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MORPHIN - A SYSTEMATIC REVIEW

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ABSTRACT

Background: Opioid dependence has emerged as a global public health emergency, with overdose mortality rising significantly over the past decade. Morphine remains the "gold standard" clinical analgesic against which all other pain-relieving medications are measured, yet its use is complicated by significant risks of physical dependence, psychological addiction, and severe adverse effects. **Objective:** This review synthesizes current scientific literature regarding the pharmacological profile, therapeutic applications, and safety considerations of morphine in modern medicine. **Mechanism & Pharmacokinetics:** Morphine exerts its primary analgesic effects by binding to μ opioid receptors within the central and peripheral nervous systems, initiating a GPCR signaling cascade that inhibits nociceptive transmission. Its pharmacokinetics are characterized by significant hepatic first-pass metabolism, low lipophilicity, and the production of active metabolites, notably morphine-6-glucuronide, which can accumulate in patients with renal impairment. **Clinical Applications:** The review examines the efficacy of various administration routes—including oral, intravenous, epidural, and intrathecal—across diverse clinical settings such as. **Acute Care:** Management of burn pain and post-operative recovery (e.g., spinal fusions and caesarean sections). **Chronic & Palliative Care:** Treatment of cancer-related pain and vaso-occlusive crises in sickle cell disease. **Off-Label Use:** Hemodynamic stabilization and pain relief in Acute Coronary Syndrome (ACS). **Safety & Limitations:** Significant attention is given to drug-drug interactions with CNS depressants and MAOIs, as well as the neuroadaptive alterations responsible for withdrawal symptoms. The review highlights the necessity of multimodal analgesia and careful dose titration to balance effective pain relief against the risks of respiratory depression, tolerance, and substance use disorder. **Conclusion:** While morphine remains an indispensable tool for managing severe pain, its administration requires rigorous patient screening, constant monitoring, and an evolving understanding of its molecular mechanisms to mitigate the ongoing opioid crisis.

KEYWORDS: Morphine, μ Opioid Receptor, Pharmacokinetics, Opioid Use Disorder, Neuraxial Analgesia, Pain Management, Respiratory Depression, Drug-Drug Interactions.

INTRODUCTION

The most effective opioid medications for treating post-operative and cancer pain are morphine, codeine, fentanyl, and buprenorphine. A high rate of abuse potential is linked to their long-term administration.[1] In addition to heroin, other opioids are also used recreationally and can lead to opioid dependence. A chronic recurrent disease of the central nervous system (CNS), substance use disorder causes personality issues, co-morbidities, and early mortality.[2] Long-term use of substances that have the potential to be abused can lead to substance use disorders, which include psychological addiction and/or physical dependence. Physical dependency is categorized as a chronic recurrent disease of the central nervous system (CNS) that causes personality disorders, co-morbidities, and early death. It is linked to the development of neuroadaptive alterations in the CNS at the molecular and cellular level.[3] The emergence of typical withdrawal symptoms upon drug cessation is caused by these alterations. Numerous factors, including the type of drug abused, dosages, duration of use, patient age, age of first drug use, and genetic predispositions, influence the type and intensity of withdrawal symptoms.[4,5] Compulsive drug usage to

enhance one's sense of wellbeing is known as psychological dependence Increased drug-seeking behavior, weakened willpower, compulsive drug use despite knowledge of the negative effects, and recurring and ongoing preoccupation, even after years of abstinence, are all common symptoms of psychological addiction in humans.[6]

According to scientific studies, the number of people with opioid use disorders is continuously rising globally, even in spite of multiple social, psychological, and medical initiatives aimed at curbing the phenomena of substance misuse. Opioid dependence is now seen as a worldwide public health emergency. The World Health Organization reports that the number of deaths from opioid overdoses rose from 69,000 in 2014[7] to 118,000 in 2015.[8] Over the past ten years, there have also been notable increases in maternal opioid usage and newborn abstinence syndrome. Therefore, in order to address the opioid problem, government and scientific initiatives should prioritize a number of goals, such as enhancing pain care using non-dependent medications, raising awareness of the risks associated with opioids, or supporting innovative pain and addiction research. Presenting the most recent research on the mechanisms underlying morphine activity that arise following acute or long-term administration is the goal of this review. Further research on the opioidergic system's action requires an understanding of morphine processes.

Mechanism of Action

Other medicines are compared to morphine, which is regarded as the traditional opioid analgesic. Morphine binds to mu (μ), kappa (κ), and delta (δ)-opioid receptors, just like other drugs in this class.[9] This medication binds to the μ-opioid receptor in the peripheral and central nervous systems (PNS and CNS) to cause the majority of its analgesic effects.[10] Morphine reduces nociceptive transmission overall by inhibiting the nociceptive afferent neurons of the PNS and activating the descending inhibitory pathways of the central nervous system. In the central nervous system (CNS), opioid receptors play a crucial role in pain regulation, controlling processes including pleasure and pain alleviation. Opioids, such as heroin and morphine, are powerful analgesics, but they also have the potential to cause dependence, tolerance, and addiction. Through the Gi and G0 proteins, their activation starts the G-protein-coupled receptor (GPCR) signaling cascade. Alpha (α), beta (β), and gamma (γ) are the three subunits that make up the intracellular complex. Depending on the receptor subtype, these receptors mostly activate the G-protein and β-arrestin signaling pathways, albeit their preferences vary. Internalization and desensitization of receptors are mediated by the β-arrestin pathway.[11]

Pharmacokinetics

Absorption: The gastrointestinal tract absorbs morphine, and the analgesic effects peak approximately 60 minutes after the drug is administered. However, because of the liver's substantial first-pass metabolism, its oral bioavailability is less than 40%. In contrast, intrathecal morphine avoids first-pass metabolism and enters the cerebrospinal fluid directly. It then slowly absorbs from the spinal cord and enters the systemic circulation, providing analgesia for a longer period of time.

Distribution: The liver, kidneys, intestines, lungs, and skeletal muscles are among the tissues that systemic morphine is extensively dispersed to. Morphine's low lipophilicity allows it to pass the blood-brain barrier, but only in small quantities. Additionally, morphine is secreted in breast milk and passes through the placental barrier.[12] 20% to 35% of the volume of distribution is reversibly bound to plasma proteins, and the range is 1 to 6 L/kg. By efficiently binding to spinal receptors, intrathecal morphine minimizes systemic redistribution and concentrates analgesic effects in the spinal cord. Respiratory depression and other delayed systemic effects, which usually appear 6 to 12 hours after treatment, are guaranteed by the intrathecal route, which also guarantees prolonged activity within the spinal cord.[13]

Metabolism: Morphine is mostly metabolized orally by conjugating with D-glucuronic acid to produce morphine-3-glucuronide and morphine-6-glucuronide. It also undergoes substantial hepatic metabolism. While morphine-3-glucuronide has no discernible analgesic effect, its metabolite, morphine-6-glucuronide, has analgesic efficacy but low blood-brain barrier penetration. Demethylation occurs in a tiny percentage.

Elimination: About 10% of morphine is eliminated unaltered in urine as glucuronide metabolites. Bile is where some metabolites are eliminated, and here is where some enterohepatic recycling takes place. Morphine has a plasma clearance of 20–30 mL/min/kg. Its terminal half-life after intravenous injection is usually two hours. Extended-release formulations, such as extended-release epidural morphine, use liposomal encapsulation to delay peak concentration in the cerebrospinal fluid (CSF), providing up to 48 hours of analgesia with a single dose.[14]

Administration

Available Dosage Forms- The most common ways to provide morphine are orally (PO), intravenously (IV), epidurally, and intrathecally. Both immediate-release and extended-release oral formulations are available to treat both acute and chronic pain. IV, epidural, and intrathecal formulations may be used in single or continuous doses to treat more severe and poorly managed pain. Patients' infusion dosages might differ greatly from one another and are mostly determined by their level of opiate naivete or tolerance. Intramuscular (IM) administration of IV morphine formulation is also frequently used. Another kind of morphine is a suppository.[15] A lot of people use and abuse morphine. People have therefore devised methods for insufflating (snorting) the drug.[16]

Additionally, morphine can be given sublingually and as an oral solution. A common medication in palliative care is sublingual morphine.

Available Strengths- Different concentrations and formulations of morphine are available for a range of medicinal applications. These consist of 15 mg and 30 mg immediate-release pills and 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg doses of extended-release tablets. Additionally, there are several strengths of extended-release capsules, such as 10 mg, 20 mg, 30 mg, 45 mg, 50 mg, 60 mg, 75 mg, 80 mg, 90 mg, 100 mg, 120 mg, and maximum dosages of 200 mg. Furthermore, morphine sulfate injectable solutions are available in strengths of 0.5, 1, 2, 4, 5, 8, 10, 15, 25, and 50 mg/mL each. There are also injectable formulations with higher potencies that come in quantities like 10 mg/mL and 25 mg/mL. Additionally, morphine sulfate comes in oral solution concentrations of 10 mg/5 mL, 20 mg/5 mL, and 20 mg/mL, as well as suppositories in dosages of 5 mg, 10 mg, 20 mg, and 30 mg.

Adult Dosage

The initial intravenous morphine dosage for adults should be between 2 and 10 mg per 70 kg of body weight, with the lowest effective dose being utilized to provide sufficient pain relief, per product labeling. The patient's reaction to the first dose of preservative-free morphine sulfate injection should be used to determine the dosage. An initial 5 mg dose in the lumbar area may effectively relieve pain for up to 24 hours when given epidurally. In order to evaluate efficacy, incremental dosages of 1 to 2 mg may be administered at intervals if sufficient relief is not seen within an hour. But in a 24-hour period, the total shouldn't be more than 10 mg.

A single dose of 0.2 to 1 mg provides relief for up to 24 hours when administered intrathecally, and the usual dosage is around one-tenth of the epidural dose. The recommended starting oral morphine dosage for individuals who are new to opioids is 15–30 mg every 4 hours, as needed, and modified to provide sufficient pain relief. Start with 15 mg every 4 hours for pediatric patients weighing at least 50 kg, up to a maximum initial dose of 30 mg. Three to six milligrams of oral morphine are equal to one milligram of parenteral morphine when converted from the latter. Because of its slower release, extended-release morphine can cause respiratory depression and greater drowsiness, therefore conversion should be done carefully. Start morphine sustained-release at 15 mg taken orally every 8 or 12 hours for patients who are not familiar with opioids. Start with 15 mg taken orally every 12 hours for people who are not tolerant to opioids. Give half of the patient's 24-hour dose as morphine sulfate controlled-release on a 12-hour schedule or one-third on an 8-hour schedule when switching from other oral morphine formulations. Stop using all opioids unless absolutely necessary for breakthrough pain in order to convert from other opioids. Because of its lengthy half-life, which can cause buildup, conversion from methadone necessitates careful monitoring. Every one to two days, dosage changes can be adjusted to balance side effects and pain management.

A study found that 100 µg of intrathecal morphine maximizes pain relief and reduces the risk of postoperative nausea and vomiting, while also providing appropriate analgesia after lower limb arthroplasty. To balance efficacy and safety, multimodal analgesia and careful dose selection are crucial, as evidenced by the elevated side effect profile that includes pruritus and urine retention.[17]

Adults with sickle cell disease should take 15 mg of the immediate release oral formulation every two to four hours as needed; children should take 0.2 to 0.5 mg/kg/dose every two to four hours as needed; the starting maximum dosage is 15 to 20 mg. Adults and children receiving intravenous (IV) morphine should take 0.1–0.2 mg/kg as an intermittent bolus every 2–4 hours as needed, up to a maximum dose of 10 mg. For patients under 50 kg in weight, the starting dose for basal infusion is 0.01 mg/kg/hr, with a dosage range of 0.01 to 0.04 mg/kg/hr. Patients weighing 50 kg or more should take 1 to 2 mg/hr.[18] One to five milligrams of intravenous morphine may be given to patients with acute coronary syndrome who continue to experience symptoms after antianginal therapy. IV.[19]

Drug-Drug Interactions[21,22]

CNS depressants: These drugs, which include alcohol, tranquilizers, sedative/hypnotics, and general anesthetics, raise the risk of respiratory depression, hypotension, deep drowsiness, and coma. When administering morphine to patients on these medications, caution should be used, and dosage should be modified appropriately.

Skeletal muscle relaxants: Morphine may intensify the neuromuscular blocking effects of these drugs, thereby increasing the severity of respiratory depression.

Mixed agonist/antagonist opioids: Patients on morphine therapy should not take mixed agonist/antagonist analgesics, such as pentazocine, nalbuphine, or butorphanol. These substances may lessen morphine's analgesic effects or hasten the onset of withdrawal symptoms.

Cimetidine: It has been noted that using morphine and cimetidine together can result in apnea, disorientation, and twitching of the muscles. When morphine and cimetidine are given together, patients should be cautiously watched for increased respiratory and central nervous system depression.

Monoamine oxidase inhibitors: The effects of morphine are greatly amplified by monoamine oxidase inhibitors (MAOIs). There have been reports of serotonin

syndrome. After stopping MAO, at least 14 days should pass.is prior to starting morphine medication.

Anticholinergics: Using morphine with anticholinergics or other drugs that have anticholinergic effects at the same time may increase the risk of severe constipation and urine retention, which can lead to paralytic ileus.

P-glycoprotein inhibitors: Quinidine is one example of a P-glycoprotein inhibitor that may increase exposure to morphine. Consequently, using morphine in combination with these inhibitors should be done with caution.

Morphine In Pain Management

Effectively managing extreme pain is essential, especially in medical settings during cancer treatment, post-operative recovery, and palliative care. The use of morphine, a potent opioid analgesic, is one of the most important components in accomplishing this objective. It has long been known that morphine effectively reduces moderate to severe pain. Because of its capacity to change how pain is perceived and offer substantial respite to individuals who are in severe or persistent agony, morphine stands out as a crucial tool. It has the potential to cause respiratory depression and addiction liability. Therefore, the current study aims to provide insights into morphine's pharmacological characteristics, structural characterisation, and extraction.[23,24]

Opium originated in Asia Minor, as evidenced by the Sumerians' use of the narcotic as early as 5000 B.C. When opium was initially produced from poppies, they were referred to as "the plant of happiness." Children were soothed and worm-induced intestinal pain was alleviated with opium. Ancient Egyptian papyrus, particularly the papyrus of Eber from 1550 B.C., mentions the use of opium. Additionally, it mentions the use of mandrake, a drug related to scopolamine and opium. A significant advance in the use of opium for medicinal purposes was made in 1,805 when Friedrich Serturner discovered morphine.[24]

This event was significant because it altered the way that opium was viewed and applied in medicine.1 Papaver somniferum, the scientific name for poppies, is the source of opium, the main ingredient in this pharmacological category. The single leaves and capsulated fruits of this plant, which is a member of the Papaveraceae family, set it apart. Papaver setegirum, a plant that flourished close to the Mediterranean, or a wild Asian species are most likely the sources of Papaver somniferum. Of all the known poppy species, only two—Papaver somniferum and Papaver bracteatum—produce significant amounts of opium.[24]

Opium poppy and morphine (Fig. 1, Fig. 2) are the gold standard for treating moderate to severe pain, and they are also the drug used to evaluate all other drugs. Morphine is also used before surgery to reduce anxiety, make people sleepy, and reduce the amount of anesthesia that is administered. Its bradycardic and vasodilatory effects make it a useful drug for the treatment of myocardial infarction. It is also used to treat pulmonary edema. Morphine produces respiratory depression and gastrointestinal side effects when administered therapeutically. Moreover, tolerance develops and physical dependence occurs with frequent use of this medication. Because of this, this medication is subject to abuse and is regulated by both national and international authorities.[25]

FIG-1 Opium poppy.

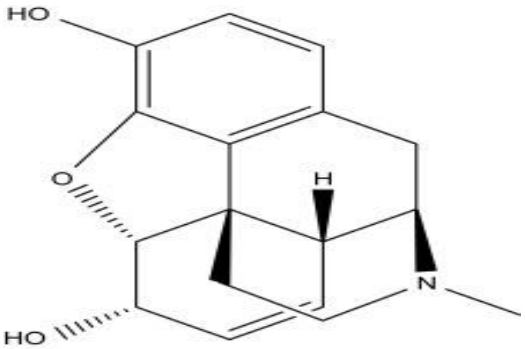

FIG-2 Chemical Structure of Morphine Molecule.

Morphine As an Analgesic[26]

There are 2 primary ways this system reduces pain sensations.

a) Hyperpolarization of interneurons: This process makes it harder for neurons to transmit pain signals.

b) Depressing neurotransmitter release: The system also reduces the release of chemicals that carry pain signals.

Function of neurotransmitters: To initiate the analgesic mechanisms, some neurotransmitters, such as enkephalin, serotonin, and norepinephrine, interact with receptors on pain-transmitting neurons. Both painful and non-painful bodily sensations as well as brain signals can initiate these processes.

The action of morphine: Medications such as morphine can strengthen the body's natural pain management systems when they malfunction. By hyperpolarizing interneurons and decreasing neurotransmitter release, morphine functions similarly to enkephalin. It can also

provide pain alleviation by activating the opioid receptors in the brain.

It is well known that morphine is a potent opioid analgesic that is necessary for efficient pain management. Nonetheless, it has intricate and varied effects on the central nervous system (CNS), which can have both beneficial and detrimental effects.

Positive and negative effects: Morphine interacts with the central nervous system. Morphine has a number of negative effects, including addiction, tolerance, and neurological abnormalities, even if it can give analgesia, or pain relief. Long-term morphine usage can cause neurotoxicity and cognitive impairments by interfering with cellular and molecular processes.

Morphine in burn pain management[27]

Both nociceptive (related to tissue damage) and neuropathic (related to nerve damage) factors contribute to the complex nature of burn pain. Effective pain management in acute conditions is difficult because of its complexity. Reducing pain is the major goal in the emergency department (ED) in order to assist patients, stay functional and avoid developing chronic pain. The first-line treatment for burn pain is emphasized to be opioids, particularly intravenous (IV) morphine. Patients receiving ED treatment for second- and third-degree burns participated in a study design. At the time of admission and one hour into therapy, the researchers used the Burn Specific Pain Anxiety Scale (BSPAS) to measure anxiety levels and the Numerical Rating Scale (NRS) to measure pain levels. The study involved thirty patients in total. More than 90% of patients complained of excruciating pain when they arrived at the emergency department, and 95.8% of them were given intravenous morphine to relieve their discomfort. Significant pain alleviation was indicated by the fact that over 65% of the patients had an NRS score of less than 3 after one hour. In the first hour, an average of 18.12±4.26 mg of IV morphine was given. There were no documented negative effects of using morphine. Furthermore, following one hour of treatment, anxiety levels as determined by the BSPAS dropped dramatically from an average of 34.8±5.6 (showing severe anxiety) at admission to 12.8±4.8 (indicating mild anxiety). According to the results, patients' anxiety levels are down and their pain is better when IV morphine is used to treat burn pain in an emergency situation.

Morphine In Chronic Pain[28]

Patients' quality of life is greatly impacted by chronic pain, which can result in problems like emotional disengagement, social despair, and organ failure. Therefore, enhancing patients' general well-being requires efficient pain treatment. When other treatments are unsuccessful, opioid medicines may be helpful for patients with chronic non-cancer pain. Most patients with cancer-related pain require strong opioid medication, and those with non-cancer-related pain may benefit as well. Opioid therapy may be quite safe and have a low incidence of side effects if the proper medications are chosen and administered. The "golden standard" for treating chronic pain is currently oral medication that releases sustained-release morphine over a predetermined amount of time. More thorough investigation is needed, although transdermal fentanyl may be an alternative.

Long-term use of opioids for chronic non-cancer pain[29]

Concern over the long-term use of opioids for chronic non-cancer pain (CNCP) is growing. Although opioids are frequently given to treat pain, growing rates of opioid dependence and abuse raise questions about their long-term safety and efficacy. For patients with chronic pain, opioids can offer substantial short-term relief; however, with time, their efficacy may wane. The main cause of this is tolerance, which causes patients to need larger dosages to get the same amount of pain relief. Numerous negative outcomes are linked to long-term opioid medication. These can include psychological effects like addiction and dependence as well as physical side effects like respiratory depression, sleepiness, and constipation.

Low-dose intravenous morphine in post-operative pain[30]

It can be difficult to manage postoperative pain following spine procedures, especially in the absence of patient-controlled analgesia (PCA) and proper monitoring.

According to the research, low-dose morphine provides comparable safety and superior analgesic efficacy, making it a better choice for postoperative pain management in patients having spinal fusion procedures. Future research could look into how low-dose intravenous morphine affects patients' pain management and recuperation after spine surgeries over the long run.

Injected morphine as an analgesic for managing post-operative pain[31]

As the quintessential analgesic, morphine serves as the benchmark by which all other painkillers are evaluated. It comes from opium and can be given intramuscularly, subcutaneously, or intravenously. Morphine at a dose of 10 mg intramuscularly is a useful analgesic for postoperative pain management. With a number required to treat (NNT) of 2.9 (range from 2.6 to 3.6) in comparison to a placebo, it offers patients with moderate to severe pain at least 50% pain reduction over the course of 4–6 hours. Although morphine is helpful, the 10 mg intramuscular dose has a far higher incidence of mild side effects than a placebo. This implies that even while morphine helps with pain management, patients should be closely watched for any negative consequences. Although morphine is a popular and efficient analgesic for postoperative pain, more thorough research is necessary to completely comprehend its

effects and guarantee its safe and efficient application in clinical settings.

Intravenous Morphine for Cancer Pain Management[32]

Because of its unique advantages in certain therapeutic settings, intravenous morphine is a crucial aspect of cancer patients' pain treatment plans. For people who are in excruciating pain or need instant relief, its quick onset and predictable effects are especially helpful. An intravenous injection of morphine is mostly prescribed for uncontrolled pain, but it can also be helpful in cases of respiratory distress, vomiting, and difficulty swallowing. More aggressive treatment may be needed for those experiencing extreme pain than oral dosage can offer. Rapid titration with IV morphine is a more effective strategy in situations involving acute pain because traditional titration techniques can prolong suffering.

FDA-Approved Indications[33,34,35]

Acute or persistent moderate to severe pain is covered under FDA-approved morphine use. Morphine, the drug most frequently used in pain management, offers people suffering from pain substantial relief. The treatment of palliative/end-of-life care, active cancer treatment, and vaso-occlusive pain during sickle cell crises are clinical scenarios when morphine medication is highly beneficial. When other treatments are not enough, the FDA has approved morphine for the treatment of both acute and chronic pain. When alternative treatment options are insufficient and severe pain necessitates opioid analgesia, injectable morphine is recommended. Although it is not recommended for use in continuous microinfusion systems, this formulation is also authorized for intrathecal or epidural administration.

Patients who need an opioid and have not responded to less intrusive pain management techniques can now manage intractable chronic pain with several morphine formulations that are specifically licensed for continuous microinfusion in intrathecal or epidural settings. When alternative therapies fail to manage severe and persistent pain that requires daily opioid medication over a lengthy period of time, extended-release oral formulations are recommended. When opioid analgesia is necessary and alternative treatments have not worked, immediate-release oral formulations, such as tablets and solutions, are used to treat both chronic pain in adults and acute pain in pediatric patients two years of age and older. Rectal morphine formulations are also authorized for the treatment of acute and chronic pain under comparable circumstances, providing an additional administration route when required.

The Centers for Disease Control and Prevention (CDC) advise against treating acute pain with extended-release/long-acting (ER/LA) opioids, such as morphine, or starting opioid treatment for chronic or subacute pain. Because ER/LA opioids have a longer half-life and longer duration of effects (including respiratory depression), they should only be used for chronic, severe pain. In order to account for incomplete opioid cross-tolerance, doctors should lower the total daily dosage when switching to an ER/LA opioid.

In order to meet the pain management requirements of cancer patients, healthcare facilities should have availability to immediate-release (IR) oral and injectable morphine, per the American Society of Clinical Oncology's (ASCO) guidelines. Healthcare professionals with the necessary training should prescribe and administer these drugs. Furthermore, access to injectable morphine as well as immediate-release and sustained-release morphine should be guaranteed in environments with low resources. For the treatment of cancer pain, this suggestion ensures that these three morphine formulations are available at both the basic and limited-resource levels.

Off-Label Uses

Off-label, morphine is frequently used to treat nearly any ailment that results in excruciating pain. When patients don't react to first- and second-line medications, morphine is administered in the emergency room for musculoskeletal, gastrointestinal, chest, and even headache pain.[36] Seldom is morphine utilized for procedure sedation. However, doctors occasionally mix a small amount of morphine with a small amount of lorazepam, a benzodiazepine, for minor procedures. Before visiting the cath lab, patients who are experiencing acute coronary syndrome are frequently given morphine in the emergency room. Since the turn of the century, morphine has been used to treat pain during myocardial infarctions (MIs). Although a 2005 observational study brought up certain issues, there aren't many practical substitutes. Morphine is a powerful opioid that reduces pain, which in turn reduces autonomic nervous system activation. When a patient is experiencing a MI, these outcomes are ideal. Furthermore, during a MI, morphine's hemodynamic side effects may be helpful.[37] Blood pressure, venous return, and heart rate can all be decreased by morphine. Additionally, local histamine-mediated activities can be stimulated by morphine.[38] Theoretically, combining these can lower the oxygen demand on the heart.

The American Heart Association's (AHA) and the American College of Cardiology's (ACC) STEMI recommendations prescribe morphine sulfate for pain management in patients with STEMI, especially those who have comorbidities including acute pulmonary edema. This drug enhances ventricular loading and lessens anxiety and respiratory problems. Because they increase the risk of death, reinfarction, hypertension, renal insufficiency, and cardiac failure, non-steroidal anti-inflammatory medicines (NSAIDs), with the exception of aspirin, are contraindicated in STEMI.[39] According to the American Society of Hematology guideline panel, unless the pain does not improve after a

number of alternative treatment options, adults and children with sickle cell disease who have newly formed or emerging chronic pain should not begin chronic opioid medication.[40]

Specific Patient Populations

Hepatic impairment: The American Association for the Study of Liver Diseases states that individuals with severe cirrhosis should take hydromorphone or oxycodone instead of opioids like morphine.[41] The oral bioavailability of morphine is 35% (range: 15% to 64%), and in patients with severe hepatic impairment, such as cirrhosis, it rises to over 100%. These patients have a longer plasma half-life, necessitating dose modifications and less frequent administration of immediate-release formulations. Morphine is also contraindicated in biliary colic because it can cause spasms of the sphincter of Oddi and bile duct.

Renal impairment: Because morphine-6-glucuronide buildup increases the risk of toxicity in cases of severe renal impairment, morphine should generally be avoided in people with hepatorenal syndrome.[42] The buildup of the medication and its metabolites, especially those eliminated by the kidneys, can be extremely dangerous for people with chronic kidney disease (CKD). Even though the kidneys are not very involved in the excretion of morphine, renal failure can cause the accumulation of morphine's active metabolites, such as morphine-6-glucuronide, which can have long-lasting effects and even be lethal. The decreased renal function in CKD patients raises the risk of overdose or severe effects, even though morphine is primarily eliminated through the liver.[43]

Pregnancy considerations: Neuraxial morphine, the most efficient type of postoperative analgesia for cesarean delivery, is administered to the majority of women in the US. For healthy obstetric patients receiving a single dosage of neuraxial morphine, current guidelines from the American Society of Anesthesiologists (ASA) and the American Society of Regional Anesthesia and Pain Medicine (ASRA) suggest respiratory monitoring requirements that might be excessively stringent. There is little data on the best way, frequency, and length of respiratory monitoring for this population. According to this Society for Obstetric Anesthesia and Perinatology (SOAP) consensus statement, multimodal analgesia and low-dose neuraxial morphine are recommended, and patient risk classification is encouraged in order to modify monitoring procedures. The focus is on reducing needless monitoring in healthy patients and focusing on heightened awareness in patients who are more susceptible to respiratory depression.[44]

Breastfeeding considerations: Low levels of morphine in breast milk are caused by the use of epidural morphine for postoperative pain after cesarean sections. On the other hand, increased levels of morphine in breast milk are linked to intravenous or oral morphine. Breastfeeding does not have to stop when a mother uses morphine. After lactation has been established, it is best to switch to non-narcotic pain relievers and limit morphine use to two to three days while keeping a close eye on the baby. A neonatologist must be consulted right away if the baby displays symptoms like excessive sleepiness, difficulties nursing, respiratory discomfort, or limpness. Furthermore, compared to patient-controlled intravenous morphine, the use of ketorolac, ibuprofen, and acetaminophen in a multimodal strategy to post-cesarean analgesia may lessen the chance that moms won't be able to nurse exclusively.[45]

Pediatric patients: In order to minimize total medication use, the American Academy of Pediatrics recommends that clinicians avoid outpatient taper use wherever possible and, if they must, establish a planned weaning plan with thorough follow-up. Infants exposed to opioids should follow both pharmacologic and non-pharmacologic treatment regimens, with non-pharmacologic therapies serving as the cornerstone of care. When non-pharmacologic treatments are not enough to treat severe opioid withdrawal syndrome (NOWS), pharmacologic therapy should be saved for such situation. The primary line of treatment for severe NOWS is opioids. Pulse oximetry should be used to closely monitor infants who need pharmacologic therapy. Because naloxone can cause fast withdrawal and possibly seizures, it should not be used to treat newborns who have been exposed to opioids for an extended period of time.[46] Infants with neonatal opioid withdrawal syndrome received less pharmacologic treatments and were admitted to neonatal critical care units as a result of the American Academy of Pediatrics' guidelines for managing the condition. These modifications demonstrate how well nonpharmacologic methods work to treat infant opioid withdrawal syndrome and could guide clinical procedures for better patient outcomes.[47]

Elderly patients: usage validated pain assessment instruments and multimodal approaches; the 2023 American Geriatrics Society Beers Criteria emphasizes clinical evidence linking opioid usage to an increased risk of delirium in older persons.[48] Because of the potential side effects and age-related loss in hepatic or renal function, morphine should be taken at the lowest dose when used in palliative care for elderly patients.[49]

Enhancing Healthcare

An interdisciplinary team of medical professionals, including doctors, advanced practice providers, nurses, and pharmacists, is needed to order and administer morphine.[50] On the other hand, while taking these drugs, patients might be moved around the hospital. Many resources, including as laboratory technologists, pharmacists, and nurses/nursing assistants, can be used in the use, monitoring, and delivery of morphine. Patients may experience severe side effects and adverse morphine reactions if they are not properly trained and closely

monitored, frequently beginning in the emergency room. Healthcare providers should look for concurrent controlled drugs in prescription drug monitoring systems.[51]

A study evaluated the morphine-sparing effects of non-opioid analgesic treatments following hip or knee replacement surgery. According to the data, a clinically significant threshold for lowering opioid use is a 5-mg decrease in 24-hour IV morphine use. This discovery aids in directing pain management choices, particularly for elderly patients having orthopaedic surgery.[52] The following are all part of the care coordination that the clinician is in charge of.

Placing the medication order[53]

keeping an eye out for respiratory depression symptoms in the patient Giving the medication.

Speaking with a pharmacist regarding the combination of morphine and other drugs that may induce respiratory depression.

contacting an expert in the event of an allergic reaction or overdose.

Prescription drug monitoring programs should be checked by doctors and pharmacists for concurrent banned substances.

Consulting with the cardiologist if using morphine in a STEMI.

In the event of an overdose, the emergency medical team should provide immediate care and consult a toxicologist and critical care physician.

Warnings and Precautions[54,55,56]

Medication mistakes (oral solution): There are many amounts of morphine available in oral solution. To prevent overdosing, care must be made to distinguish between milliliters and milligrams. To guarantee precise dosing, especially with the high-concentration formulation, always use the included calibrated oral syringe.

Respiratory depression: Especially in elderly, disabled, or pre-existing respiratory patients, morphine can result in severe respiratory depression. Non-opioid analgesics should be taken into consideration when necessary, and monitoring is crucial.

Abuse, diversion, and misuse: Morphine is a Schedule II controlled substance, which means that it is very susceptible to abuse and diversion. To reduce abuse, doctors should check for risk factors and inform patients about the significance of taking medications as directed. Long-term opioid prescriptions (more than 90 days) greatly raise the chance of developing a new opioid use disorder, according to the CDC. When compared to no opioid prescription, the adjusted odds ratios for the risk were 15 for low doses (1 to 36 MME daily), 29 for medium doses (36 to 120 MME daily), and 122 for high doses (≥120 MME daily).

Head injury and elevated intracranial pressure: In patients with head injuries, morphine may exacerbate respiratory depression and raise intracranial pressure. These side effects should be avoided in situations where they could obscure important neurological symptoms.

Hypotension: Patients who are already hemodynamically compromised may have hypotension as a result of morphine. People experiencing circulatory shock or low blood pressure should be treated with caution.

Effects on the gastrointestinal tract: Because morphine decreases gastrointestinal motility, it should not be administered to patients who have ileus or gastrointestinal blockage as this could exacerbate their condition and make it more difficult to diagnose acute abdominal problems.

Use in pancreatic/biliary tract disease: Morphine can exacerbate pancreatitis and biliary tract disease by causing sphincter of Oddi spasms in individuals. Opioids were long discouraged as a pancreatic illness treatment because of worries about sphincter of Oddi spasm, but they are now crucial for treating severe pain in acute pancreatitis. Tramadol, oxycodone, and fentanyl are frequently used opioids, but no opioid has been shown to be better than the others. However, new research indicates that buprenorphine is more effective than diclofenac at controlling pain. Use cautious; more research is needed.

Driving and operating machinery: Patients should be advised that morphine, particularly when taken with other CNS depressants, may make it more difficult for them to engage in tasks that call for mental or physical attentiveness, such as operating machinery or driving.

Child safety: It is important to keep morphine out of the hands of young people. If accidental consumption happens, prompt medical assistance is required because it can have potentially fatal implications.

Allodynia/opioid-induced hyperalgesia: Opioid-induced hyperalgesia (OIH) is the condition in which using opioids causes an enhanced sensitivity to pain, which is the reverse of the analgesic effect that is anticipated. The symptoms, which frequently show no signs of opioid withdrawal or disease development, can include increased pain with dose escalation, decreased pain with dose reduction, or pain from non-painful stimuli (allodynia). To address OIH and prevent more problems, opioid rotation or dose reduction should be considered if suspected.

Contraindications[57.58]

When taken carefully, morphine is a very helpful drug. However, this medicine may be strongly contraindicated in specific circumstances. Given that morphine might further reduce respiratory drive, patients with severe

respiratory depression and asthma exacerbation instances require extra caution. Morphine should also be avoided if there have been prior hypersensitivity responses, and it should be stopped right once if there is an active reaction. Additionally, because monoamine oxidase inhibitors (MAOIs) have an additive effect with morphine, caution is required while using these drugs together.

Patients may experience enhanced respiratory depression, serotonin syndrome, or severe hypotension as a result of this combination. Another significant contraindication is GI blockage. Patients having a history of substance abuse, particularly those who have abused opioids in the past, are contraindicated for opioid administration. The majority of clinicians concur that pain management is necessary, despite the fact that this is a very contentious issue. Most will, however, concur and admit that opioid analgesics are not the only option.

Respiratory depression: Acute or chronic respiratory depression lasting up to 24 hours may result with a single dose of neuraxial morphine. Patients receiving preservative-free morphine sulfate injections by intrathecal or epidural routes are required to be closely monitored in a properly equipped institution for a minimum of 24 hours following the initial dosage due to the possibility of severe responses. When preservative-free morphine sulfate injection is used, particularly at the start of treatment or after a dosage increase, severe, perhaps fatal respiratory depression may result. To reduce the risk of respiratory depression, proper dose and titration are essential.

Opioid use disorder: Abuse, abuse, and addiction to morphine are risks that can result in overdose or death. Before writing a prescription, doctors must weigh the risk.

Alcohol and other central nervous system depressants, such as benzodiazepines, can cause severe drowsiness, respiratory depression, coma, and even death when used in combination with opioids. Only in cases where other treatment choices are not adequate should this combination be administered.

Neonatal opioid withdrawal syndrome: Long-term opioid usage during pregnancy raises the risk of this potentially fatal illness if it is not detected and treated right away. This danger should be explained to patients who need long-term opioid therapy while pregnant, and neonatologists should be consulted for care.

Monitoring[59,60]

Both subjective and objective data can be used to evaluate the therapeutic index and effectiveness of morphine. The ultimate objective of morphine use is to control pain, which is typically the first symptom assessed in patients. Blood pressure, respiratory drive, mental state, and misuse/overuse are additional critical characteristics that need to be monitored.[4] It is essential to keep an eye on concurrent drugs. Prescription drugs are on this list, however they are not the only ones. Every morphine user should be aware that avoiding other substances that can cause respiratory depression is essential. These drugs include, but are not restricted to, barbiturates, benzodiazepines, alcohol, and other opioids. When morphine is used with any of these drugs, patients may have apnea at lower dosages.

When it comes to QT interval prolongation, morphine is regarded as minimal risk. However, care must be taken with those who have congenital long QT syndrome or prior cardiac conditions.[61,62] With no influence on postoperative nausea and vomiting or post-mastectomy pain, nociception level monitor (NOL)-oriented monitoring analgesia successfully lowers intraoperative opioid usage. To investigate long-term advantages, particularly with reference to opioid optimization in breast cancer surgery, more extensive randomized controlled trials are required.[63] Prescription drug monitoring programs should be checked for concurrent restricted drugs by doctors and pharmacists.

Toxicity
(Sign And Symptoms)

When used improperly, morphine has the potential to be a deadly drug.[64] Numerous CNS depression symptoms are brought on by this drug. The most dreaded side effect of morphine overdose is severe respiratory depression. Numerous symptoms, including as respiratory depression, skeletal muscle flaccidity, cold and clammy skin, hypoglycemia, bradycardia, hypotension, constricted pupils, pulmonary edema, somnolence that progresses to coma, and partial or whole airway blockage, might be indicative of an acute morphine overdose.

Management of Overdose

Securing the breathing, circulation, and airway is the first line of treatment. In cases of severe overdose, intubation and mechanical ventilation may be necessary. If there is a life-threatening arrhythmia or cardiac arrest, advanced cardiac life support should be administered. To counteract the effects of morphine, naloxone must be injected right away. You can also get intranasal naloxone. In cases of opioid overdose, bystander administration of the naloxone nasal spray offers quick absorption and may be a life-saving measure.[65]

Administering naloxone can cause acute withdrawal symptoms in people who are physically reliant on opioids. Repeated doses of naloxone may be necessary since its duration of action is less than that of intrathecal or epidural morphine. There have been reports of unintentional intrathecal morphine overdoses brought on by mistakes like mishandled syringes or improper vial usage. In addition to CSF drainage, mechanical breathing, and blood pressure control, care entails using naloxone to counteract the effects of opioids.[66]

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