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Synthetic Narcotics

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Narcotics were among the earliest drugs used. Opium, a narcotic, was one of the most potent drugs of our ancient pharmacopeia, with a very long history of abuse. Narcotics, whether natural or synthetic, pharmacologically impact us by binding to specific narcotic receptor sites located in the central **[p. 756 ↓]** nervous system and in other tissues. There are several different classes of these receptors, such as the delta, kappa, and mu receptors. Further, there are respective subtypes to the various classes of receptors, each of which have a specific neurological response. Accordingly, as different natural or synthetic narcotics bind to different receptors they produce varying pharmacodynamic responses. One of the most profound pharmacological effects of most narcotics, both natural and synthetic, is analgesia; antidiarrheal and cough suppressant functions have also been utilized. Habitual use of these substances, unfortunately, can readily progress to dependence. Narcotic abuse has been one of the primary targets for developers of drug policies.

In the early 19th century, Friedrich W. Serturner, a German pharmacist, successfully isolated morphine, a constituent of the latex obtained from opium poppies *(Papaver somniferum).* This landmark scientific discovery opened up an entire new field of study, alkaloidal chemistry. Many other opiates, the various alkaloids derived from opium, were subsequently discovered; these include substances such as codeine, narceine, narcotine, papaverine, and thebaine. These opiates can also be synthesized. For example, codeine, although a natural opiate contained in opium, can be synthesized by methylation of the 3-hydroxy group of the morphine ring. Opioids are biochemical synthetics that produce similar effects to opiates. Heroin is a semisynthetic narcotic that was created in 1874 by C. R. Wright, a British chemist. Many other semisynthetic narcotics, also known as semisynthetic opioids, were synthesized, such as hydromorphone, hydrcodone, oxymorphone, oxycodone, dihydrodesoxymorphine, nicomorphine, and nalbuphine. In addition to the semisynthetic narcotics there are many synthetic narcotics.

Substances

A vast array of synthetic narcotics, also known as synthetic opioids, has been created. These substances have similar action to morphine and other opiates and many exhibit cross-tolerance. Synthetic narcotics are usually created in a laboratory with the intent of producing a substance that will have the pharmacological properties of a narcotic but, hopefully, with less liability for abuse and dependence. Some of these synthetic narcotics are drugs such as meperdine (Demerol), methadone (Dolophine), and propoxyphene (Darvon).

The synthetic narcotics can be separated into several different families, each of which consists of several different drugs. The families of the synthetic narcotics include phenylpiperidines, diphenylpropylamine derivatives, benzomorphan derivatives, oripavine derivatives, anilidopiperidines, morphinan derivatives, and others.

Phenylpiperidines

The phenylpiperidine group of synthetic narcotics includes substances such as meperdine, ketobemidone, and prodine. Meperdine, which is a synthetic opium derivative, was first made in 1939 by O. Eisleb and O. Schaumann of I. G. Farbenindustric in Hoechst-am-Main, Germany; they referred to it as dolantin. Meperdine, also known as pethidine, was first thought to have less dependence potential than morphine; however, its addictive nature was soon recognized. Meperdine has a shorter duration of action compared to morphine, as well as having less pronounced antidiarrheal and antitussive effects. Meperdine has a short half-life, three to four hours, and it also has a toxic metabolite, normeperidine. Accordingly, it should only be used for acute dosing, not for chronic analgesia, and it should also be avoided in the elderly and patients in renal failure. Under the Controlled Substances Act (21 U.S. 801–8886) of the Comprehensive Drug Abuse Prevention and Control Act and its amendments, meperdine is listed as a Schedule II substance regulated by the Drug Enforcement Administration (DEA No. 9230).

Meperdine was the first totally synthesized narcotic and its discovery led to the synthesizing of a series of phenylpiperidine derived drugs. For example, diphenoxilate was one such substance created to help reduce intestinal hypermobility. Ketobemidone was first synthesized during World War II by O. Eisled and others at I. G. Farbenindustric. Ketobemidone is a powerful narcotic analgesic, similar to morphine in effectiveness. The results of experimental research on recovering narcotic addicts indicated that ketobemidone could be even more addictive than other narcotics. Thus, in 1954 the United Nations Economic and Social Council **[p. 757 ↓]** promulgated a resolution that urged member governments to cease the manufacture and use of ketobemidone.

Accordingly, ketobemidone is mainly used in Scandinavian nations, being most prevalent in Denmark. Currently the United Kingdom is the only manufacturer and exporter of ketobemidone. Under the Controlled Substances Act, ketobemidone is listed in the United States as a Schedule I substance (DEA No. 9628). Ketobemidone is included in Schedule IV of the 1961 Single Convention on Narcotic Drugs.

Prodine is a synthetic narcotic analgesic that is an analogue of meperdine. There are two main isomers of prodine, alphaprodine and betaprodine. Betaprodine is more potent, but metabolized more rapidly than alphaprodine; thus, only alphaprodine has been developed for medical purposes, where it is used mainly in dentistry and during childbirth. Alphaprodine has similar effects to meperdine but with a faster onset and a shorter duration of action, from one to two hours. Under the Controlled Substances Act, alphaprodine is listed as a Schedule II substance (DEA No. 9010); it is marketed primarily as Nisentil or Prisilidine. Other substances belonging to the phenylpiperidine family of synthetic narcotics include allylprodine, (DEA No. 9602), MPPP (DEA No. 9661), and PEPAP (DEA No. 9663); all listed as Schedule I substances under the Controlled Substances Act. They are also included in Schedule I of the 1961 Single Convention on Narcotic Drugs.

Diphenylpropylamine Derivatives

The diphenylpropylamine derivatives include methadone, levo-alpha-acetylmethadol, propoxyphene, piritramide, bezitramide, and loperamide. Methadone was

developed around 1939 by Max Bockmuhl and Gustav Ehrgart while working at I. G. Farbenindustrie. Methadone was first called Hoechst 10820 and then it was referred to as polamidon; after World War II, Eli Lilly, an American pharmaceutical company, called it Dolophine. Soon after its introduction, it was recognized that methadone had a high potential for being addictive.

Methadone was first used by German soldiers during World War II for analgesic purposes as a substitute for morphine. When administered chronically methadone hydrochloride use leads to the development of tolerance, sedation, lethargy, and edema. However, the onset of the acute abstinence syndrome to methadone is slower than that produced by morphine or heroin. Methadone use also impedes learning and immediate recall. At any rate, methadone is commonly used to manage narcotic addiction.

Under the Controlled Substances Act, methadone is highly regulated as a Schedule II substance (DEA No. 9250). The United States is the leading global producer of methadone, as it is of many other synthetic narcotics. Levo-alpha-acetylmethadol, or LAAM, is a synthetic narcotic developed in the 1940s that has a slow onset and a long duration that made it unsuitable for pain management. However, LAAM seemed to be an appropriate substance for treating those chronically dependent on narcotics; accordingly, LAAM was formerly being administered to some individuals who were on methadone maintenance. In fact, LAAM was approved in 1994 by the Food and Drug Administration (FDA) for treating narcotic addiction. LAAM has a relatively long duration of action varying from 48 to 72 hours, which permitted longer times between office visits. However, beginning in 2003 the availability of buprenorphine, which does not cause heart problems, led to the sudden discontinuation of the use of LAAM for treating addicts.

Propoxyphene, also known as dextropropoxyphene is another synthetic narcotic in this family. The half life of propoxyphene is four to six hours, with a duration of action of six to 12 hours. Propoxyphene hydrochloride, a mild analgesic, similar in effects to codeine, was first marketed in 1957 as Darvon and its abuse potential has since been well established. For instance, the nonmedical use of propoxyphene was particularly prevalent among U.S. soldiers stationed in what was then known as West Germany. In fact, many fatalities have been attributed to propoxyphene. Propoxyphene is a

mu receptor agonist and is commonly used to ease withdrawal symptoms in narcotic addicts; it is also useful in relieving symptoms associated with restless leg syndrome. Propoxyphene napsylate was introduced in the hope that it was less liable to be abused, being insoluble in water and not readily injected. The United States is largest producer of **[p. 758 ↓]** propoxyphene led by Eli Lilly and Company, with India as the second leading producer.

Under the Controlled Substances Act, propoxyphene itself is listed as a Schedule II substance (DEA No. 9273), while preparations containing propoxyphene are listed under Schedule IV (DEA No. 9278). It is also included in Schedule II of the 1961 Single Convention on Narcotic Drugs. Methadone, levo-alpha-acetylmethadol, and propoxyphene are all derivatives of diphenylheptane. It is important to recognize that neither methadone nor propoxyphene will be detected in typical urinalysis drug tests, focused on standard opiates and opioids, as they are not chemically related.

Piritramide is a narcotic that was first synthesized in Belgium at Janssen Pharmaceutical and has been marketed under trade names such as Pirium, Piridolan, and Dipidolar, used mainly in Europe for postoperative pain. Piritramide is listed as a Schedule I substance (DEA No. 9642). Bezitramide is another synthetic narcotic that in 1961 was also created in Belgium at Janssen Pharmaceutical and marketed in Europe as Burgodin. Loperamide is another synthetic narcotic created at Janssen Pharmaceutical; it is a derivative of piperidine that is widely used to treat diarrhea. Other substances belonging to the diphenylpropylamine derivatives family of synthetic narcotics include dextromoramide (DEA No. 9613), difenoxin (DEA No. 9168), and dipipanone (DEA No. 9622), which are all listed as Schedule I substances under the Controlled Substances Act, and diphenoxylate (DEA No. 9170), which is listed as a Schedule II.

Benzomorphan Derivatives

The benzomorphan derivatives, which are also known as the benzazocines, include pentazocine, and phenazocine. Under the Controlled Substances Act, phenazocine (DEA No. 9715) is classified as a Schedule II substance while pentazocine is classified as a Schedule IV substance. Pentazocine was first introduced in 1967

and was marketed as Talwin. Pentazocine was widely used in the illicit drug market in combination with tripelennamine. In an effort to reduce its illicit abuse, another formulation, marketed as Talwin Nx, was produced by adding naloxone, a narcotic antagonist, hoping to counter the narcotic effects if pentazocine is used by injection. Other benzomorphan derivatives include cyclazocine and dezocine.

Anilidopiperidines

The anilidopiperidine family of synthetic narcotics includes fentanyl, sufentanil, alfentanil, beta-hydroxyfentanyl, and carfentanil. Fentanyl was initially synthesized by Paul Janssen in 1959 at a pharmaceutical company he started in Belgium. Fentanyl is a synthetic narcotic that is much more potent than morphine or heroin. In fact, fentantl is estimated to be about 100 times more potent than morphine. It has been indicated that fentanyl interacts preferentially with the mu receptors. Since fentanyl has a high clinical potency and is not considerably difficult to synthesize, adulterated heroin is sometimes cut with fentanyl. Unfortunately this heroin-fentanyl mixture has resulted in many fatal cases of drug overdose. Controlled release patches are an increasingly popular way to administer fentanyl.

Sufentanil and alfentanil are two other narcotic analgesics related to fentanyl. Sufentanil is more potent than fentanyl, and alfentanil is much faster acting. Beta-hydroxyfentanyl is another fentanyl analogue that was being sold in the early 1980s before the passage of the Federal Analog Act of the Controlled Substances Act that attempted to control entire families of drugs with similar chemical structures, rather than scheduling each substance as appearing. Beta-hydroxyfentanyl is listed as a Schedule I substance (DEA No. 9830). Fentanyl, sufentanil, alfentanil, beta-hydroxyfentanyl are all included in Schedule I of the Single Convention on Narcotic Drugs. Carfentanil is another fentanyl analogue that is extremely more potent than fentanyl; accordingly, it is approved for use in veterinary medicine to sedate large animals.

Fentanyl and its several synthetic analogues have been abused. However, none of these substances are detected by typical drug screening tests, which are focused on morphine-like substances; this is because fentanyl and its close analogues are not structurally related to other opiates. Other substances belonging to the anilidopiperidine

family of synthetic narcotics include alphamethylfentanyl, ohmefentanyl, and remifentanyl. Numerous other fentanyl analogues have been sold illicitly with names like “China White.” These include, but are not limited **[p. 759 ↓]** to, 3-methylfentanyl, 3-methylthiofentanyl, alpha-methylfentanyl, alpha-methylthiofentanyl, beta-hydroxyfentanyl, beta-hydroxy-3-methylfentanyl, and thiofentanyl. These analogues are relatively more resistant to being metabolized, which results in a lengthier duration of action, otherwise known as a longer “high.” All of these substances are listed as Schedule I substances under the Controlled Substance Act and are banned under the Federal Analog Act (21 U.S.C. Section 813) of January 22, 2002.

Oripavine Derivatives

The oripavine derivatives include etorphine, buprenorphine, and dihydroetorphine. Etorphine was first synthesized in the 1960s by K. W. Bentley and D. G. Hardy at Edinburgh, Scotland; etorphine is mainly used as a sedative in veterinary medicine. Etorphine itself, but not its hydrochloride salt, is classified as a Schedule I substance under the Controlled Substance Act (DEA No. 9056). Etorphine is included in Schedule IV of the 1961 Single Convention on Narcotic Drugs. Buprenorphine is a derivative of thebaine that was approved in 2002 by the FDA for treating narcotic addiction. American physicians can a complete specialized training program as authorized by the Drug Addiction Treatment Act of 2000 to be able to prescribe buprenorphine products. Buprenorphine is used outside the United States as well, such as in France for maintenance treatment of addiction.

Buprenorphine is also being used along with methadone for the treatment of narcotic dependence. Of course, drug interactions must always be an area of concern. Cocaine, for example, has significant effects on the pharmokinetics of both methadone and buprenorphine. There are also clinically significant drug interactions between buprenorphine and methadone; and between buprenorphine and various antiviral medications. Buprenorphine is usually administered as a sublingual tablet; although, a buprenorphine transdermal patch is being considered as an alternative way to conduct narcotic detoxification.

Since the use of buprenorphine alone has the potential for abuse it is also produced in a formulation combined with naloxone, known as Suboxone, which is hoped to reduce abuse. Under the Controlled Substances Act in the United States, buprenorphine (DEA No. 9064) is classified as a Schedule III substance. Dihydroetorphine is another oripavine derivative, actually a derivative of etorphine. Dihydroetorphine is used mainly in China as a powerful analgesic, but also occasionally as a substitute for narcotic maintenance therapy. Under the Controlled Substances Act in the United States, dihydroetorphine (DEA No. 9334) is classified as a Schedule II substance. Dihydroetorphine is included in Schedule I of the 1961 Single Convention on Narcotic Drugs.

Morphinan Derivatives

The morphinan derivatives include levorphanol and butorphanol. Morphinan is the base chemical structure for this family of synthetic narcotics. For example, levorphanol is the laevorotary stereoisomer of morphinan; it is a pure narcotic agonist that binds to the delta, kappa, and mu receptors. Levorphanol was initially synthesized in Germany in 1946 and introduced as a potent orally active analgesic. Levorphanol has a longer half-life, 12 to 16 hours, and is more potent than morphine, with duration of action of six to eight hours.

Under the Controlled Substance Act, levorphanol is listed as a Schedule II drug. Butorphanol can be synthesized from thebaine, but is typically totally synthesized. Butorphanol tartrate was first manufactured generically as an injectable preparation for medical purposes and also sold for veterinary medicine, then marketed under names like Butorphic, Torbutrol or Torbugesic. Butorphanol is more effective as an analgesic in women than men; it can be used to control labor pains. It was then manufactured as a nasal spray, marketed as Stadol, which resulted in greater illicit use. Since 1997 butorphanol was listed under Schedule IV of the Controlled Substance Act (DEA N0. 9720) and is no longer sold in the United States under the brand name Stadol. The International Federation for Equestrian Sports considers it to be a Class A drug. Other morphinan derivatives include nalbuphine and levomethorphan.

Other Types

There are several other types of synthetic narcotics that do not belong to the various families mentioned. One of these, for instance, is tramadol. Tramadol **[p. 760 ↓]** is a synthetic analogue of codeine. Tramadol was developed in the late 1970s by the German pharmaceutical company Chemie Grunenthal of Stolberg-am-Rhein. Tramadol hydrochloride (Ultram) has been diverted for abuse purposes. Tramadol is also another substance in the long history of narcotics, both natural and synthetic, that was introduced with the hoped for promise of low abuse potential.

It was initially believed that tramadol would be effective in treating pain but that it would tend not to be abused. However, greater numbers of instances of abuse, dependence and withdrawal were reported among users in different countries and thus treatment approaches had to be designed, including those based on the administration of methadone. Nevertheless, it currently seems that there is less abuse and dependence of tramadol than for hydrocodone. However, the FDA recently added a warning of suicide risk to the labels of tramadol. Tramadol can also be produced in formulations combined with other substances, such as a tramadol and acetaminophen product marketed as Ultracet. Some other synthetic narcotics not included in the families listed include lefetamine, meptazinol, and tilidine.

Work on the design and synthesis of new synthetic narcotics is ongoing. In fact, new analogues of various synthetic narcotics continue to be introduced. Much of this research is directed toward the objective of developing more effective substances without the undesired side effects of earlier synthetic narcotics.

Trends in Synthetic Narcotic Use

Synthetic narcotic are now among the most frequently used drugs by American youths, and numerous authorities argue that the increased use of synthetic narcotics is now the most troubling drug trend in the U.S. Based on Monitoring the Future data, approximately 9 percent of high school seniors report using a synthetic narcotic without a physician's prescription at least once a year. This consumption rate has remained

stable since 2002, despite the general trend of decreasing rates of illegal drug use among high school seniors.

Conclusion

A vast array of synthetic narcotics has been created. The synthetic narcotics can be characterized into several families, which generally resulted from the synthesis of prototypical substances. Meperidine, for instance, was the prototype for the phenylpiperidine series of drugs; methadone was the prototype for the diphenylpropylamine derivatives; fentanyl for the anilidopiperidines; pentazocine for the benzomorphane series; and, levorpanol for the morphinane series.

Further work into the design and synthesis of new synthetic narcotics is an ongoing endeavor and the illicit drug market evolves as well. Accordingly, drug policies must be dynamic to keep abreast. Many of the synthetic narcotics have been used for assorted medical purposes. Synthetic narcotics are primarily used in medicine as powerful analgesics. However, due to the development of tolerance, the dosage of synthetic narcotics must gradually be increased; this can lead to dependence.

Many of the synthetic narcotics are listed as Schedule I substances under the Controlled Substance Act, meaning they do not have any currently accepted medical use in the United States. The Federal Analog Act regulates groups of substances, rather than separately as they appear. The synthetic narcotics are also controlled by the Single Convention on Narcotic Drugs and subsequent UN conventions, including the Convention Against the Illicit Traffic in Narcotic Drugs and Psychotropic Substances.

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See Also:

Further Readings

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