Morphine in Cancer Pain

Multiple Uses and Misconceptions about Addiction

by Debra B. Gordon, R.N., M.S.

MORPHINE has long been considered the gold standard for the treatment of moderate to severe cancer pain. Named after Morpheus, the Greek god of dreams, morphine was first isolated in 1806 as a natural product contained in opium.[1] This drug has a wide variety of dosage forms and well-known pharmacokinetics. It is also generally available, and is reasonably priced.[2] Today, morphine is the prototype to which all other natural and synthetic opioids are compared.

The bioavailability of morphine varies widely by its route of administration. The drug can be given orally, parenterally, rectally, sublingually, vaginally, epidurally, intrathecally, intraventricularly, and in a nebulized inhaler. Both immediate-release (IR) and slow-release formulations are available.

Morphine acts by binding to opioid receptors (thought to be located primarily in the central nervous system), which results in a diverse range of pharmacological effects, including:[3]

- Analgesia (absence of pain)
- Sedation
- Mental clouding
- Respiratory depression
- Nausea and vomiting
- Cough suppression
- Constipation
- Physical dependence
- Itching.

More recently, morphine has also been shown to produce local analgesic effects when administered peripherally such as in joints and wounds.[4,5]

Because of its impressive versatility and effectiveness, morphine is one of two opioids included in the model list of essential drugs for the treatment of cancer pain by the World Health Organization (WHO).[6] In fact, the WHO uses morphine consumption as an index of improvement in pain management by individual countries.[7]

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Morphine has no standard dose. As with all opioids, the amount of analgesia and the side effects produced by a particular dose vary by individual. And, as with most opioids, morphine has no analgesic ceiling so there is no maximum dose that can be administered. Dosages must be titrated over time to obtain optimal pain relief.

Morphine has two long-acting, active metabolites—morphine-3-glucuronide [M-3-G] and morphine-6-glucuronide [M-6-G]—that can accumulate and result in dose-limiting side effects, including somnolence (drowsiness), delirium, hyperalgesia (excessive sensitivity to pain), and myoclonus (sudden, involuntary contractions of skeletal muscles).[8,9] Myoclonus can be a particular problem in the elderly and patients with renal insufficiency, who clear metabolites less efficiently than others.

CHALLENGING MORPHINE MYTHS

Unwarranted fear of morphine addiction continues to greatly limit the efficacy and proper use of the drug. This fear is partly due to confusion and misconceptions about physical dependence, tolerance, and addiction.

The development of ***physical dependence*** is a normal physiologic response to chronic dosing of opioids. Abrupt cessation of the agent results in a drug-class-specific withdrawal syndrome.[10] If morphine is abruptly discontinued after several weeks of regular use, patients experience an abstinence syndrome that includes rhinitis (inflammation of nasal passages), myalgia (muscular pain),

abdominal cramping, and occasionally diarrhea. Withdrawal symptoms should not be confused with addiction and should always be avoided by gradually tapering doses when the opioid is no longer required.

Tolerance is a separate and succinct physiologic adaptation to a drug that results in a diminution of one or more of the drug's effects over time.[10] A patient who develops drug tolerance will require increasingly higher doses to achieve the same effect. Tolerance may occur to both opioid side effects (with the exception of constipation) and analgesia.

Tolerance to opioid side effects is both expected and desirable, since tolerance improves a patient's ability to cope with long-term administration of the drug.[11] However, tolerance to opioid side effects is highly variable among individuals and occurs at different rates for different side effects.[11] Most predictably, patients receiving long-term opioid therapy develop a tolerance to respiratory depression.[2]

Tolerance to analgesia appears to be a problem for only a small group of patients and can often be dealt with by simply increasing the dose or switching to another opioid. At times, the need for an increased dosage is erroneously labeled tolerance when the need is, in fact, a result of disease progression, new disease, increased physical activity, lack of compliance, change in medication, addiction, and/or drug interactions (a pseudotolerance).[12]

Opioids play a crucial role in pain management, and their use in the treatment of chronic cancer pain continues to grow.

Addiction is a complex phenomena that involves genetic and biopsychosocial factors. Unfortunately, symptoms of physical dependence and tolerance are often confused with addiction, but neither one constitutes addiction. Although morphine and other opioids are subject to addiction, no evidence exists, in the 200 plus years of its medical use, to suggest that morphine creates an addiction when used to treat pain.

Clinicians, patients, and families need to understand that the proper use of morphine—even at heroic doses and for prolonged periods of time—does not produce changes in the brain that confer vulnerability to subsequent drug abuse (addiction).[13] Health care professionals and patients should know that such fears are scientifically groundless and impede the proper and humane treatment of pain.

Although the incidence of addiction disorders in patients with cancer is unknown, clinicians are much more likely to see situations of pseudoaddiction, a term used to describe patient behavior that looks like addiction but is really the result of undertreatment or anxiety related to undertreatment.[14] Patients with pseudoaddiction exhibit "drug-seeking" behavior, often becoming obsessed with obtaining and taking the opioid.

Opioids play a crucial role in pain management, and their use in the treatment of chronic cancer pain continues to grow.[15] Even with this increase in opioid use, patients with cancer continue to be undertreated for chronic pain. Misunderstandings about morphine phenomena continue to inhibit the optimal use of morphine and other opioid analgesics. For more information about morphine and management of cancer pain, see *http://www.ahrq.gov/clinic/epcsums/canpainsum/htm.*

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