oxymorphone (Opana®).
- Morphine (Kadian®, Avinza®).
- Codeine.
- Fentanyl.
- Hydromorphone.
- Tapentadol.
- Methadone.

Heroin is a morphine derivative drug that's exclusively used for recreational purposes and is illegal.

What should I tell my healthcare provider before taking opioids?

In a discussion with your healthcare provider about whether you need to take opioids, you should discuss the following topics:

- Whether there are other medicines or therapies that might treat your pain.
- The risks and benefits of taking opioids.
- Your medical history.
- If you or anyone in your family have a history of substance use or addiction to drugs or alcohol.
- Any other medicines and supplements you're taking, which may interact with the opioid.
- How much alcohol you drink.
- If you're pregnant or planning to become pregnant.
- If you use marijuana/cannabis (prescription or otherwise).
- If you use any street drugs.

You also need to tell your provider about any medical conditions you have. Opioids can worsen the effects of certain conditions and vice versa. For example:

- People with lung conditions and breathing issues may not be able to manage the respiratory depression caused by opioids.
- If people with liver or kidney issues take opioids, they may have poor excretion and metabolism, which may result in the accumulation of harmful byproducts.
- People with certain adrenal gland and thyroid issues may be more sensitive to opioids.

Why are opioids addictive?

The main reason opioids have a high addiction potential is because they not only relieve pain, but also create a sense of euphoria (intense happiness), which many people find pleasurable.

People who use opioids regularly soon develop tolerance to these effects. They may then use more and more of the drug in an attempt to get the original intensity of pain relief and euphoria. Chronic use or misuse of opioids can lead to psychological and physical dependence.

People are psychologically dependent when a drug is so central to their thoughts, emotions and activities that the need to continue its use becomes a craving or compulsion despite negative consequences.

With physical dependence, your body has adapted to the presence of the drug, and withdrawal symptoms happen if you suddenly stop taking the drug or you take a reduced dosage.

People who are physically dependent on opioids experience withdrawal symptoms when they stop taking the drug. These symptoms are often unpleasant, so they may be more likely to take more of the drug to stop the withdrawal symptoms.

Does everyone who is prescribed an opioid become addicted?

No, not everyone taking a prescription opioid becomes addicted to them. When prescription instructions are carefully followed, the chances of becoming addicted are decreased.

Opioids are useful for treating acute pain through short-term use. However, when a prescription drug is used outside of the instructions or for chronic pain, the risk of developing opioid use disorder increases.

https://nida.nih.gov/publications/drugfacts/prescription-opioids

Prescription Opioids DrugFacts

What are prescription opioids?

Opioids are a class of drugs naturally found in the opium poppy plant. Some prescription opioids are made from the plant directly, and others are made by scientists in labs using the same chemical structure. Opioids are often used as medicines because they contain chemicals that relax the body and can relieve pain. Prescription opioids are used mostly to treat moderate to severe pain, though some opioids can be used to treat coughing and diarrhea. Opioids can also make people feel very relaxed and "high" - which is why they are sometimes used for non-medical reasons. This can be dangerous because opioids can be highly addictive, and overdoses and death are common. Heroin is one of the world's most dangerous opioids, and is never used as a medicine in the United States.

What are common prescription opioids?

- hydrocodone (Vicodin®) oxycodone (OxyContin®, Percocet®)
- oxymorphone (Opana®)
- morphine (Kadian®, Avinza®)
- codeine
- fentanyl

How do people misuse prescription opioids?

Prescription opioids used for pain relief are generally safe when taken for a short time and as prescribed by a doctor, but they can be misused. People misuse prescription opioids by:

- taking the medicine in a way or dose other than prescribed
- taking someone else's prescription medicine
- taking the medicine for the effect it causes-to get high

When misusing a prescription opioid, a person can swallow the medicine in its normal form. Sometimes people crush pills or open capsules, dissolve the powder in water, and inject the liquid into a vein. Some also snort the powder.

How do prescription opioids affect the brain?

Opioids bind to and activate opioid receptors on cells located in many areas of the brain, spinal cord, and other organs in the body, especially those involved in feelings of pain and pleasure. When opioids attach to these receptors, they block pain signals sent from the brain to the body and release large amounts of dopamine throughout the body. This release can strongly reinforce the act of taking the drug, making the user want to repeat the experience.

What are some possible effects of prescription opioids on the brain and body?

In the short term, opioids can relieve pain and make people feel relaxed and happy. However, opioids can also have harmful effects, including:

- drowsiness
- confusion
- nausea
- constipation
- euphoria
- slowed breathing

Opioid misuse can cause slowed breathing, which can cause hypoxia, a condition that results when too little oxygen reaches the brain. Hypoxia can have short- and long-term psychological and neurological effects, including coma, permanent brain damage, or death. Researchers are also investigating the long-term effects of opioid addiction on the brain, including whether damage can be reversed.

What are the other health effects of opioid medications?

Older adults are at higher risk of accidental misuse or abuse because they typically have multiple prescriptions and chronic diseases, increasing the risk of drug-drug and drug-disease interactions, as well as a slowed metabolism that affects the breakdown of drugs. Sharing drug injection equipment and having impaired judgment from drug use can increase the risk of contracting infectious diseases such as HIV and from unprotected sex.

Prescription Opioids and Heroin

Prescription opioids and heroin are chemically similar and can produce a similar high. In some places, heroin is cheaper and easier to get than prescription opioids, so some people switch to using heroin instead. Data from 2011 showed that an estimated 4 to 6 percent who misuse prescription opioids switch to heroin[1,2,3] and about 80 percent of people who used heroin first misused prescription opioids.[1,2,3] More recent data suggest that heroin is frequently the first opioid

people use. In a study of those entering treatment for opioid use disorder, approximately one-third reported heroin as the first opioid they used regularly to get high.[4]

This suggests that prescription opioid misuse is just one factor leading to heroin use. Read more about this intertwined problem in our *Prescription Opioids and Heroin Research Report*.

Can I take prescription opioids if I'm pregnant?

If a woman uses prescription opioids when she's pregnant, the baby could develop dependence and have withdrawal symptoms after birth. This is called neonatal abstinence syndrome, which can be treated with medicines. Use during pregnancy can also lead to miscarriage and low birth weight. Read more in the *Substance Use in Women Research Report*.

It can be difficult for a person with an opioid addiction to quit, but pregnant women who seek treatment have better outcomes than those who quit abruptly. Methadone and buprenorphine are the standard of care to treat opioid-dependent pregnant women. Methadone or buprenorphine maintenance combined with prenatal care and a comprehensive drug treatment program can improve many of the adverse outcomes associated with untreated opioid addiction. If a woman is unable to quit before becoming pregnant, treatment with methadone or buprenorphine during pregnancy improves the chances of having a healthier baby at birth.

In general, it is important to closely monitor women who are trying to quit drug use during pregnancy and to provide treatment as needed.

Tolerance vs. Dependence vs. Addiction

Long-term use of prescription opioids, even as prescribed by a doctor, can cause some people to develop a **tolerance**, which means that they need higher and/or more frequent doses of the drug to get the desired effects.

Drug **dependence** occurs with repeated use, causing the neurons to adapt so they only function normally in the presence of the drug. The absence of the drug causes several physiological reactions, ranging from mild in the case of caffeine, to potentially life threatening, such as with heroin. Some chronic pain patients are dependent on opioids and require medical support to stop taking the drug.

Drug **addiction** is a chronic disease characterized by compulsive, or uncontrollable, drug seeking and use despite harmful consequences and long-lasting changes in the brain. The changes can result in harmful behaviors by those who misuse drugs, whether prescription or illicit drugs.

Can a person overdose on prescription opioids?

Yes, a person can overdose on prescription opioids. An opioid overdose occurs when a person uses enough of the drug to produce life-threatening symptoms or death. When people overdose on an opioid medication, their breathing often slows or stops. This can decrease the amount of oxygen that reaches the brain, which can result in coma, permanent brain damage, or death.

How can an opioid overdose be treated?

If you suspect someone has overdosed, the most important step to take is to call 911 so he or she can receive immediate medical attention. Once medical personnel arrive, they will administer naloxone. Naloxone is a medicine that can treat an opioid overdose when given right away. It works by rapidly binding to opioid receptors and blocking the effects of opioid drugs. Naloxone is available as an injectable (needle) solution and nasal sprays (NARCAN® Nasal Spray and KLOXXADO®).

Some states have passed laws that allow pharmacists to dispense naloxone without a personal prescription. Friends, family, and others in the community can use the nasal spray versions of naloxone to save someone who is overdosing.

Read more in our Naloxone DrugFacts.

Can use of prescription opioids lead to addiction?

Yes, repeated misuse of prescription opioids can lead to a substance use disorder (SUD), a medical illness which ranges from mild to severe and from temporary to chronic. Addiction is the most severe form of an SUD. An SUD develops when continued misuse of the drug changes the brain and causes health problems and failure to meet responsibilities at work, school, or home.

People addicted to an opioid medication who stop using the drug can have severe withdrawal symptoms that begin as early as a few hours after the drug was last taken. These symptoms include:

- muscle and bone pain
- sleep problems
- diarrhea and vomiting
- cold flashes with goose bumps
- uncontrollable leg movements
- severe cravings

These symptoms can be extremely uncomfortable and are the reason many people find it so difficult to stop using opioids. There are medicines being developed to help with the withdrawal process, including lofexidine, a non-opioid medicine designed to reduce opioid withdrawal symptoms that was approved by the U.S. Food and Drug Administration (FDA) in 2018. The FDA has also approved sale of a device, NSS-2 Bridge, that can help ease withdrawal symptoms. The NSS-2 Bridge is a small electrical nerve stimulator placed behind the person's ear, that can be used for up to five days during the acute withdrawal phase.

What type of treatment can people get for addiction to prescription opioids?

A range of treatments including medicines and behavioral therapies are effective in helping people with opioid addiction.

Medications for opioid use disorders are safe, effective, and save lives. These medicines interact with the same opioid receptors in the brain on which other prescription opioids act. However, depending on the prescription drug(s) an individual develops an addiction to, these medicines

taken as prescribed may not produce the same effects as other prescription opioids do when they are misused.

- Methadone, an opioid receptor **full agonist**, attaches to and activates opioid receptors to ease withdrawal symptoms and cravings.
- Buprenorphine, an opioid receptor **partial agonist**, attaches to and partially activates opioid receptors to ease withdrawal symptoms and cravings.
- Naltrexone, an opioid receptor **antagonist**, prevents opioids from attaching to opioid receptors, thus blocking their effects.

Learn more about medications for opioid overdose, withdrawal and addiction.

Behavioral therapies for addiction to prescription opioids help people modify their attitudes and behaviors related to drug use, increase healthy life skills, and persist with other forms of treatment, such as medication. Some examples include, cognitive behavioral therapy which helps modify the patient's drug use expectations and behaviors, and also effectively manage triggers and stress. Multidimensional family therapy, developed for adolescents with drug use problems, addresses a range of personal and family influences on one's drug use patterns and is designed to improve overall functioning. These behavioral treatment approaches have proven effective, especially when used along with medicines. Read more about drug addiction treatment on the Treatment webpage.

Points to Remember

- Prescription opioids are used mostly to treat moderate to severe pain, though some opioids can be used to treat coughing and diarrhea.
- People misuse prescription opioids by taking the medicine in a way other than prescribed, taking someone else's prescription, or taking the medicine to get high. When misusing a prescription opioid, a person may swallow, inject, or snort the drug.
- Opioids bind to and activate opioid receptors on cells located in the brain, spinal cord, and other organs in the body, especially those involved in feelings of pain and pleasure, and can strongly reinforce the act of taking the drug, making the user want to repeat the experience.
- People who use prescription opioids can feel relaxed and happy, but also experience drowsiness, confusion, nausea, constipation, and slowed breathing.
- Prescription opioids have effects similar to heroin. While prescription opioid misuse is a risk factor for starting heroin use, only a small fraction of people who misuse opioid pain relievers switch to heroin.
- A person can overdose on prescription opioids. Naloxone is a medicine that can treat an opioid overdose when given right away.
- Prescription opioid use, even when used as prescribed by a doctor can lead to a substance use disorder, which takes the form of addiction in severe cases. Withdrawal symptoms include muscle and bone pain, sleep problems, diarrhea and vomiting, and severe cravings.

- A range of treatments including medicines and behavioral therapies are effective in helping people with an opioid use disorder.

https://en.wikipedia.org/wiki/Opioid

Opioids are a class of drugs that derive from, or mimic, natural substances found in the opium poppy plant. Opioids work in the brain to produce a variety of effects, including pain relief. As a class of substances, they act on opioid receptors to produce morphine-like effects.[2][3]

The terms 'opioid' and 'opiate' are sometimes used interchangeably, but there are key differences based on the manufacturing processes of these medications.[4]

Medically they are primarily used for pain relief, including anesthesia.[5] Other medical uses include suppression of diarrhea, replacement therapy for opioid use disorder, reversing opioid overdose, and suppressing cough.[5] Extremely potent opioids such as carfentanil are approved only for veterinary use.[6][7][8] Opioids are also frequently used recreationally for their euphoric effects or to prevent withdrawal.[9] Opioids can cause death and have been used for executions in the United States.

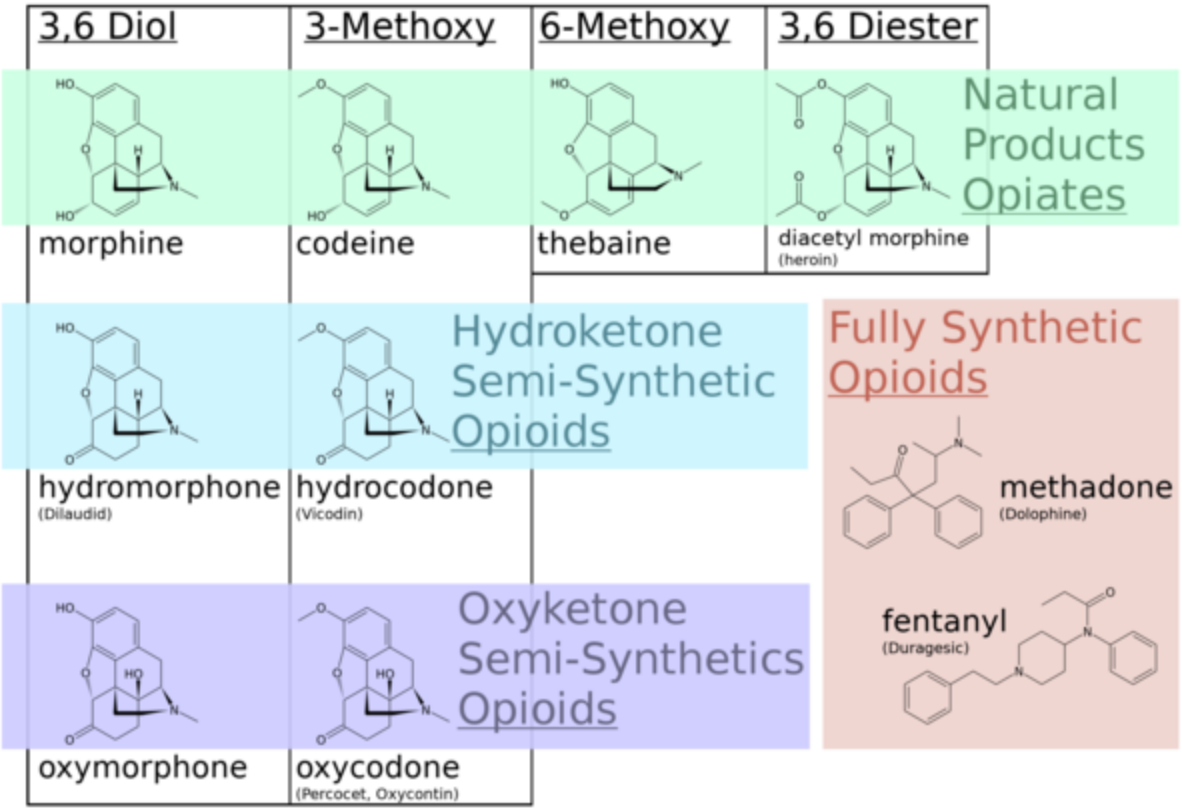
Side effects of opioids may include itchiness, sedation, nausea, respiratory depression, constipation, and euphoria. Long-term use can cause tolerance, meaning that increased doses are required to achieve the same effect, and physical dependence, meaning that abruptly discontinuing the drug leads to unpleasant withdrawal symptoms.[10] The euphoria attracts recreational use, and frequent, escalating recreational use of opioids typically results in addiction. An overdose or concurrent use with other depressant drugs like benzodiazepines commonly results in death from respiratory depression.[11]

Opioids act by binding to opioid receptors, which are found principally in the central and peripheral nervous system and the gastrointestinal tract. These receptors mediate both the psychoactive and the somatic effects of opioids. Opioid drugs include partial agonists, like the anti-diarrhea drug loperamide and antagonists like naloxegol for opioid-induced constipation, which do not cross the blood–brain barrier, but can displace other opioids from binding to those receptors in the myenteric plexus.

Because opioids are addictive and may result in fatal overdose, most are controlled substances. In 2013, between 28 and 38 million people used opioids illicitly (0.6% to 0.8% of the global population between the ages of 15 and 65).[12] In 2011, an estimated 4 million people in the United States used opioids recreationally or were dependent on them.[13] As of 2015, increased rates of recreational use and addiction are attributed to over-prescription of opioid medications and inexpensive illicit heroin.[14][15][16] Conversely, fears about overprescribing, exaggerated side effects, and addiction from opioids are similarly blamed for under-treatment of pain.[17][18]

Duration: 14 minutes and 1 second.14:01Subtitles available.CCEducational video on opioid dependence.

Terminology



Opiates and opioids with chemical structures indicated. Many classical opiates are also referred to as opioids in modern nomenclature.

Opioids include *opiates*, an older term that refers to such drugs derived from opium, including morphine itself.[19] Other opioids are semi-synthetic and synthetic drugs such as hydrocodone, oxycodone, and fentanyl; antagonist drugs such as naloxone; and endogenous peptides such as endorphins.[20] The terms *opiate* and *narcotic* are sometimes encountered as synonyms for opioid. *Opiate* is properly limited to the natural alkaloids found in the resin of the opium poppy although some include semi-synthetic derivatives.[19][21] *Narcotic*, derived from words meaning 'numbness' or 'sleep', as an American legal term, refers to cocaine and opioids, and their source materials; it is also loosely applied to any illegal or controlled psychoactive drug.[22][23] In some jurisdictions all controlled drugs are legally classified as *narcotics*. The term can have pejorative connotations and its use is generally discouraged where that is the case.[24][25]

Medical uses

Pain

The weak opioid codeine, in low doses and combined with one or more other drugs, is commonly available in prescription medicines and without a prescription to treat mild pain.[26][27][28] Other opioids are usually reserved for the relief of moderate to severe pain.[27]

Acute pain

Opioids are effective for the treatment of acute pain (such as pain following surgery).[29] For immediate relief of moderate to severe acute pain, opioids are frequently the treatment of choice due to their rapid onset, efficacy and reduced risk of dependence. However, a new report showed a clear risk of prolonged opioid use when opioid analgesics are initiated for an acute pain management following surgery or trauma.[30] They have also been found to be important in palliative care to help with the severe, chronic, disabling pain that may occur in some terminal conditions such as cancer, and degenerative conditions such as rheumatoid arthritis. In many cases opioids are a successful long-term care strategy for those with chronic cancer pain.

Just over half of all states in the US have enacted laws that restrict the prescribing or dispensing of opioids for acute pain.[31]

Chronic non-cancer pain

Guidelines have suggested that the risk of opioids is likely greater than their benefits when used for most non-cancer chronic conditions including headaches, back pain, and fibromyalgia.[32] Thus they should be used cautiously in chronic non-cancer pain.[33] If used the benefits and harms should be reassessed at least every three months.[34]

In treating chronic pain, opioids are an option to be tried after other less risky pain relievers have been considered, including paracetamol or NSAIDs like ibuprofen or naproxen.[35] Some types of chronic pain, including the pain caused by fibromyalgia or migraine, are preferentially treated with drugs other than opioids.[36][37] The efficacy of using opioids to lessen chronic neuropathic pain is uncertain.[38]

Opioids are contraindicated as a first-line treatment for headache because they impair alertness, bring risk of dependence, and increase the risk that episodic headaches will become chronic.[39] Opioids can also cause heightened sensitivity to headache pain.[39] When other treatments fail or are unavailable, opioids may be appropriate for treating headache if the patient can be monitored to prevent the development of chronic headache.[39]

Opioids are being used more frequently in the management of non-malignant chronic pain.[40][41][42] This practice has now led to a new and growing problem with addiction and misuse of opioids.[33][43] Because of various negative effects the use of opioids for long-term management of chronic pain is not indicated unless other less risky pain relievers have been found ineffective. Chronic pain which occurs only periodically, such as that from nerve pain, migraines, and fibromyalgia, frequently is better treated with medications other than opioids.[36] Paracetamol and nonsteroidal anti-inflammatory drugs including ibuprofen and naproxen are considered safer alternatives.[44] They are frequently used combined with opioids, such as paracetamol combined with oxycodone (Percocet) and ibuprofen combined with hydrocodone (Vicoprofen), which boosts the pain relief but is also intended to deter recreational use.[45][46]

Other

Cough

Codeine was once viewed as the "gold standard" in cough suppressants, but this position is now questioned.[47] Some recent placebo-controlled trials have found that it may be no better than a placebo for some causes including acute cough in children.[48][49] As a consequence, it is not recommended for children.[49] Additionally, there is no evidence that hydrocodone is useful in children.[50] Similarly, a 2012 Dutch guideline regarding the treatment of acute cough does not recommend its use.[51] (The opioid analogue dextromethorphan, long claimed to be as effective a cough suppressant as codeine,[52] has similarly demonstrated little benefit in several recent studies.[53])

Low dose morphine may help chronic cough but its use is limited by side effects.[54]

Diarrhea

In cases of diarrhea-predominate irritable bowel syndrome, opioids may be used to suppress diarrhea. Loperamide is a peripherally selective opioid available without a prescription used to suppress diarrhea.

The ability to suppress diarrhea also produces constipation when opioids are used beyond several weeks.[55] Naloxegol, a peripherally-selective opioid antagonist is now available to treat opioid induced constipation.[56]

Shortness of breath

Opioids may help with shortness of breath particularly in advanced diseases such as cancer and COPD among others.[57][58] However, findings from two recent systematic reviews of the literature found that opioids were not necessarily more effective in treating shortness of breath in patients who have advanced cancer.[59][60]

Restless legs syndrome

Though not typically a first line of treatment, opioids, such as oxycodone and methadone, are sometimes used in the treatment of severe and refractory restless legs syndrome.[61]

Hyperalgesia

Main article: Opioid-induced hyperalgesia

Opioid-induced hyperalgesia (OIH) has been evident in patients after chronic opioid exposure.[62][63]

Adverse effects

See also: Opioid overdose

Adverse effects of opioids

Common and short term

- *Itching*[64]
- *Nausea*[64]
- *Vomiting*[64]

- *Constipation*[64]
- *Drowsiness*[64]
- *Dry mouth*[64]

Other

- *Cognitive effects*
- *Opioid dependence*
- *Dizziness*
- *Loss of appetite*
- *Delayed gastric emptying*
- *Decreased sex drive*
- *Impaired sexual function*
- *Decreased testosterone levels*
- *Depression*
- *Immunodeficiency*
- *Increased pain sensitivity*
- *Irregular menstruation*
- *Increased risk of falls*
- *Slowed breathing*
- *Coma*

Each year 69,000 people worldwide die of opioid overdose, and 15 million people have an opioid addiction.[65]

In older adults, opioid use is associated with increased adverse effects such as "sedation, nausea, vomiting, constipation, urinary retention, and falls".[66] As a result, older adults taking opioids are at greater risk for injury.[67] Opioids do not cause any specific organ toxicity, unlike many other drugs, such as aspirin and paracetamol. They are not associated with upper gastrointestinal bleeding and kidney toxicity.[68]

Prescription of opioids for acute low back pain and management of osteoarthritis seem to have long-term adverse effects[69][70]

According to the USCDC, methadone was involved in 31% of opioid related deaths in the US between 1999–2010 and 40% as the sole drug involved, far higher than other opioids.[71] Studies of long term opioids have found that many stop them, and that minor side effects were

common.[72] Addiction occurred in about 0.3%.[72] In the United States in 2016 opioid overdose resulted in the death of 1.7 in 10,000 people.[73]

Reinforcement disorders

Main article: Opioid use disorder

Tolerance

Tolerance is a process characterized by neuroadaptations that result in reduced drug effects. While receptor upregulation may often play an important role other mechanisms are also known.[74] Tolerance is more pronounced for some effects than for others; tolerance occurs slowly to the effects on mood, itching, urinary retention, and respiratory depression, but occurs more quickly to the analgesia and other physical side effects. However, tolerance does not develop to constipation or miosis (the constriction of the pupil of the eye to less than or equal to two millimeters). This idea has been challenged, however, with some authors arguing that tolerance *does* develop to miosis.[75]

Tolerance to opioids is attenuated by a number of substances, including:

- calcium channel blockers[76][77][78]
- intrathecal magnesium[79][80] and zinc[81]
- NMDA antagonists, such as dextromethorphan, ketamine,[82] and memantine.[83]
- cholecystokinin antagonists, such as proglumide[84][85][86]
- Newer agents such as the phosphodiesterase inhibitor ibudilast have also been researched for this application.[87]

Tolerance is a physiologic process where the body adjusts to a medication that is frequently present, usually requiring higher doses of the same medication over time to achieve the same effect. It is a common occurrence in individuals taking high doses of opioids for extended periods, but does not predict any relationship to misuse or addiction.

Physical dependence

Physical dependence is the physiological adaptation of the body to the presence of a substance, in this case opioid medication. It is defined by the development of withdrawal symptoms when the substance is discontinued, when the dose is reduced abruptly or, specifically in the case of opioids, when an antagonist (*e.g.*, naloxone) or an agonist-antagonist (*e.g.*, pentazocine) is administered. Physical dependence is a normal and expected aspect of certain medications and does not necessarily imply that the patient is addicted.

The withdrawal symptoms for opiates may include severe dysphoria, craving for another opiate dose, irritability, sweating, nausea, rhinorrea, tremor, vomiting and myalgia. Slowly reducing the intake of opioids over days and weeks can reduce or eliminate the withdrawal symptoms.[88] The speed and severity of withdrawal depends on the half-life of the opioid; heroin and morphine withdrawal occur more quickly than methadone withdrawal. The acute withdrawal phase is often followed by a protracted phase of depression and insomnia that can last for months. The symptoms

of opioid withdrawal can be treated with other medications, such as clonidine.[89] Physical dependence does not predict drug misuse or true addiction, and is closely related to the same mechanism as tolerance. While there is anecdotal claims of benefit with ibogaine, data to support its use in substance dependence is poor.[90]

Critical patients who received regular doses of opioids experience iatrogenic withdrawal as a frequent syndrome.[91]

Addiction

Drug addiction is a complex set of behaviors typically associated with misuse of certain drugs, developing over time and with higher drug dosages. Addiction includes psychological compulsion, to the extent that the affected person persists in actions leading to dangerous or unhealthy outcomes. Opioid addiction includes insufflation or injection, rather than taking opioids orally as prescribed for medical reasons.[88]

In European nations such as Austria, Bulgaria, and Slovakia, slow-release oral morphine formulations are used in opiate substitution therapy (OST) for patients who do not well tolerate the side effects of buprenorphine or methadone. Buprenorphine can also be used together with naloxone for a longer treatment of addiction. In other European countries including the UK, this is also legally used for OST although on a varying scale of acceptance.

Slow-release formulations of medications are intended to curb misuse and lower addiction rates while trying to still provide legitimate pain relief and ease of use to pain patients. Questions remain, however, about the efficacy and safety of these types of preparations. Further tamper resistant medications are currently under consideration with trials for market approval by the FDA.[92][93]

The amount of evidence available only permits making a weak conclusion, but it suggests that a physician properly managing opioid use in patients with no history of substance use disorder can give long-term pain relief with little risk of developing addiction, or other serious side effects.[72]

Problems with opioids include the following:

1. Some people find that opioids do not relieve all of their pain.[94]
2. Some people find that opioids side effects cause problems which outweigh the therapy's benefit.[72]
3. Some people build tolerance to opioids over time. This requires them to increase their drug dosage to maintain the benefit, and that in turn also increases the unwanted side effects.[72]
4. Long-term opioid use can cause opioid-induced hyperalgesia, which is a condition in which the patient has increased sensitivity to pain.[95]

All of the opioids can cause side effects.[64] Common adverse reactions in patients taking opioids for pain relief include nausea and vomiting, drowsiness, itching, dry mouth, dizziness, and constipation.[64][88]

Nausea and vomiting

Tolerance to nausea occurs within 7–10 days, during which antiemetics (*e.g.* low dose haloperidol once at night) are very effective. Due to severe side effects such as tardive dyskinesia, haloperidol is now rarely used. A related drug, prochlorperazine is more often used, although it has similar risks. Stronger antiemetics such as ondansetron or tropisetron are sometimes used when nausea is severe or continuous and disturbing, despite their greater cost. A less expensive alternative is dopamine antagonists such as domperidone and metoclopramide. Domperidone does not cross the blood–brain barrier and produce adverse central antidopaminergic effects, but blocks opioid emetic action in the chemoreceptor trigger zone. This drug is not available in the U.S.

Some antihistamines with anticholinergic properties (e.g. orphenadrine, diphenhydramine) may also be effective. The first-generation antihistamine hydroxyzine is very commonly used, with the added advantages of not causing movement disorders, and also possessing analgesic-sparing properties. Δ^9-tetrahydrocannabinol relieves nausea and vomiting;[96][97] it also produces analgesia that may allow lower doses of opioids with reduced nausea and vomiting.[98][99]

- 5-HT_3 antagonists (*e.g.* ondansetron)
- Dopamine antagonists (*e.g.* domperidone)
- Anti-cholinergic antihistamines (*e.g.* diphenhydramine)
- Δ^9-tetrahydrocannabinol (*e.g.* dronabinol)

Vomiting is due to gastric stasis (large volume vomiting, brief nausea relieved by vomiting, oesophageal reflux, epigastric fullness, early satiation), besides direct action on the chemoreceptor trigger zone of the area postrema, the vomiting centre of the brain. Vomiting can thus be prevented by prokinetic agents (*e.g.* domperidone or metoclopramide). If vomiting has already started, these drugs need to be administered by a non-oral route (*e.g.* subcutaneous for metoclopramide, rectally for domperidone).

- Prokinetic agents (*e.g.* domperidone)
- Anti-cholinergic agents (*e.g.* orphenadrine)

Evidence suggests that opioid-inclusive anaesthesia is associated with postoperative nausea and vomiting.[100]

Patients with chronic pain using opioids had small improvements in pain and physically functioning and increased risk of vomiting.[101]

Drowsiness

Tolerance to drowsiness usually develops over 5–7 days, but if troublesome, switching to an alternative opioid often helps. Certain opioids such as fentanyl, morphine and diamorphine (heroin) tend to be particularly sedating, while others such as oxycodone, tilidine and meperidine (pethidine) tend to produce comparatively less sedation, but individual patients responses can vary markedly and some degree of trial and error may be needed to find the most suitable drug for a particular patient. Otherwise, treatment with CNS stimulants is generally effective.[102][103]

- Stimulants (*e.g.* caffeine, modafinil, amphetamine, methylphenidate)

Itching

Itching tends not to be a severe problem when opioids are used for pain relief, but antihistamines are useful for counteracting itching when it occurs. Non-sedating antihistamines such as fexofenadine are often preferred as they avoid increasing opioid induced drowsiness. However, some sedating antihistamines such as orphenadrine can produce a synergistic pain relieving effect permitting smaller doses of opioids be used. Consequently, several opioid/antihistamine combination products have been marketed, such as *Meprozine* (meperidine/promethazine) and *Diconal* (dipipanone/cyclizine), and these may also reduce opioid induced nausea.

- Antihistamines (*e.g.* fexofenadine)

Constipation

Opioid-induced constipation (OIC) develops in 90 to 95% of people taking opioids long-term.[104] Since tolerance to this problem does not generally develop, most people on long-term opioids need to take a laxative or enemas.[105]

Treatment of OIC is successional and dependent on severity.[106] The first mode of treatment is non-pharmacological, and includes lifestyle modifications like increasing dietary fiber, fluid intake (around 1.5 L (51 US fl oz) per day), and physical activity.[106] If non-pharmacological measures are ineffective, laxatives, including stool softeners (*e.g.*, polyethylene glycol), bulk-forming laxatives (*e.g.*, fiber supplements), stimulant laxatives (*e.g.*, bisacodyl, senna), and/or enemas, may be used.[106] A common laxative regimen for OIC is the combination of docusate and bisacodyl.[106][107][108] Osmotic laxatives, including lactulose, polyethylene glycol, and milk of magnesia (magnesium hydroxide), as well as mineral oil (a lubricant laxative), are also commonly used for OIC.[107][108]

If laxatives are insufficiently effective (which is often the case),[109] opioid formulations or regimens that include a peripherally-selective opioid antagonist, such as methylnaltrexone bromide, naloxegol, alvimopan, or naloxone (as in oxycodone/naloxone), may be tried.[106][108][110] A 2018 (updated in 2022) Cochrane review found that the evidence was moderate for alvimopan, naloxone, or methylnaltrexone bromide but with increased risk of adverse events.[111] Naloxone by mouth appears to be the most effective.[112] A daily 0.2 mg dose of naldemedine has been shown to significantly improve symptoms in patients with OIC.[113]

Opioid rotation is one method suggested to minimise the impact of constipation in long-term users.[114] While all opioids cause constipation, there are some differences between drugs, with studies suggesting tramadol, tapentadol, methadone and fentanyl may cause relatively less constipation, while with codeine, morphine, oxycodone or hydromorphone constipation may be comparatively more severe.

Respiratory depression

Respiratory depression is the most serious adverse reaction associated with opioid use, but it usually is seen with the use of a single, intravenous dose in an opioid-naïve patient. In patients

taking opioids regularly for pain relief, tolerance to respiratory depression occurs rapidly, so that it is not a clinical problem. Several drugs have been developed which can partially block respiratory depression, although the only respiratory stimulant currently approved for this purpose is doxapram, which has only limited efficacy in this application.[115][116] Newer drugs such as BIMU-8 and CX-546 may be much more effective.[117][118][119]

- Respiratory stimulants: carotid chemoreceptor agonists (*e.g.* doxapram), 5-HT_4 agonists (*e.g.* BIMU8), δ-opioid agonists (*e.g.* BW373U86) and AMPAkines (*e.g.* CX717) can all reduce respiratory depression caused by opioids without affecting analgesia, but most of these drugs are only moderately effective or have side effects which preclude use in humans. 5-HT_{1A} agonists such as 8-OH-DPAT and repinotan also counteract opioid-induced respiratory depression, but at the same time reduce analgesia, which limits their usefulness for this application.
- Opioid antagonists (*e.g.* naloxone, nalmefene, diprenorphine)

The initial 24 hours after opioid administration appear to be the most critical with regard to life-threatening OIRD, but may be preventable with a more cautious approach to opioid use.[120]

Patients with cardiac, respiratory disease and/or obstructive sleep apnoea are at increased risk for OIRD.[121]

Increased pain sensitivity

Main article: Opioid-induced hyperalgesia

Opioid-induced hyperalgesia – where individuals using opioids to relieve pain paradoxically experience more pain as a result of that medication – has been observed in some people. This phenomenon, although uncommon, is seen in some people receiving palliative care, most often when dose is increased rapidly.[122][123] If encountered, rotation between several different opioid pain medications may decrease the development of increased pain.[124][125] Opioid induced hyperalgesia more commonly occurs with chronic use or brief high doses but some research suggests that it may also occur with very low doses.[126][127]

Side effects such as hyperalgesia and allodynia, sometimes accompanied by a worsening of neuropathic pain, may be consequences of long-term treatment with opioid analgesics, especially when increasing tolerance has resulted in loss of efficacy and consequent progressive dose escalation over time. This appears to largely be a result of actions of opioid drugs at targets other than the three classic opioid receptors, including the nociceptin receptor, sigma receptor and Toll-like receptor 4, and can be counteracted in animal models by antagonists at these targets such as J-113,397, BD-1047 or (+)-naloxone respectively.[128] No drugs are currently approved specifically for counteracting opioid-induced hyperalgesia in humans and in severe cases the only solution may be to discontinue use of opioid analgesics and replace them with non-opioid analgesic drugs. However, since individual sensitivity to the development of this side effect is highly dose dependent and may vary depending which opioid analgesic is used, many patients can avoid this side effect simply through dose reduction of the opioid drug (usually accompanied by the addition of a supplemental non-opioid analgesic), rotating between different opioid drugs, or by

switching to a milder opioid with a mixed mode of action that also counteracts neuropathic pain, particularly tramadol or tapentadol.[129][130][131]

- NMDA receptor antagonists such as ketamine
- SNRIs such as milnacipran
- Anticonvulsants such as gabapentin or pregabalin

Other adverse effects

Low sex hormone levels

Clinical studies have consistently associated medical and recreational opioid use with hypogonadism (low sex hormone levels) in different sexes. The effect is dose-dependent. Most studies suggest that the majority (perhaps as much as 90%) of chronic opioid users develop hypogonadism. A 2015 systematic review and meta-analysis found that opioid therapy suppressed testosterone levels in men by about 165 ng/dL (5.7 nmol/L) on average, which was a reduction in testosterone level of almost 50%.[132] Conversely, opioid therapy did not significantly affect testosterone levels in women.[132] However, opioids can also interfere with menstruation in women by limiting the production of luteinizing hormone (LH). Opioid-induced hypogonadism likely causes the strong association of opioid use with osteoporosis and bone fracture, due to deficiency in estradiol. It also may increase pain and thereby interfere with the intended clinical effect of opioid treatment. Opioid-induced hypogonadism is likely caused by their agonism of opioid receptors in the hypothalamus and the pituitary gland.[133] One study found that the depressed testosterone levels of heroin addicts returned to normal within one month of abstinence, suggesting that the effect is readily reversible and is not permanent. As of 2013, the effect of low-dose or acute opioid use on the endocrine system is unclear.[134][135][136][137] Long-term use of opioids can affect the other hormonal systems as well.[134]

Disruption of work

Use of opioids may be a risk factor for failing to return to work.[138][139]

Persons performing any safety-sensitive task should not use opioids.[140] Health care providers should not recommend that workers who drive or use heavy equipment including cranes or forklifts treat chronic or acute pain with opioids.[140] Workplaces which manage workers who perform safety-sensitive operations should assign workers to less sensitive duties for so long as those workers are treated by their physician with opioids.[140]

People who take opioids long term have increased likelihood of being unemployed.[141] Taking opioids may further disrupt the patient's life and the adverse effects of opioids themselves can become a significant barrier to patients having an active life, gaining employment, and sustaining a career.

In addition, lack of employment may be a predictor of aberrant use of prescription opioids.[142]

Increased accident-proneness

Opioid use may increase accident-proneness. Opioids may increase risk of traffic accidents[143][144] and accidental falls.[145]

Reduced Attention

Opioids have been shown to reduce attention, more so when used with antidepressants and/or anticonvulsants.[146]

Rare side effects

Infrequent adverse reactions in patients taking opioids for pain relief include: dose-related respiratory depression (especially with more potent opioids), confusion, hallucinations, delirium, urticaria, hypothermia, bradycardia/tachycardia, orthostatic hypotension, dizziness, headache, urinary retention, ureteric or biliary spasm, muscle rigidity, myoclonus (with high doses), and flushing (due to histamine release, except fentanyl and remifentanil).[88] Both therapeutic and chronic use of opioids can compromise the function of the immune system. Opioids decrease the proliferation of macrophage progenitor cells and lymphocytes, and affect cell differentiation (Roy & Loh, 1996). Opioids may also inhibit leukocyte migration. However the relevance of this in the context of pain relief is not known.

Pregnancy

This section is an excerpt from Opioids and pregnancy.

Opioid use during pregnancy can have significant implications for both the mother and the developing fetus.

Opioids are a class of drugs that include prescription painkillers (e.g., oxycodone, hydrocodone) and illicit substances like heroin. Opioid use during pregnancy is associated with an increased risk of complications, including an elevated risk of preterm birth, low birth weight, intrauterine growth restriction, and stillbirth. Opioids are substances that can cross the placenta, exposing the developing fetus to the drugs. This exposure can potentially lead to various adverse effects on fetal development, including an increased risk of birth defects. One of the most well-known consequences of maternal opioid use during pregnancy is the risk of neonatal abstinence syndrome (NAS). NAS occurs when the newborn experiences withdrawal symptoms after birth due to exposure to opioids in the womb. Maternal opioid use during pregnancy can also have long-term effects on the child's development. These effects may include cognitive and behavioral problems, as well as an increased risk of substance use disorders later in life.

Interactions

Physicians treating patients using opioids in combination with other drugs keep continual documentation that further treatment is indicated and remain aware of opportunities to adjust treatment if the patient's condition changes to merit less risky therapy.[147]

With other depressant drugs

The concurrent use of opioids with other depressant drugs such as benzodiazepines or ethanol increases the rates of adverse events and overdose.[147] Despite this, opioids and benzodiazepines are concurrently dispensed in many settings.[148][149] As with an overdose of opioid alone, the

combination of an opioid and another depressant may precipitate respiratory depression often leading to death.[150] These risks are lessened with close monitoring by a physician, who may conduct ongoing screening for changes in patient behavior and treatment compliance.[147]

Opioid antagonist

Main article: Opioid antagonist

Opioid effects (adverse or otherwise) can be reversed with an opioid antagonist such as naloxone or naltrexone.[151] These competitive antagonists bind to the opioid receptors with higher affinity than agonists but do not activate the receptors. This displaces the agonist, attenuating or reversing the agonist effects. However, the elimination half-life of naloxone can be shorter than that of the opioid itself, so repeat dosing or continuous infusion may be required, or a longer acting antagonist such as nalmefene may be used. In patients taking opioids regularly it is essential that the opioid is only partially reversed to avoid a severe and distressing reaction of waking in excruciating pain. This is achieved by not giving a full dose but giving this in small doses until the respiratory rate has improved. An infusion is then started to keep the reversal at that level, while maintaining pain relief. Opioid antagonists remain the standard treatment for respiratory depression following opioid overdose, with naloxone being by far the most commonly used, although the longer acting antagonist nalmefene may be used for treating overdoses of long-acting opioids such as methadone, and diprenorphine is used for reversing the effects of extremely potent opioids used in veterinary medicine such as etorphine and carfentanil. However, since opioid antagonists also block the beneficial effects of opioid analgesics, they are generally useful only for treating overdose, with use of opioid antagonists alongside opioid analgesics to reduce side effects, requiring careful dose titration and often being poorly effective at doses low enough to allow analgesia to be maintained.

Naltrexone does not appear to increase risk of serious adverse events, which confirms the safety of oral naltrexone.[152] Mortality or serious adverse events due to rebound toxicity in patients with naloxone were rare.[153]

Pharmacology

See also: Opioid receptor

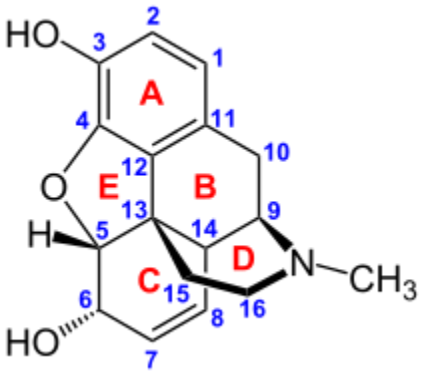
Opioid comparison

Drug	Relative Potency [154]	Nonionized Fraction	Protein Binding	Lipid Solubility [155][156][157]
Morphine	1	++	++	++
Pethidine (meperidine)	0.1	+	+++	+++

Hydromorphone	10		+	+++
Alfentanil	10–25	++++	++++	+++
Fentanyl	50–100[158][159][160]	+	+++	++++
Remifentanil	250	+++	+++	++
Sufentanil	500–1000	++	++++	++++
Etorphine	1000–3000			
Carfentanil	10000			

Show more

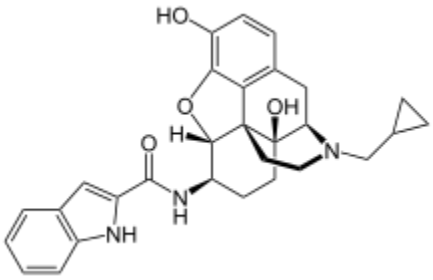
Opioids bind to specific opioid receptors in the nervous system and other tissues. There are three principal classes of opioid receptors, μ, κ, δ (mu, kappa, and delta), although up to seventeen have been reported, and include the ε, ι, λ, and ζ (Epsilon, Iota, Lambda and Zeta) receptors. Conversely, σ (Sigma) receptors are no longer considered to be opioid receptors because their activation is not reversed by the opioid inverse-agonist naloxone, they do not exhibit high-affinity binding for classical opioids, and they are stereoselective for dextro-rotatory isomers while the other opioid receptors are stereo-selective for levo-rotatory isomers. In addition, there are three subtypes of μ-receptor: μ_1 and μ_2, and the newly discovered μ_3. Another receptor of clinical importance is the opioid-receptor-like receptor 1 (ORL1), which is involved in pain responses as well as having a major role in the development of tolerance to μ-opioid agonists used as analgesics. These are all G-protein coupled receptors acting on GABAergic neurotransmission.



Locants of the morphine molecule

The pharmacodynamic response to an opioid depends upon the receptor to which it binds, its affinity for that receptor, and whether the opioid is an agonist or an antagonist. For example,

the supraspinal analgesic properties of the opioid agonist morphine are mediated by activation of the μ_1 receptor; respiratory depression and physical dependence by the μ_2 receptor; and sedation and spinal analgesia by the κ receptor. Each group of opioid receptors elicits a distinct set of neurological responses, with the receptor subtypes (such as μ_1 and μ_2 for example) providing even more [measurably] specific responses. Unique to each opioid is its distinct binding affinity to the various classes of opioid receptors (*e.g.* the μ, κ, and δ opioid receptors are activated at different magnitudes according to the specific receptor binding affinities of the opioid). For example, the opiate alkaloid morphine exhibits high-affinity binding to the μ-opioid receptor, while ketazocine exhibits high affinity to κ receptors. It is this combinatorial mechanism that allows for such a wide class of opioids and molecular designs to exist, each with its own unique effect profile. Their individual molecular structure is also responsible for their different duration of action, whereby metabolic breakdown (such as *N*-dealkylation) is responsible for opioid metabolism.



INTA: selective agonist of KOR-DOR and KOR-MOR heteromers. Does not recruit β-arrestin II. Antinociceptive devoid of aversion, tolerance, and dependence in mice.[161]

Functional selectivity

A new strategy of drug development takes receptor signal transduction into consideration. This strategy strives to increase the activation of desirable signalling pathways while reducing the impact on undesirable pathways. This differential strategy has been given several names, including functional selectivity and biased agonism. The first opioid that was intentionally designed as a biased agonist and placed into clinical evaluation is the drug oliceridine. It displays analgesic activity and reduced adverse effects.[162]

Opioid comparison

Main article: Equianalgesic

Extensive research has been conducted to determine equivalence ratios comparing the relative potency of opioids. Given a dose of an opioid, an equianalgesic table is used to find the equivalent dosage of another. Such tables are used in opioid rotation practices, and to describe an opioid by comparison to morphine, the reference opioid. Equianalgesic tables typically list drug half-lives, and sometimes equianalgesic doses of the same drug by means of administration, such as morphine: oral and intravenous.

Binding profiles

Binding profiles of opioids at opioid receptors (K_i, nM)

Usage

Global estimates of drug users in 2016 (in millions of users)[184]

Substance	Best estimate	Low estimate	High estimate
Amphetamine-type stimulants	34.16	13.42	55.24
Cannabis	192.15	165.76	234.06
Cocaine	18.20	13.87	22.85
Ecstasy	20.57	8.99	32.34
Opiates	19.38	13.80	26.15
Opioids	34.26	27.01	44.54

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Opioid prescriptions in the US increased from 76 million in 1991 to 207 million in 2013.[185]

In the 1990s, opioid prescribing increased significantly. Once used almost exclusively for the treatment of acute pain or pain due to cancer, opioids are now prescribed liberally for people experiencing chronic pain. This has been accompanied by rising rates of accidental addiction and accidental overdoses leading to death. According to the International Narcotics Control Board, the United States and Canada lead the per capita consumption of prescription opioids.[186] The number of opioid prescriptions per capita in the United States and Canada is double the consumption in the European Union, Australia, and New Zealand.[187] Certain populations have been affected by the opioid addiction crisis more than others, including First World communities[188] and low-income populations.[189] Public health specialists say that this may result from the unavailability or high cost of alternative methods for addressing chronic pain.[190] Opioids have been described as a cost-effective treatment for chronic pain, but the impact of the opioid epidemic and deaths caused by opioid overdoses should be considered in assessing their cost-effectiveness.[191] Data from 2017 suggest that in the U.S. about 3.4 percent of the U.S. population are prescribed opioids for daily pain management.[192] Calls for opioid deprescribing have led to broad scale opioid tapering practices with little scientific evidence to support the safety or benefit for patients with chronic pain.

History

Naturally occurring opioids

A sample of raw opium

Opioids are among the world's oldest known drugs.[193] The earliest known evidence of *Papaver somniferum* in a human archaeological site dates to the Neolithic period around 5,700–5,500 BCE. Its seeds have been found at Cueva de los Murciélagos in the Iberian Peninsula and La Marmotta in the Italian Peninsula.[194][195][196]

Use of the opium poppy for medical, recreational, and religious purposes can be traced to the fourth century BC, when ideograms on Sumerians clay tablets mention the use of "Hul Gil", a "plant of joy".[197][198][199] Opium was known to the Egyptians, and is mentioned in the Ebers Papyrus as an ingredient in a mixture for the soothing of children,[200][199] and for the treatment of breast abscesses.[201]

Opium was also known to the Greeks.[200] It was valued by Hippocrates (c. 460 – c. 370 BC) and his students for its sleep-inducing properties, and used for the treatment of pain.[202] The Latin saying "Sedare dolorem opus divinum est", trans. "Alleviating pain is the work of the divine", has been variously ascribed to Hippocrates and to Galen of Pergamum.[203] The medical use of opium is later discussed by Pedanius Dioscorides (c. 40 – 90 AD), a Greek physician serving in the Roman army, in his five-volume work, *De Materia Medica*.[204]

During the Islamic Golden Age, the use of opium was discussed in detail by Avicenna (c. 980 – June 1037 AD) in *The Canon of Medicine*. The book's five volumes include information on opium's preparation, an array of physical effects, its use to treat a variety of illness, contraindications for its use, its potential danger as a poison and its potential for addiction. Avicenna discouraged opium's use except as a last resort, preferring to address the causes of pain rather than trying to minimize it with analgesics. Many of Avicenna's observations have been supported by modern medical research.[205][200]

Exactly when the world became aware of opium in India and China is uncertain, but opium was mentioned in the Chinese medical work *K'ai-pao-pen-tsdo* (973 AD)[199] By 1590 AD, opium poppies were a staple spring crop in the Subahs of Agra region.[206]

The physician Paracelsus (c. 1493–1541) is often credited with reintroducing opium into medical use in Western Europe, during the German Renaissance. He extolled opium's benefits for medical use. He also claimed to have an "arcanum", a pill which he called laudanum, that was superior to all others, particularly when death was to be cheated. ("Ich hab' ein Arcanum – heiss' ich

Laudanum, ist über das Alles, wo es zum Tode reichen will.")[207] Later writers have asserted that Paracelsus' recipe for laudanum contained opium, but its composition remains unknown.[207]

Laudanum

The term laudanum was used generically for a useful medicine until the 17th century. After Thomas Sydenham introduced the first liquid tincture of opium, "laudanum" came to mean a mixture of both opium and alcohol.[207] Sydenham's 1669 recipe for laudanum mixed opium with wine, saffron, clove and cinnamon.[208] Sydenham's laudanum was used widely in both Europe and the Americas until the 20th century.[200][208] Other popular medicines, based on opium, included Paregoric, a much milder liquid preparation for children; Black-drop, a stronger preparation; and Dover's powder.[208]

The opium trade

Opium became a major colonial commodity, moving legally and illegally through trade networks involving India, the Portuguese, the Dutch, the British and China, among others.[209] The British East India Company saw the opium trade as an investment opportunity in 1683 AD.[206] In 1773 the Governor of Bengal established a monopoly on the production of Bengal opium, on behalf of the East India Company. The cultivation and manufacture of Indian opium was further centralized and controlled through a series of acts, between 1797 and 1949.[206][210] The British balanced an economic deficit from the importation of Chinese tea by selling Indian opium which was smuggled into China in defiance of Chinese government bans. This led to the First (1839–1842) and Second Opium Wars (1856–1860) between China and Britain.[211][210][209][212]

Morphine

In the 19th century, two major scientific advances were made that had far-reaching effects. Around 1804, German pharmacist Friedrich Sertürner isolated morphine from opium. He described its crystallization, structure, and pharmacological properties in a well-received paper in 1817.[211][213][208][214] Morphine was the first alkaloid to be isolated from any medicinal plant, the beginning of modern scientific drug discovery.[211][215]

The second advance, nearly fifty years later, was the refinement of the hypodermic needle by Alexander Wood and others. Development of a glass syringe with a subcutaneous needle made it possible to easily administer controlled measurable doses of a primary active compound.[216][208][199][217][218]

Morphine was initially hailed as a wonder drug for its ability to ease pain.[219] It could help people sleep,[211] and had other useful side effects, including control of coughing and diarrhea.[220] It was widely prescribed by doctors, and dispensed without restriction by pharmacists. During the American Civil War, opium and laudanum were used extensively to treat soldiers.[221][219] It was also prescribed frequently for women, for menstrual pain and diseases of a "nervous character".[222]:85 At first it was assumed (wrongly) that this new method of application would not be addictive.[211][222]

Codeine

Codeine was discovered in 1832 by Pierre Jean Robiquet. Robiquet was reviewing a method for morphine extraction, described by Scottish chemist William Gregory (1803–1858). Processing the

residue left from Gregory's procedure, Robiquet isolated a crystalline substance from the other active components of opium. He wrote of his discovery: "Here is a new substance found in opium ... We know that morphine, which so far has been thought to be the only active principle of opium, does not account for all the effects and for a long time the physiologists are claiming that there is a gap that has to be filled."[223] His discovery of the alkaloid led to the development of a generation of antitussive and antidiarrheal medicines based on codeine.[224]

Semi-synthetic and synthetic opioids

Synthetic opioids were invented, and biological mechanisms for their actions discovered, in the 20th century.[199] Scientists have searched for non-addictive forms of opioids, but have created stronger ones instead. In England Charles Romley Alder Wright developed hundreds of opiate compounds in his search for a nonaddictive opium derivative. In 1874 he became the first person to synthesize diamorphine (heroin), using a process called acetylation which involved boiling morphine with acetic anhydride for several hours.[211]

Heroin received little attention until it was independently synthesized by Felix Hoffmann (1868–1946), working for Heinrich Dreser (1860–1924) at Bayer Laboratories.[225] Dreser brought the new drug to market as an analgesic and a cough treatment for tuberculosis, bronchitis, and asthma in 1898. Bayer ceased production in 1913, after heroin's addictive potential was recognized.[211][226][227]

Several semi-synthetic opioids were developed in Germany in the 1910s. The first, oxymorphone, was synthesized from thebaine, an opioid alkaloid in opium poppies, in 1914.[228] Next, Martin Freund and Edmund Speyer developed oxycodone, also from thebaine, at the University of Frankfurt in 1916.[229] In 1920, hydrocodone was prepared by Carl Mannich and Helene Löwenheim, deriving it from codeine. In 1924, hydromorphone was synthesized by adding hydrogen to morphine. Etorphine was synthesized in 1960, from the oripavine in opium poppy straw. Buprenorphine was discovered in 1972.[228]

The first fully synthetic opioid was meperidine (Demerol), found serendipitously by German chemist Otto Eisleb (or Eislib) at IG Farben in 1932.[228] Meperidine was the first opioid to have a structure unrelated to morphine, but with opioid-like properties.[199] Its analgesic effects were discovered by Otto Schaumann in 1939.[228] Gustav Ehrhart and Max Bockmühl, also at IG Farben, built on the work of Eisleb and Schaumann. They developed "Hoechst 10820" (later methadone) around 1937.[230] In 1959 the Belgian physician Paul Janssen developed fentanyl, a synthetic opioid with 30 to 50 times the potency of heroin.[211][231] Nearly 150 synthetic opioids are now known.[228]

Criminalization and medical use

Non-clinical use of opium was criminalized in the United States by the Harrison Narcotics Tax Act of 1914, and by many other laws.[232][233] The use of opioids was stigmatized, and it was seen as a dangerous substance, to be prescribed only as a last resort for dying patients.[211] The Controlled Substances Act of 1970 eventually relaxed the harshness of the Harrison Act.

In the United Kingdom the 1926 report of the Departmental Committee on Morphine and Heroin Addiction under the Chairmanship of the President of the Royal College of Physicians reasserted medical control and established the "British system" of control—which lasted until the 1960s.[234]

In the 1980s the World Health Organization published guidelines for prescribing drugs, including opioids, for different levels of pain. In the U.S., Kathleen Foley and Russell Portenoy became leading advocates for the liberal use of opioids as painkillers for cases of "intractable non-malignant pain".[235][236] With little or no scientific evidence to support their claims, industry scientists and advocates suggested that people with chronic pain would be resistant to addiction.[211][237][235]

The release of OxyContin in 1996 was accompanied by an aggressive marketing campaign promoting the use of opioids for pain relief. Increasing prescription of opioids fueled a growing black market for heroin. Between 2000 and 2014 there was an "alarming increase in heroin use across the country and an epidemic of drug overdose deaths".[237][211][238]

As a result, health care organizations and public health groups, such as Physicians for Responsible Opioid Prescribing, have called for decreases in the prescription of opioids.[237] In 2016, the Centers for Disease Control and Prevention (CDC) issued a new set of guidelines for the prescription of opioids "for chronic pain outside of active cancer treatment, palliative care, and end-of-life care" and the increase of opioid tapering.[239]

"Remove the Risk"

In April 2019 the U.S. Food and Drug Administration announced the launch of a new education campaign to help Americans understand the important role they play in removing and properly disposing of unused prescription opioids from their homes. This new initiative is part of the FDA's continued efforts to address the nationwide opioid crisis (see below) and aims to help decrease unnecessary exposure to opioids and prevent new addiction. The "Remove the Risk" campaign is targeting women ages 35–64, who are most likely to oversee household health care decisions and often serve as the gatekeepers to opioids and other prescription medications in the home.[240]

Society and culture

Main article: Opioid epidemic

Definition

The term "opioid" originated in the 1950s.[241] It combines "opium" + "-oid" meaning "opiate-like" ("opiates" being morphine and similar drugs derived from opium). The first scientific publication to use it, in 1963, included a footnote stating, "In this paper, the term, 'opioid', is used in the sense originally proposed by George H. Acheson (personal communication) to refer to any chemical compound with morphine-like activities".[242] By the late 1960s, research found that opiate effects are mediated by activation of specific molecular receptors in the nervous system, which were termed "opioid receptors".[243] The definition of "opioid" was later refined to refer to substances that have morphine-like activities that are mediated by the activation of opioid receptors. One modern pharmacology textbook states: "the term opioid applies to all agonists and antagonists with morphine-like activity, and also the naturally occurring and synthetic opioid peptides".[244] Another pharmacology reference eliminates the *morphine-like* requirement: "Opioid, a more modern term, is used to designate all substances, both natural and synthetic, that bind to opioid receptors (including antagonists)".[2] Some sources define the term *opioid* to exclude *opiates*, and others use *opiate* comprehensively instead of *opioid*, but *opioid* used inclusively is considered modern, preferred and is in wide use.[19]

Efforts to reduce recreational use in the US

In 2011, the Obama administration released a white paper describing the administration's plan to deal with the opioid crisis. The administration's concerns about addiction and accidental overdosing have been echoed by numerous other medical and government advisory groups around the world.[190][245][246][247]

As of 2015, prescription drug monitoring programs exist in every state, except for Missouri.[248] These programs allow pharmacists and prescribers to access patients' prescription histories in order to identify suspicious use. However, a survey of US physicians published in 2015 found that only 53% of doctors used these programs, while 22% were not aware that the programs were available to them.[249] The Centers for Disease Control and Prevention was tasked with establishing and publishing a new guideline, and was heavily lobbied.[250] In 2016, the United States Centers for Disease Control and Prevention published its Guideline for Prescribing Opioids for Chronic Pain, recommending that opioids only be used when benefits for pain and function are expected to outweigh risks, and then used at the lowest effective dosage, with avoidance of concurrent opioid and benzodiazepine use whenever possible.[34] Research suggests that the prescription of high doses of opioids related to chronic opioid therapy (COT) can at times be prevented through state legislative guidelines and efforts by health plans that devote resources and establish shared expectations for reducing higher doses.[251]

On 10 August 2017, Donald Trump declared the opioid crisis a (non-FEMA) national public health emergency.[252]

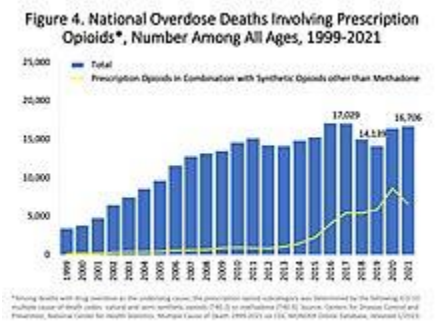
Global shortages

Morphine and other poppy-based medicines have been identified by the World Health Organization as essential in the treatment of severe pain. As of 2002, seven countries (USA, UK, Italy, Australia, France, Spain and Japan) use 77% of the world's morphine supplies, leaving many emerging countries lacking in pain relief medication.[253] The current system of supply of raw poppy materials to make poppy-based medicines is regulated by the International Narcotics Control Board under the provision of the 1961 Single Convention on Narcotic Drugs. The amount of raw poppy materials that each country can demand annually based on these provisions must correspond to an estimate of the country's needs taken from the national consumption within the preceding two years. In many countries, underprescription of morphine is rampant because of the high prices and the lack of training in the prescription of poppy-based drugs. The World Health Organization is now working with administrations from various countries to train healthworkers and to develop national regulations regarding drug prescription to facilitate a greater prescription of poppy-based medicines.[254]

Another idea to increase morphine availability is proposed by the Senlis Council, who suggest, through their proposal for Afghan Morphine, that Afghanistan could provide cheap pain relief solutions to emerging countries as part of a second-tier system of supply that would complement the current INCB regulated system by maintaining the balance and closed system that it establishes while providing finished product morphine to those in severe pain and unable to access poppy-based drugs under the current system.

Recreational use

See also: Opioid use disorder and Recreational drug use



Prescription opioid pain reliever overdose deaths in the United States over years

Opioids can produce strong feelings of euphoria[255] and are frequently used recreationally. Traditionally associated with illicit opioids such as heroin, prescription opioids are misused recreationally.

Drug misuse and non-medical use include the use of drugs for reasons or at doses other than prescribed. Opioid misuse can also include providing medications to persons for whom it was not prescribed. Such diversion may be treated as crimes, punishable by imprisonment in many countries.[256][257] In 2014, almost 2 million Americans abused or were dependent on prescription opioids.[258][259]

Classification

There are a number of broad classes of opioids:[260]

- Natural opiates: alkaloids contained in the resin of the opium poppy, primarily morphine, codeine, and thebaine, but not papaverine and noscapine which have a different mechanism of action
- Esters of morphine opiates: slightly chemically altered but more natural than the semi-synthetics, as most are morphine prodrugs, diacetylmorphine (morphine diacetate; heroin), nicomorphine (morphine dinicotinate), dipropanoylmorphine (morphine dipropionate), desomorphine, acetylpropionylmorphine, dibenzoylmorphine, diacetyldihydromorphine;[261][262]
- Semi-synthetic opioids: created from either the natural opiates or morphine esters, such as hydromorphone, hydrocodone, oxycodone, oxymorphone, ethylmorphine and buprenorphine;
- Fully synthetic opioids: such as fentanyl, pethidine, levorphanol, methadone, tramadol, tapentadol, and dextropropoxyphene;
- Endogenous opioid peptides, produced naturally in the body, such as endorphins, enkephalins, dynorphins, and endomorphins.

- Endogenous opioids, non-peptide: Morphine, and some other opioids, which are produced in small amounts in the body, are included in this category.
- Natural opioids, non-animal, non-opiate: the leaves from Mitragyna speciosa (kratom) contain a few naturally-occurring opioids, active via Mu- and Delta receptors. Salvinorin A, found naturally in the Salvia divinorum plant, is a kappa-opioid receptor agonist.[263]

Tramadol and tapentadol, which act as monoamine uptake inhibitors also act as mild and potent agonists (respectively) of the μ-opioid receptor.[264] Both drugs produce analgesia even when naloxone, an opioid antagonist, is administered.[265]

Some minor opium alkaloids and various substances with opioid action are also found elsewhere, including molecules present in kratom, *Corydalis*, and *Salvia divinorum* plants and some species of poppy aside from *Papaver somniferum*. There are also strains which produce copious amounts of thebaine, an important raw material for making many semi-synthetic and synthetic opioids. Of all of the more than 120 poppy species, only two produce morphine.

Amongst analgesics there are a small number of agents which act on the central nervous system but not on the opioid receptor system and therefore have none of the other (narcotic) qualities of opioids although they may produce euphoria by relieving pain—a euphoria that, because of the way it is produced, does not form the basis of habituation, physical dependence, or addiction. Foremost amongst these are nefopam, orphenadrine, and perhaps phenyltoloxamine or some other antihistamines. Tricyclic antidepressants have painkilling effect as well, but they're thought to do so by indirectly activating the endogenous opioid system. Paracetamol is predominantly a centrally acting analgesic (non-narcotic) which mediates its effect by action on descending serotoninergic (5-hydroxy triptaminergic) pathways, to increase 5-HT release (which inhibits release of pain mediators). It also decreases cyclo-oxygenase activity. It has recently been discovered that most or all of the therapeutic efficacy of paracetamol is due to a metabolite, AM404, which enhances the release of serotonin and inhibits the uptake of anandamide.

Other analgesics work peripherally (*i.e.*, not on the brain or spinal cord). Research is starting to show that morphine and related drugs may indeed have peripheral effects as well, such as morphine gel working on burns. Recent investigations discovered opioid receptors on peripheral sensory neurons.[266] A significant fraction (up to 60%) of opioid analgesia can be mediated by such peripheral opioid receptors, particularly in inflammatory conditions such as arthritis, traumatic or surgical pain.[267] Inflammatory pain is also blunted by endogenous opioid peptides activating peripheral opioid receptors.[268]

It was discovered in 1953, that humans and some animals naturally produce minute amounts of morphine, codeine, and possibly some of their simpler derivatives like heroin and dihydromorphine, in addition to endogenous opioid peptides. Some bacteria are capable of producing some semi-synthetic opioids such as hydromorphone and hydrocodone when living in a solution containing morphine or codeine respectively.

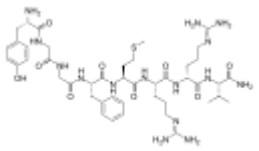
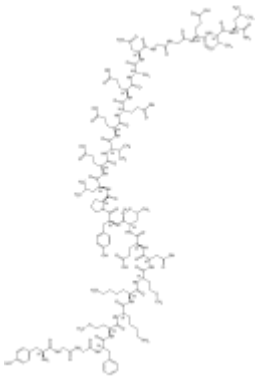
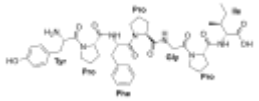
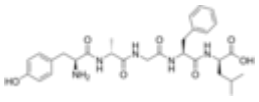
Many of the alkaloids and other derivatives of the opium poppy are not opioids or narcotics; the best example is the smooth-muscle relaxant papaverine. Noscapine is a marginal case as it does

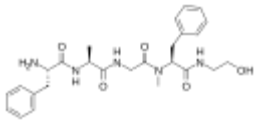
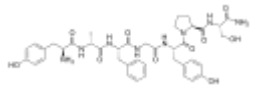
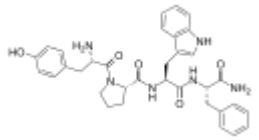
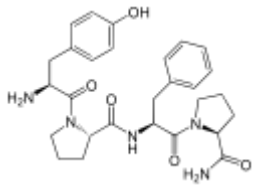
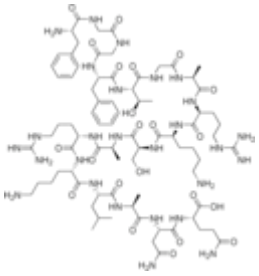
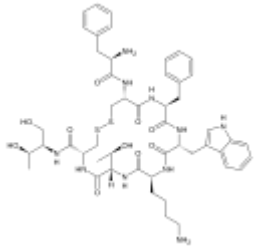
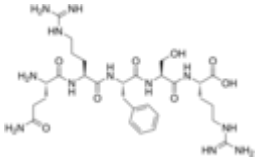
have CNS effects but not necessarily similar to morphine, and it is probably in a category all its own.

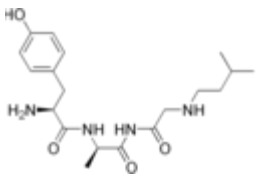
Dextromethorphan (the stereoisomer of levomethorphan, a semi-synthetic opioid agonist) and its metabolite dextrorphan have no opioid analgesic effect at all despite their structural similarity to other opioids; instead they are potent NMDA antagonists and sigma 1 and 2-receptor agonists and are used in many over-the-counter cough suppressants.

Salvinorin A is a unique selective, powerful κ-opioid receptor agonist. It is not properly considered an opioid nevertheless, because:

1. chemically, it is not an alkaloid; and
2. it has no typical opioid properties: absolutely no anxiolytic or cough-suppressant effects. It is instead a powerful hallucinogen.

Opioid peptides	**Skeletal molecular images**
Adrenorphin	
Amidorphin	
Casomorphin	
DADLE	

DAMGO	
Dermorphin	
Endomorphin	
Morphiceptin	
Nociceptin	
Octreotide	
Opiorphin	

TRIMU 5	

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Endogenous opioids

Opioid-peptides that are produced in the body include:

- Endorphins
- Enkephalins
- Dynorphins
- Endomorphins

β-endorphin is expressed in Pro-opiomelanocortin (POMC) cells in the arcuate nucleus, in the brainstem and in immune cells, and acts through μ-opioid receptors. β-endorphin has many effects, including on sexual behavior and appetite. β-endorphin is also secreted into the circulation from pituitary corticotropes and melanotropes. α-neoendorphin is also expressed in POMC cells in the arcuate nucleus.

Met-enkephalin is widely distributed in the CNS and in immune cells; [met]-enkephalin is a product of the proenkephalin gene, and acts through μ and δ-opioid receptors. leu-enkephalin, also a product of the proenkephalin gene, acts through δ-opioid receptors.

Dynorphin acts through κ-opioid receptors, and is widely distributed in the CNS, including in the spinal cord and hypothalamus, including in particular the arcuate nucleus and in both oxytocin and vasopressin neurons in the supraoptic nucleus.

Endomorphin acts through μ-opioid receptors, and is more potent than other endogenous opioids at these receptors.

Opium alkaloids and derivatives

Opium alkaloids

Phenanthrenes naturally occurring in (opium):

- Codeine
- Morphine
- Thebaine
- Oripavine[269]

Preparations of mixed opium alkaloids, including papaveretum, are still occasionally used.

Esters of morphine

- Diacetylmorphine (morphine diacetate; heroin)
- Nicomorphine (morphine dinicotinate)
- Dipropanoylmorphine (morphine dipropionate)
- Diacetyldihydromorphine
- Acetylpropionylmorphine
- Desomorphine
- Methyldesorphine
- Dibenzoylmorphine

Ethers of morphine

- Dihydrocodeine
- Ethylmorphine
- Heterocodeine

Semi-synthetic alkaloid derivatives

- Buprenorphine
- Etorphine
- Hydrocodone
- Hydromorphone
- Oxycodone (sold as OxyContin)
- Oxymorphone

Synthetic opioids

Anilidopiperidines

- Fentanyl (see also list of fentanyl analogues)
- Alphamethylfentanyl
- Alfentanil
- Sufentanil
- Remifentanil
- Carfentanyl
- Ohmefentanyl

- Ohmecarfentanil

Benzimidazoles

Main article: List of benzimidazole opioids

Benzimidazoles opioids are also known as nitazenes.

- Metodesnitazene (Metazene)
- Etodesnitazene (Etazene)
- Metonitazene
- Etonitazene
- Etonitazepyne
- Etonitazepipne
- Isotonitazene
- Clonitazene

Phenylpiperidines

- Pethidine (meperidine)
- Ketobemidone
- MPPP
- Allylprodine
- Prodine
- PEPAP
- Promedol

Diphenylpropylamine derivatives

- Propoxyphene
- Dextropropoxyphene
- Dextromoramide
- Bezitramide
- Piritramide
- Methadone
- Dipipanone
- Levomethadyl acetate (LAAM)

- Difenoxin
- Diphenoxylate
- Loperamide (does cross the blood–brain barrier but is quickly pumped into the non-central nervous system by P-Glycoprotein. Mild opiate withdrawal in animal models exhibits this action after sustained and prolonged use including rhesus monkeys, mice, and rats.)

Benzomorphan derivatives

- Dezocine—agonist/antagonist
- Pentazocine—agonist/antagonist
- Phenazocine

Oripavine derivatives

- Buprenorphine—partial agonist
- Dihydroetorphine
- Etorphine

Morphinan derivatives

- Butorphanol—agonist/antagonist
- Nalbuphine—agonist/antagonist
- Levorphanol
- Levomethorphan
- Racemethorphan

Others

- Lefetamine
- Meptazinol
- Mitragynine
- Tilidine
- Tramadol
- Tapentadol
- Eluxadoline
- Bucinnazine
- 7-Hydroxymitragynine

Allosteric modulators

Plain allosteric modulators do not belong to the opioids, instead they are classified as opioidergics.

Opioid antagonists

- Nalmefene
- Naloxone
- Naltrexone
- Methylnaltrexone (Methylnaltrexone is only peripherally active as it does not cross the blood–brain barrier in sufficient quantities to be centrally active. As such, it can be considered the antithesis of loperamide.)
- Naloxegol (Naloxegol is only peripherally active as it does not cross the blood–brain barrier in sufficient quantities to be centrally active. As such, it can be considered the antitheses of loperamide.)