# Current Issues in Sickle Cell Pain and Its Management

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**Pain is the insignia of sickle cell disease and the acute painful crisis is the number-one cause of hospital admissions. Tissue damage due to vaso-occlusion releases numerous inflammatory mediators that initiate the transmission of painful stimuli and the perception of pain. The acute sickle cell painful crisis evolves along four distinct phases coupled with changes in certain markers of the disease. Hospital readmission within 1 week occurs in about 16% of discharged patients. Failure to treat acute pain aggressively may lead to chronic pain syndrome. Management of sickle pain is primarily pharmacologic in nature, and opioids are the analgesics used most often. Cellular and molecular mechanisms of opioids explain individual differences among patients and justify the use of individualized treatment plans.**

## Introduction

Sickle cell disease (SCD) is a quadrumvirate of anemia and its sequelae, pain syndromes, organ damage including infection, and comorbid conditions.[1-6] Pain, however, is the hallmark, the insignia, of the disease, and dominates its clinical picture throughout the life of the patient. The acute painful crisis is the number-one cause of hospital admissions of patients with SCD.[7] Pain may also precipitate or be itself evoked by the other three components of the quadrumvirate. The review will cover the pathogenesis of pain beyond vaso-occlusion, describe the anatomy of the acute painful crisis and its evolution, and discuss the current pharmacologic therapy of sickle cell pain with emphasis on opioids and their complications. This approach may help providers in designing individualized treatment plans for their patients and encourage them to consider conducting certain research projects.

## Pathogenesis of Pain

Sickle cell vaso-occlusion, which may involve both the micro- and macrovasculature, is the most important pathophysiologic event in SCD and explains most of its clinical manifestation.[1,2,8,9] Major factors that contribute to vaso-occlusion are listed in **Table 1** and have been described in numerous reports.[1,9-14] Vaso-occlusion is the *de facto* prerequisite for the development of acute sickle cell pain. Tissue damage due to vaso-occlusion initiates a horde of complex biochemical, neurologic, and electrochemical sequence of events, collectively referred to as nociception, that culminate in the perception of acute pain, which, in turn, may become chronic in nature. Vaso-occlusion is also responsible for creating a state of chronic vascular inflammation that explains many features of SCD.[15,16] Moreover, psychologic, social, cultural, and spiritual factors often unite and conspire with vaso-occlusion to initiate the unique nature of sickle cell pain.

## Nociceptive Pain

Nociception involves four major pathophysiologic processes that explain the pain experience (**Figure 1**; see Color Figures, page 513): transduction, transmission, modulation, and perception.[17-22] Transduction is the process through which noxious inflammatory mediators (collectively referred to as inflammatory soup, including prostaglandins, histamines, bradykinin, $H^+$, $K^+$, cytokines, serotonin, substance P, leukotrienes, and others) are generated by tissue damage. These inflammatory mediators sensitize or activate nociceptors by converting chemical or mechanical energy to an electrochemical impulse in the primary afferent nerve fibers. The relative abundance of these mediators may explain some clinical findings. Interleukin-1 (IL-1) is an endogenous pyrogen and also activates the cyclo-oxygenase gene, which leads to synthesis of prostaglandins $E_2$ and $I_2$. Bradykinin, potassium, hydrogen ions, and serotonin activate nociceptive afferent nerve fibers and evoke a pain response. Prostaglandins, leukotrienes, nerve growth

**Table 1. Factors that culminate in vaso-occlusion in patients with sickle cell disease.**

Factors intrinsic to red blood cells (RBCs)

- Sickle hemoglobin polymerization
- Rheology of sickle RBCs
  - Cellular dehydration
  - RBC deformability and mechanical fragility
  - Dense cells

Factors extrinsic to red blood cells

- Whole blood viscosity
- White blood cell factors
- Endothelial factors
  - Adhesion of sickle RBCs to endothelium
  - Intimal hyperplasia
- Hemostatic factors
- Vascular factors

factor, and bradykinin sensitize peripheral nerve endings and facilitate the transmission of painful stimuli that reach the cerebral cortex via the spinal cord and the thalamus. Moreover, activated nociceptors release stored substance P in peripheral nerves and in the spinal cord, which itself facilitates the transmission of painful stimuli. Bradykinin and substance P also cause vasodilatation with extravasation of fluids that can lead to local swelling and tenderness. Prostaglandins increase the effective renal blood flow and effective renal plasma flow in children and young adults.[2] Prostaglandins $PGE_2$ and $PGI_2$ infused directly into the renal arteries of dogs increase renal blood flow and provoke diuresis, natriuresis, and kaliuresis.[23] The painful stimulus is then transmitted along A-δ and C peripheral nerve fibers to the dorsal horn of the spinal cord, where it may be enhanced or suppressed by several receptors. Most important. Most important among these is the N-methyl-D-aspartate (NMDA) receptor at the dorsal horn that facilitates the transmission of the painful stimulus once activated. From there, the stimulus crosses to the contralateral side and ascends along the spinothalamic tracts to the thalamus, which is a relay station, and interacts with the hypothalamus, reticular formation (associated with awareness and behavior), and the limbic system, including the amygdala, the hippocampus (associated with memory), and nucleus accumbens. The limbic system also contains the brain's reward/pleasure circuit, as will be discussed below. Modulation refers to descending fibers from the midbrain to the dorsal horn that can inhibit the transmission of the painful stimuli via endogenous endorphins, serotonin, and norepinephrine. Taken together, communications and interactions among the thalamus, hypothalamus, the reticular formation, the limbic system, and the descending modulation system enhance or ameliorate the intensity of pain perceived at the level of the cerebral cortex.

### Neuropathic Pain

Although sickle cell pain is primarily a nociceptive type of pain due to tissue damage, it may also have a neuropathic component[24] characterized by sensations of burning, tingling, shooting numbness, and lancinating. These symptoms may occur in the presence or absence of obvious central or peripheral nerve injury. The mechanism of neuropathic pain presumably involves aberrant somatosensory processing in the central or peripheral nervous system. Mental nerve neuropathy, trigeminal neuralgia, acute proximal median mononeuropathy, entrapment neuropathy, and acute demyelinating polyneuropathy have been described in SCD.[3,5] A thorough history and physical examination help determine whether sickle cell pain is associated with a neuropathic component that can be managed using special adjuvants, including anticonvulsants, as mentioned below.

### The Acute Sickle Cell Painful Crisis

Several acute pain syndromes punctuate the clinical course of SCD. These include but are not limited to the acute painful crisis, dactylitis, acute chest syndrome, priapism, avascular necrosis, splenic infarcts, hepatic crisis, and leg ulcers. The acute sickle cell painful crisis, however, is the insignia of SCD and the number-one cause of hospitalization.[7] It is unpredictable in nature and may be precipitated by known or unknown risk factors and triggers.[3] Patients with sickle cell anemia and relatively high hemoglobin (Hb) level, for example, are more likely to experience more frequent painful episodes than those patients with sickle cell anemia and lower Hb level. Stress of any kind, traumatic, physical, psychologic, physiologic, etc., may trigger the onset of a painful episode. Sickle pain may involve any part of the body, and the severity, location, and duration of the pain vary latitudinally among patients and longitudinally in the same patients.

The concept that the painful crisis evolves along phases was first introduced by Ballas and Smith[25] and Akinola et al,[26] who independently and almost simultaneously described the presence of two phases of the uncomplicated painful crisis in prospective longitudinal studies of adults with SCD. Akinola et al[26] studied 20 patients over 16 months, and Ballas and Smith[25] studied 117 painful crises affecting 36 patients with sickle cell anemia over 6 years. Both studies indicated the presence of two phases. The initial phase was associated with increasing pain, decreased RBC deformability, increase in the number of dense cells, red cell distribution width (RDW), hemoglobin distribution width (HDW), reticulocyte count, leukocytosis and decrease in the number of platelets. The second phase was characterized by established pain of maximum severity and gradual reversal of the abnormalities of the first phase. Later, Ballas[27] revised the description of the painful crisis and refined its evolution into four phases by including observation by several other investigators (**Figure 2**). The phases were called prodromal, initial, established, and resolving phases. Beyer et al[28] found that the painful crisis also evolves along phases in children but the phases were broken down into 7 and were labeled differently. Jacob et al[29] studied 40 crises affecting 27 children over 9 months. Their findings supported previous observations related to changes during the evolution of painful episodes that may be occurring in phases. Although the phases were given different names, the concepts were similar.

The evolution of the uncomplicated painful crisis along phases dispels the notion that there are no objective signs of its occurrence. Serial determinations of certain lab parameters compared with steady-state values clearly reveal the presence of objective lab data of the crisis in most patients. Moreover, the presence of phases allows the provider to monitor the progress of the crisis and manage it according to a rational basis, thus avoiding the conflicts that often arise between patients and providers about the authenticity of pain.

The decrease in Hb level with the increase in reticulocyte count seems to be due to hyperhemolysis that occurs in some patients during uncomplicated painful crises.[30] The

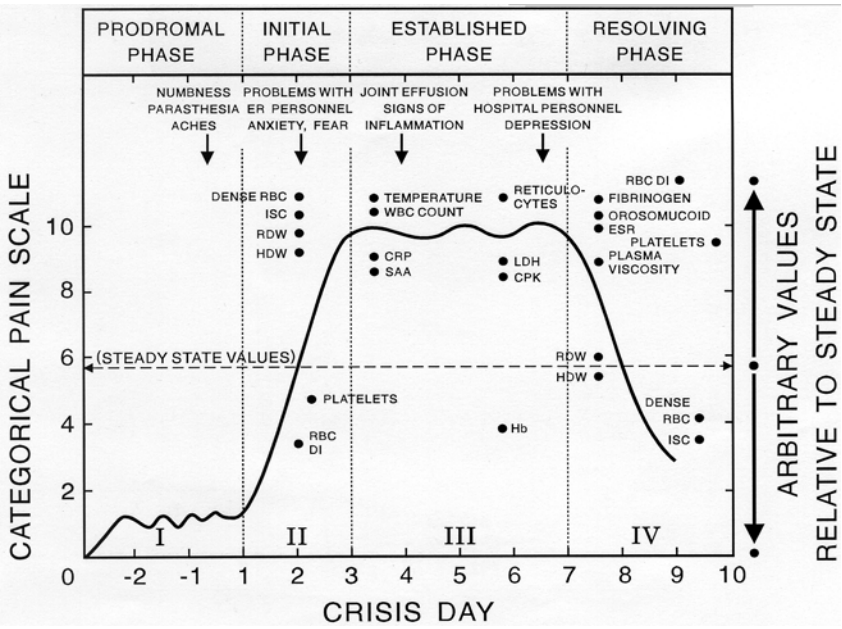


**Figure 2. A typical profile of the events that develop during the evolution of a severe sickle cell painful crisis in an adult in the absence of overt infection or other complications.** Such events are usually treated in the hospital with an average length of hospital stay of 9-11 days in adults. Pain becomes most severe by day 3 of the crisis and starts decreasing by day 6 or 7. The Roman numerals refer to the phase of the crisis: I. Prodromal Phase; II. Initial Phase; III. Established Phase; and IV. Resolving Phase. Changes that may occur during the crisis are indicated by dots: their location on the X-axis indicates the time when they become apparent and their location on the Y-axis indicates their relative value in comparison to that of the steady state indicated by the horizontal dashed line. Arrows indicate the time when certain clinical signs and symptoms may become apparent.
Abbreviations: ISC, irreversibly sickled cells; RDW, red cell distribution width; HDW, Hb distribution width; RBC DI, red cell deformability index; CRP, C-reactive protein; SAA, serum amyloid A; LDH, lactate dehydrogenase; CPK, creatinine phosphokinase; ESR, erythrocyte sedimentation rate.
Reprinted with permission from Ballas SK.[27]

increase in platelet count, fibrinogen and blood viscosity as the crisis resolves indicates the presence of a hypercoagulable state that may cause recurrence of the crisis. This may explain, in part, why about 16% of patients are readmitted to the hospital with a painful crisis within one week after discharge.[7,25] Other possible causes of readmission include premature discharge or the development of withdrawal syndrome after discharge. More recently, Ballas and Lusardi[7] and Jacob et al[30] reported a blunted response to pain relief after the fourth to sixth hospital day in some patients. These patients continue to have a relatively high score of pain severity by the time they are discharged and are most likely to be readmitted within one week after discharge. The reasons for this blunting in pain relief are not known. Possible etiologies include inadequate pain management, increase in the levels of acute phase reactants that bind to opioids and make them unavailable to induce pain relief, the development of tolerance to opioids, hyperalgesia, or changes at the opioid receptor sites. Patients with frequent painful crises that require hospital admission seem to have more morbidity and mortality than otherwise.

The above data suggest that special attention has to be paid at the resolving phase of the painful crisis. Measures should be considered to avoid the possibility of hospital readmission soon after discharge. Providers should consider continuing aggressive pain therapy during hospitalization, if needed, rule out the possibility of tolerance and consider opioid rotation, design discharge instructions that avoid causing withdrawal after discharge, and arrange for follow-up soon after discharge. To that end, the establishment of a post-discharge clinic to evaluate patients within a few days after discharge to ensure compliance with discharge instructions is recommended.

## Transition to Chronic Pain

There are two types of chronic sickle cell pain: chronic pain due to obvious pathophysiology (leg ulcers, avascular necrosis, chronic osteomyelitis) and intractable chronic pain with no obvious sign, where the only complaint is the patient's self-report of pain that does not go away. Failure to treat recurrent severe acute painful crises aggressively can eventually create the intractable chronic pain syndrome. The pathophysiology of this transition is not well known. Possibilities include recruitment and activation of dormant afferent nerve fibers that transmit stimuli and result in "central sensitization" whereby the pain threshold is lowered to a degree that ambient innocuous events cause severe pain —a condition referred to as allodynia.[3,5] Moreover, "central sensitization" changes the way the brain and nervous system respond to pain; new pathways develop that can lead to the sensation of chronic pain.[21,22] This type of pain may have features similar to those of neuropathic pain. Once chronic pain sets in, it usually becomes independent of vaso-occlusion and the percentage of Hb S. Nevertheless, chronic pain syndrome continues to be punctuated with superimposed acute painful crises due to vaso-occlusion.

Management of chronic sickle cell pain should be multidisciplinary. Leg ulcers necessitate the input of wound care centers, whereas avascular necrosis entails the involvement of orthopedics, physical therapy, rehabilitation, and rheumatology. Intractable pain (central sensitization) dic-

tates the use of nonpharmacologic approaches, of adjuvants, and inevitably, in sickle cell chronic pain, of long-acting or extended-release opioids with short-acting opioids for breakthrough pain.

## Pharmacologic Management of Sickle Cell Pain

Rational and effective management of sickle cell pain is a function of thorough assessment and individualization of therapy coupled with the use of nonpharmacologic and pharmacologic approaches to therapy. The former include the use of heat or ice packs, relaxation, distraction, music, massage, vibration, prayer, therapeutic exercises, menthol cream rub, self-hypnosis, acupressure, acupuncture, transcutaneous electrical nerve stimulation (TENS), and biofeedback. There are no controlled clinical trials on the efficacy of any of these modalities in the management of sickle cell pain. Nevertheless, anecdotes from patients and providers attest that these approaches are effective in relieving mild pain and decreasing the amount of opioid consumption if the pain is severe.

Pharmacologic management of sickle cell pain entails the use of three major classes of compounds: non-opioids, opioids, and adjuvants (**Table 2**). In addition, some patients use complementary and alternative supplements on their own based on hearsay, advertisements or the media. Such medications are available over the counter or at health food outlets and include antioxidants, vitamins, herbal products, magnesium, garlic extract, glucosamine, etc. Patients should be advised to use these products only after discussion and approval by their care providers in order to avoid possible deleterious interactions with approved opioids and non-opioids. On a positive note, Niprisan (a phytomedicine), in a phase 2B study including 82 patients with SCD, was effective in reducing episodes of painful crises associated with severe pain over a 6-month period with no serious side effects.[31] Niprisan, however, did not affect the risk of severe complications or the level of anemia. Results of a phase 3 multicenter trial using Naprisan in patients with SCD have not been reported to date. Brousseau et al[32] treated 19 hospitalized children with SCD with intravenous magnesium sulfate and reported significantly shorter length of hospital stay compared with historic controls. The dose of magnesium sulfate in 12 of their patients was 40 mg/kg (maximum 1.5 g) in the emergency department (ED) and 8 and 16 hours later. The remaining 7 patients received magnesium sulfate 40 mg/kg (maximum, 2.5 g) in the ED and every 8 hours for up to 4 inpatient days. Because the results of the two protocols were combined for analysis, it is not clear if the response to magnesium sulfate is dose dependent. Further controlled studies are needed to confirm these promising findings.

A major difference between opioids and nonopioids is that the latter have a ceiling effect, a dose above which there is no additive analgesic effect, and are associated with serious systemic side effects (gastropathy, nephropathy, and hemostatic defects). Opioid analgesics have fewer

**Table 2. Pharmacologic agents commonly used in the management of sickle pain.**

**Non-Opioid Analgesics**

- Acetaminophen (Tylenol)
- Non-selective COX inhibitors
  - o Acetylsalicylic acid (aspirin)
  - o Nonacetylated salicytates
  - o Ibuprofen (Motrin, Advil)
  - o Naproxen (Naprosyn)
  - o Ketorolac (Toradol)
- Selective COX2 inhibitors
  - o Celecoxib (Celebrex)
- Ultram IR, ER (Tramadol)

**Opioid Analgesics**

- Codeine
- Hydrocodone/Acetaminphen (Vicodin)
- Hydrocodone/Ibuprofen (Vicoprofen)
- Oxycodone (IR, ER: Oxycontin)
- Oxycodone with codeine (Percocet, Tylox, Roxicet)
- Morphine (Morphine IR; Morphine ER: MS Contin, Oramorph, Kadian, Avinza)
- Meperidine (Demerol, Pethidine)
- Hydromorphone (Dilaudid)
- Levorphanol (Levo-Dromoran, LA)
- Oxymorphone (IM/SC: Numorphan; PO: Opana IR, ER)
- Methadone (Dolophine, Methadose, LA)
- Fentanyl
  - o Parenteral preparations (Sublimaze)
  - o Transdermal patch (Duragesic)
  - o Transmucosal lozenges (Actiq)
  - o Effervescent buccal tablet (Fentora)

**Partial Agonists**

- Buprenorphine (Buprenex, Subutex)
- Buprenorphine/Naloxone (Suboxone)

**Mixed Agonists-Antagonists**

- Pentazocine (Talwin, Talwin NX)
- Nalbuphine (Nubain)
- Butorphanol (Stadol, Stadol NS)

**Antagonists**

- Naloxone (Narcan)
- Nalmefene (Revex)
- Naltrexone (Revia, Viritrol)

**Adjuvants**

- Antihistamines
- Antidepressants
- Anticonvulsants
- Benzodiazepines
- Phenothiazines
- Antiemetics, laxatives
- $\alpha$2-Adrenergic agonists (Clonidine)
- Other miscellaneous agents

Abbreviations: COX, cyclooxygenase; IR, immediate release; ER, extended release; LA, long-acting; NX, naloxone.

systemic side effects than non-steroidal anti-inflammatory drugs (NSAIDs), but their use in SCD is associated with misconceptions and phobias that will be discussed below. These are most often used in the management of sickle cell pain. Opioid agonists can be given by several routes (orally, subcutaneously, intramuscularly, intravenously, transdermally, transmucosally) and methods of administration (continuous intravenous drip, patient-controlled analgesia [PCA] pump, or intermittent parenteral injections). Other routes of administration such as nebulization, iontophoresis, topical, epidural, or implantable intrathecal drug delivery systems are rarely, if ever, used in SCD. Meperidine, morphine, hydromorphone, and fentanyl are the major opioid analgesics used in the treatment of severe pain in the ED and the hospital. Oxycodone with codeine is most often used to treat painful episodes of mild or moderate severity at home.[33] Opioids such as extended release (ER) oxycodone and ER morphine or long-acting opioids such as methadone and levorphanol are useful in the management of chronic pain at home in combination with short-acting opioids for breakthrough pain.

The coadministration of adjuvants with the primary opioid analgesics can enhance their analgesic potential and obviate or ameliorate opioid side effects. Anticonvulsants can be useful also whenever sickle cell pain has a neuropathic component.

The choice of an opioid, its dose, and route of administration should be individualized based on past history and experience. No one opioid constitutes a panacea for all patients. The general trend today is to avoid the use of meperidine and to administer opioids orally for mild pain and intravenously or subcutaneously for severe pain and avoid the intramuscular route if possible. The use of meperidine continues to be controversial. Meperidine is associated with seizures in 1% to 12% of patients with SCD.[34,35] A recent retrospective study of hospitalized children reported a very low rate of seizures in sickle cell patients receiving meperidine, which was comparable with that observed in patients receiving morphine.[36] There is a subset of adult patients with SCD for whom meperidine is the only opioid that gives them relief without serious side effects. The use of implantable intravenous devices in patients with SCD seems to be associated with a higher rate of infection than in other disease groups.[37] Decisions to switch from one opioid to another (opioid rotation) should follow equianalgesic dosing equivalents, taking into consideration the comparative absorption, availability, and half-life of the opioids in question. Thus, the dose of oral methadone to replace the dose of ER morphine will be one-sixth the dose of morphine, since methadone absorption is twice that of morphine and its half-life is three times longer than that of morphine. Moreover, the dose of methadone will take five half-lives to stabilize orally. If the comparative absorption and half-lives are not known, it is advisable to do gradual conversion from one opioid to another.

In order to manage sickle pain effectively with opioids, it is essential to know their pharmacokinetics and pharmacodynamics, including their side effects and complications. Pharmacokinetics refers to "what the body does to the drug," including absorption, distribution, binding to tissues, metabolism and excretion.[3,21,22,38,39] Pharmacodynamics, on the other hand, refers to "what the drug does to the body" in terms of the mechanism by which the drug produces its effects.[3,21,22,38,39]

An important step in the pharmacokinetics of opioids is their conversion into metabolites that could be active or inactive (**Table 3**).[21,22,38,39] Prodrugs are drugs that are not active by themselves, but their metabolites are. Thus, codeine is a prodrug without an analgesic effect by itself, but its metabolite morphine is the active analgesic. The conversion into an active metabolite depends on the presence of the required enzyme and the polymorphic variants of the enzyme. About 5% to 10% of the population (African American or not) lack the enzyme CYP2D6 and, hence, will not achieve pain relief by using codeine alone. Moreover, the enzyme is polymorphic, and some variants are more efficient in the conversion into active metabolite than others. The same principles apply to the conversion of hydrocodone into hydromorphone and oxycodone into oxymorphone. Morphine is unique in that it is an active drug itself, and its metabolites morphine-6-gluconide (M6G) and morphine-3-glucuronide (M3G) are also active (**Table 3**).

Opioid agonists produce their effect by binding into μ receptors.[21,22,38-43] It is the L-isomers of opioids that exert their analgesic activity. The binding affinity or strength with which a drug binds to its receptors varies considerably among opioids, with fentanyl, for example, having a higher binding affinity than morphine. The binding affinity of opioids seems to correlate well with their analgesic potency. Once bound to receptors, opioids initiate a series of biochemical events, including activation of G-proteins, inhibition of adenylate cyclase activity and extrusion of $K^+$ that results in hyperpolarization of cell membranes, which delays or prevents the transmission of painful stimuli. Moreover, receptors are also polymorphic with many variants, some of which are more efficient in mediating the

**Table 3. Metabolism of opioid agonists.**

| Drug | Active metabolite |
|---|---|
| Codeine | Morphine |
| Hydrocodone | Hydromorphone |
| Meperidine | Normeperidine |
| Oxycodone | Oxymorphone |
| Morphine | M6G and M3G |
| Hydromorphone | None |
| Oxymorphone | None |
| Fentanyl | None |

Abbreviations: M6G, morphine-6-glucoronide; M3G, morphine-3-glucoronide

analgesic effect of opioids than others. Thus, the response to opioids depends not only on the type of opioid used, but also on the number and activity of the opioid receptors that a certain patient has. An opioid that has poor affinity and that binds to one or two receptors, for example, is unlikely to produce effective analgesia in certain patients even if the dose is high. On the other hand, an opioid with moderate or high binding affinity that binds to several efficient receptors would provide effective analgesia even if used in small doses. This state of affairs, albeit not extensively studied in patients with SCD, does offer an explanation for the immense variability among patients in response to opioid analgesics.

## Characteristics of Selected Opioids

### *Morphine*

Morphine is a strong μ-opioid agonist and the gold standard for the treatment of cancer pain.[3,21,22,38,39] It is a naturally occurring alkaloid derived from the opium poppy. It is hydrophilic and thus is rapidly distributed to tissues and organs. It may be administered by any route and is available in both immediate and extended release formulation. Morphine is metabolized into M6G and M3G. The former is four times more potent and has a longer half life than its parent drug—this explains why repeated administration of morphine results in severe sedation in some patients. Both morphine and M6G are associated with toxicity in patients with renal failure. Morphine is highly histaminergic and is often associated with pruritus that may be severe in some cases. Other recently reported side effects of morphine include increased risk of acute chest syndrome in patients with SCD,[44,45] acceleration of renal injury,[46] and retinopathy[47] in transgenic sickle mice. In a retrospective study of hospitalized children with SCD, Buchanan et al reported that patients on morphine were more likely to develop acute chest syndrome and had longer hospital stays than patients receiving Nubain.[45]

**Table 4. Commonly prescribed drugs with potential for QT prolongation.**

- Clarithromycin
- Erythromycin
- Levofloxacin
- Fluoxetine
- Amitriptyline
- Sertraline
- Salmeterol
- Sumatriptan
- Venlafaxine
- Indapamide
- Doxepin
- Tamoxifen
- Imipramine
- Risperidone

### *Methadone*

Methadone is a synthetic potent-opioid agonist.[3,21,22,38] It has a long half-life (at least 36 hours) but short duration of analgesic effect (4 to 6 hours). This discrepancy between long plasma half-life and duration of analgesia may predispose to drug accumulation following the initiation of therapy or dose escalation. Methadone is associated with cardiotoxicity due to prolongation of the QTc interval with arrhythmia that could be fatal. It is associated with mortality more than any other opioid. Other medications such as antibiotics and antidepressants (**Table 4**) contribute to its cardiotoxic effect, and their use with methadone should be avoided or monitored carefully. Nevertheless, methadone is an excellent analgesic that is useful in treating chronic pain provided the prescriber knows its pharmacology and has experience in its use. Careful monitoring of patients coupled with initiation of a low dose followed with gradual stepwise dose escalation or reduction decrease the risk of toxicity from its accumulation. Monitoring should include performing EKGs periodically. Oral and parenteral preparations of methadone are available; subcutaneous injections cause local skin toxicity and are not recommended.

## Opioid Antagonists

Traditionally, the use of opioid antagonists has been primarily limited to counteract the depressive effects of opioid agonists. Recently, however, there have been reports showing that small doses of antagonists in combination with agonists appear to enhance the analgesic effect and prevent or delay tolerance to opioid agonists.[48] Moreover, new formulations in development include the use of naltrexone in combination with oxycodone or morphine in order to deter abuse; this is reminiscent of the use of disulfiram (Antabuse) with alcohol.

## Adverse Effects and Complications of Opioids

Adverse effects of opioid analgesics include pruritus, hives, nausea, vomiting, constipation, and respiratory depression. Seizures may be associated with opioids, especially with the prolonged use of meperidine and the consequent accumulation of its major metabolite, normeperidine, in some patients. The effects of meperidine and normeperidine on seizure induction are more pronounced in the presence of renal failure. Other opioids may also induce seizure, albeit less often than meperidine, if used in high doses over a long period of time. The mechanism of seizure induction by other opioids is different from that by meperidine and seems to be related to the excitatory effects of opioids. The incidence of seizure due to morphine has been reported to be 1.2%.[49] As mentioned above, the metabolites of morphine may accumulate to toxic levels in the presence of renal failure.

The serious complications of opioids that are often misunderstood and confused with each other are collectively referred to as aberrant behavior and include addiction, physical dependence, withdrawal, tolerance, and

pseudoaddiction. Their definitions according to the American Academy of Pain Medicine, American Pain Society, and American Academy of Addiction Medicine consensus document (2001) are as follows:

*Addiction.* A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

*Abberrant drug-taking behaviors less predictive of addiction.* Aggressive demand for more drug, drug hoarding (e.g., obtaining drug from more than one source), unsanctioned dose escalation, unapproved use of drug.

*Abberrant drug-taking behaviors more predictive of addiction.* Selling prescription drugs, forging prescriptions, stealing drugs, frequent prescription "loss," injecting oral/topical formulations, concurrent abuse of illicit drugs.

*Physical dependence.* A state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Signs and symptoms of withdrawal include tremor, shakiness, anxiety, depression, lacrimation, rhinorhea, fatigue, irritability, and diarrhea.

*Tolerance.* A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

*Pseudoaddiction.* The seeking of additional medication, secondary to undertreatment of pain. When the pain is treated properly, all inappropriate behavior ceases.[50]

Complications of opioids are best understood by knowing their mechanisms, which include the following:

1. Histaminergic effect of opioids
2. Excitatory effect of opioids (hyperalgesia)
3. Dopaminergic effect of opioids
4. Proserotonergic effect of opioids

### *Histaminergic effect of opioids*

Histamine is a neurotransmitter in the brain and an autacoid stored in the granules of mast cell and basophiles which accumulate at sites of injury or potential injury. Opioids in general and morphine in particular release both neuronal and non-neuronal histamine. Released histamine causes vasodilatation, bronchoconstriction, smooth muscle activation, pruritus and hives. It is for this reason that antihistamines are usually given as adjuvants to opioids in treating sickle cell pain. The antihistamines most commonly used as adjuvants include hydroxyzine (Vistaril) and diphenhydramine (Benadryl). The former is a piperazine anti-histamine and the latter is an H1 receptor antagonist.

### *Opioid-induced hyperalgesia*

Paradoxically, the chronic administration of opioid analgesics to treat pain may contribute to or cause pain, a condition referred to as secondary hyperalgesia.[6,51] This has been described most often with morphine administration but could occur with other opioids such as hydromorphone and methadone. The pathophysiology of this is not well understood. In the case of morphine, it seems to be due to an excitatory pathway initiated by the M3G metabolite. Morphine has a major inhibitory effect that controls pain and a minor excitatory effect that initiates tolerance and hyperalgesia. With chronic use, the excitatory pathway is magnified and its effect becomes dominant. The pain caused by drug-induced hyperalgesia usually involves the same sites involved by the pain due to vaso-occlusion, but its quality is usually different. It is more neuropathic than nociceptive in nature. A major quality is allodynia, where ambient minor stimuli induce severe pain that is usually superficial, not deep, burning, tingling, and lancinating in nature.

### *Dopaminergic effect of opioids*

All opioids have a dopaminergic effect that affects the reward/pleasure circuitry of the brain.[21,22,52] This circuitry includes three major neurons in the brain: the ventral tegmental area, nucleus accumbens, and the prefrontal cortex. The fundamental reward neurotransmitter in the brain is dopamine. This circuitry subserves natural rewards of all kinds, including food, listening to music, watching a favorite movie, etc. Opioids derive their abuse potential from acting upon the reward/pleasure circuitry in the brain by increasing the level of dopamine, which in turn enhances the desire to achieve reward/pleasure. Depending on the environment and the genetic potential, this dopaminergic effect of opioids may lead to addiction in some individuals. To that end, addiction is a disease by itself and should be treated as such. Recent reports suggest that topiramate is effective in the treatment of drug dependence.[53]

### *Proserotonergic effects of opioids*

The serotonin syndrome is a clinical triad of altered mental states, autonomic dysfunction, and neuromuscular abnormalities.[54] It is not an idiopathic drug reaction but the result of excess use of central and peripheral nervous system serotonergic drugs. **Table 5** lists some of the drugs associated with the serotonin syndrome. Signs and symptoms of this syndrome range from tremors and diarrhea in mild cases

**Table 5. Drugs associated with the serotonin syndrome.**

- Antidepressants, including SSRIs
- MAOIs
- Anticonvulsants
- Analgesics
- Antiemetic agents
- Cough and cold remedies
- Antimigraine drugs

Adapted from Boyer and Shannon.[53]

to delirium, neuromuscular rigidity, and hyperthermia in life-threatening cases. The classic example of this syndrome is the use of meperidine and monoamine oxide inhibitors, which continues to occur sporadically as was recently reported.[53] Hospitalized patients with painful crises are at risk to develop this syndrome. As was mentioned above, modulation of the painful stimuli includes the release of serotonin in the central nervous system to inhibit pain transmission. In addition, it is not unusual for such patients to receive a number of proserotenergic medications that are listed in **Table 5**, including an antidepressant, an opioid, an antiemitic, an anticonvulsant, and an antibiotic. The net result of such combinations may increase the level of serotonin to cause the syndrome. The signs and symptoms of the serotonin syndrome overlap with those of withdrawal but careful history may differentiate the two. Care providers should be aware of this syndrome and its management.


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