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The Fentanyl Story

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Abstract: Fentanyl, introduced more than 50 years ago, has become the most often used opioid for intraoperative analgesia. Since the early 1990s the fentanyl patch has been available for management of chronic pain of all forms of cancer as well as the persistent, intense pain from many noncancerous maladies. More than a half dozen rapid-onset transmucosal fentanyl preparations have been developed, approved, launched, and popularized for "breakthrough" pain syndromes in the past 20 years. The purpose of this article is to describe why this opioid has become so important in the treatment of pain in modern clinical practice. The data indicate that fentanyl's popularity has occurred because it has minimal cardiovascular effects, does not result in increases in plasma histamine, is relatively short in onset of action and duration of effect, is easy and inexpensive to synthesize and prepare for the marketplace, and is now familiar to clinicians working in pain and perioperative medicine throughout the world.

***Perspective:** Fentanyl has become one of the most important opioids in the management of pain because it is available for administration intravenously, transdermally, and transmucosally. Its flexibility, potency, familiarity, and physical characteristics explain why it has become so valuable to clinicians managing pain throughout the world.*

***Key words:** Fentanyl, rapid-acting opioids, sublingual, patch, nasal, oral transmucosal.*

Fentanyl (Fig 1), a potent synthetic μ receptor–stimulating opioid, was first synthesized by Dr. Paul Janssen and the Janssen Company of Beerse, Belgium, in December 1960.[45,46] The drug was first used as an intravenous analgesic clinically in Europe in 1963 and in the United States (as a component of Innovar) in 1968 and since then has become one of the world's most important and frequently used opioid analgesics. Today, fentanyl is the opioid most often used intravenously for intraoperative analgesia in the United States, the rest of North America, Central and South America, throughout Europe, the Middle East, and most of developed Asia and Africa. In some of the world, the fentanyl patch is often used for the chronic pain of all forms of cancer as well as the persistent, intense pain from many noncancerous maladies.[45,46] In the last 20 years, more than a half dozen rapid-onset transmucosal fentanyl preparations have been developed, approved, launched, and popularized for "breakthrough" pain syndromes.[46] Few physicians practicing anesthesia or managing all sorts of patients with chronic pain with the many fentanyl preparations now available appreciate how and why this compound has become so widely used in anesthesiology and is so valuable in the management of pain throughout much of the world.

The author received no financial support related to the creation and/or production of this manuscript. The author was the inventor and developer of oral transmucosal fentanyl citrate, including Actiq and Oralet, but has no relationship with TEVA or any of the generic companies that currently market these products. The author also has no relationship to any of the companies that are developing or have developed and/or market or sell any of the other rapid-acting fentanyl products or the fentanyl patches currently being sold today except he is a director of the Board of a public company Insys Therapeutics. Insys developed and currently markets and sells Subsys, a rapid-onset sublingual fentanyl spray that is approved for breakthrough cancer pain in opioid-tolerant patients.

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The Pre-Fentanyl Years (1953–1960)

One of the interests of Dr. Paul Janssen, who founded his company Janssen Pharmaceutica in 1953, was creating potent, effective, rapid-acting analgesics to treat the many pain problems of the time.[45] In 1953, both morphine and meperidine were known and available. Dr. Janssen and his colleagues in his company believed that the piperidine ring (Fig 2), present in both morphine and meperidine, was the most important chemical structure that produced analgesia in these molecules. They began working with meperidine, rather than morphine, as the parent molecule in the production

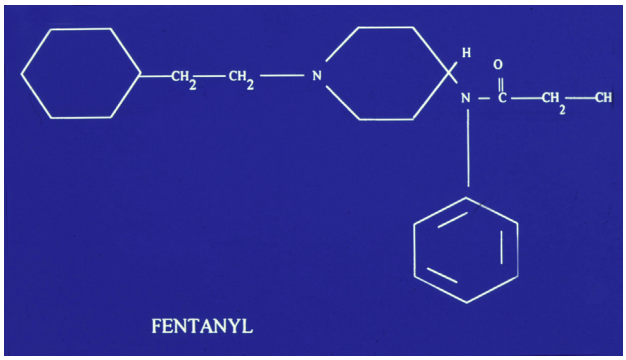

Figure 1. The chemical structure of fentanyl.

of newer and better compounds because it was much less complex a molecule and thus easier to manipulate. Their strategy was to find new molecules that were more powerful and specific analgesics than either morphine or meperidine. They hoped these newer molecules would have fewer unwanted side effects and have higher safety margins (therapeutic indices). The Janssen research team realized that both morphine and meperidine were poor and slow-onset analgesics because they could not easily penetrate into the central nervous system. Therefore, they concluded that they needed to synthesize more fat-soluble derivatives. In order to do this, they began adding to and/or replacing numerous chemical entities (N, benzene rings, methyl or ethyl groups, etc) to the meperidine molecule and thus created many new, more lipid-soluble drugs, most with greater potency and faster onset of analgesic action, presumably because of better penetration through the blood-brain barrier. The chemists knew that more than increased fat solubility was required for greater analgesic potency. The compounds would also have to bind with a receptor (at that time, the μ receptor had not yet been identified, but the concept of a pain receptor was well known). Thus, other chemical entities that they believed would enhance binding of the new compounds with the pain receptor were added, positioned properly, and the new compounds then tested.[45]

Between 1953 and 1957, dozens of new, more potent, lipid-soluble analgesics were created by the Janssen team until in August 1957 phenoperidine was synthesized (Fig 3).[45] Phenoperidine was 25 times more potent than morphine and more than 50 times more potent than meperidine in most animals in which it was tested. It was also, at the time it was first synthesized, the most potent opioid in the world. Phenoperidine was introduced into many European countries, but not the United States (because the Janssen Company did not have a U.S. organization at that time), as a potent, fast onset of action, short-lasting analgesic for anesthetic use. It is still available in many of the countries into which it was introduced.

The Janssen research team continued to create new molecules related to phenoperidine in the late 1950s and first synthesized fentanyl in 1960.[45] Fentanyl was more than 10 times more potent than phenoperidine and 100 to 200 times more potent than morphine in most animal models. It was also the most lipid-soluble (octanol/water partition coefficient = 813) and most potent opioid in the world when it was first created and had the fastest onset of action and highest therapeutic index (277 vs 4.7, 71, and 39.1 for meperidine, morphine, and phenoperidine respectively) ever measured in an opioid. The Janssen team only considered fentanyl useful as an intravenous analgesic when it was first synthesized because approximately 60 to 70% of

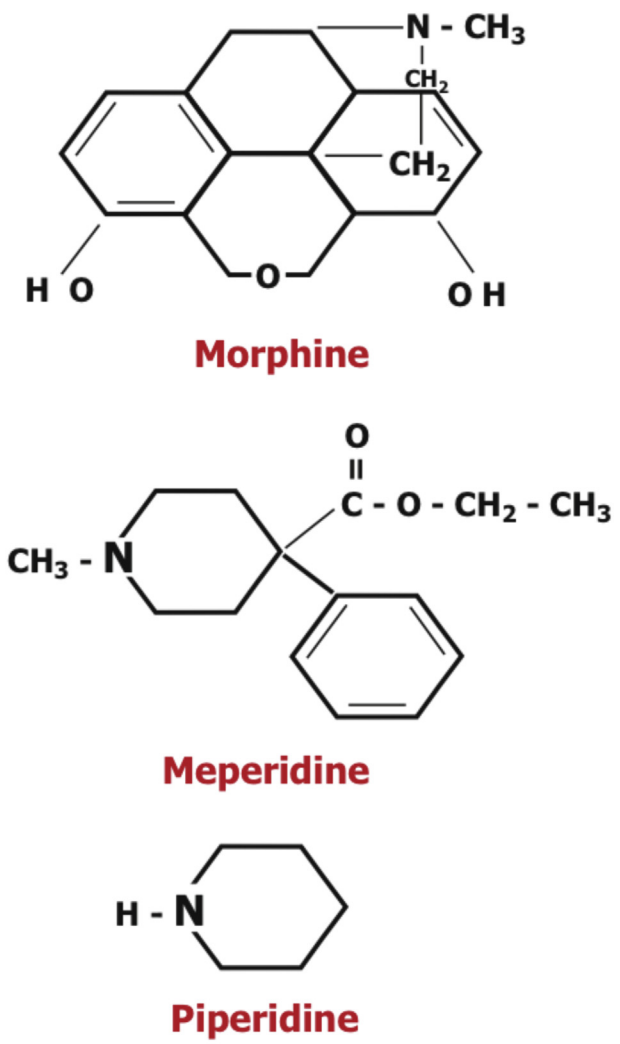

Figure 2. The chemical structures of morphine, meperidine, and piperidine.

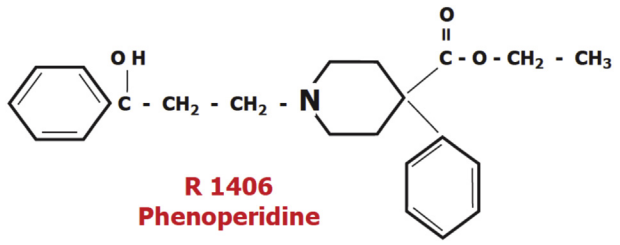

Figure 3. The chemical structure of phenoperidine, a precursor of fentanyl.