# Chapter 5
# Side Effects of Opioid Analgesic Therapy


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While this chapter will emphasize the acute side effects in the ICU, no discussion of the consequences of opioids is complete without reference to the crisis of opioid use disorder (OUD) in America and around the world. The first epidemic of OUD in the United States began perhaps as early as the 1840s with the huge influx of opium and morphine to the American continent. In the Civil War era, opioids were considered the panacea of pain relief but came to be banned in the early twentieth century. Later, they were redeployed again and legalized for well-moderated medical uses [3]. This period of medical redemption was short lived and OUD has skyrocketed since the arrival of OxyContin in 1996 and the advent of pain as the fifth vital sign; a concept that was endorsed by the Joint Commission in 2001 [3, 4]. From 1999 to 2018, opioid prescriptions increased by almost 400% [5], (Fig. 5.1). In recent years, their use has begun to decrease in the face of the increasing death toll and rising public awareness and concern [5]. Though a key tool instrument to alleviate suffering, opioids are certainly not without significant consequences and their many receptor targets involve nearly every physiologic system (Fig. 5.2). Regardless, about 80% of Americans using heroin began their opioid use with a legal narcotic prescription and, overall, 4–6% of those given a narcotic prescription will go on to use heroin [5, 3].

In the intensive care unit, as many as 80% of patients needing mechanical ventilation receive opioids. *Analgesia-first* sedation is associated with improved outcomes and fewer ventilator-dependent days, leading to very significant utilization of opioids like fentanyl in ICU settings [6, 7]. Moreover, anywhere from 33% to 73% of ICU survivors develop chronic pain syndromes [8]. It is logical to conclude a high rate of subsequent ongoing use and abuse, but study of the topic is lacking. Of overall ICU survivors, approximately 12% remain on opioids at

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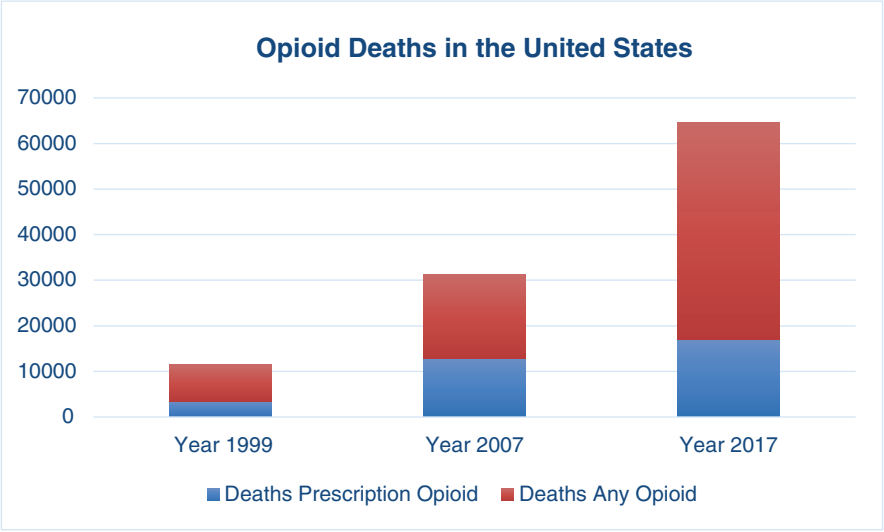


**Fig. 5.1** Opioid deaths have increased exponentially in America. While prescription opioid control has conferred a lower percentage of overall opioid deaths, up to 6% of those given a script will develop an opioid use disorder (OUD). The vast majority of those using heroin began their OUD with a prescription. These individuals ultimately begin using heroin in response to a lack of access or affordability of prescription opioids. (Data from the Centers for Disease Control and Prevention)

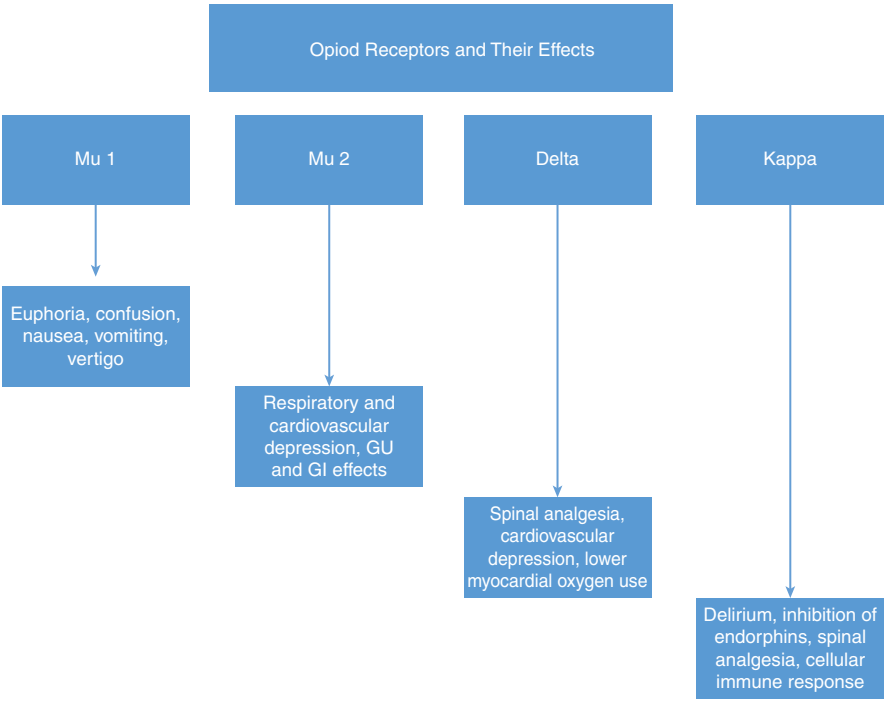


**Fig. 5.2** A depiction of the various opioid receptors and their effects with activation. (Data from Molina et al. [1] and Plein et al. [2])

discharge from hospital and 4.4% are thought to still be obtaining prescriptions 4 years after discharge [8]. In a limited international study, length of hospitalization but not length of ICU stay was associated with increased chronic use [9]. Long-term post ICU OUD and the role that in-hospital opioid use plays in it is ultimately not well studied, but it is certainly worth being aware of given the potential societal toll. The topic of OUD will be covered more extensively elsewhere in this book. For the purposes of this chapter, we will now focus on a system-by-system discussion of the in-hospital consequences of opioid therapy.

## Neurologic Side Effects

### *Physiologic Dependence*

*Description:* Physiologic dependence is a state of altered physiology secondary to chronic opioid use which confers a risk of withdrawal when the medication is abruptly discontinued. It is related to increased somatic and autonomic activity [10, 11].

*Incidence:* Physiologic dependence is common in ICU patients [10, 11]. Opioid withdrawal in the ICU may be as frequent as 30% of mechanically ventilated patients who receive high-dose opioids for at least 1 week [11–13].

*Diagnosis:* Symptoms related to physiologic dependence may impact many body systems. This can include rhinorrhea, myalgias, nausea, vomiting, and autonomic hyperactivity including hypertension, tachycardia, hyperreflexia, and tachypnea. Validated clinical scores which aid in the diagnosis of opiate withdrawal exist and include the Clinical Opiate Withdrawal Scale (COWS), which assigns a diagnostic score based upon 11 clinical signs and symptoms [14].

*Management:* Dependence is best treated by prevention. Opioids should be utilized only as necessary and in the smallest possible doses. Multimodal pain management regimens avoiding opioids should be pursued whenever possible. Opioid withdrawal should be managed with therapy aimed at relieving symptoms (Fig. 5.3). The medication may also be given intermittently rather than in infusion form. If the sudden cessation of opioids was not intentional, the medication may be restarted and the doses tapered as tolerated.

### *Tolerance*

*Description:* Tolerance is defined by a loss of analgesic potency for a given dose and may make dosing difficult, leading to uncontrolled pain [10]. Tolerance may be either innate or acquired. Innate tolerance is conferred by genetic factors, while acquired tolerance is derived from pharmacokinetic, pharmacodynamic, and learned factors [10]. Opioid tolerance is not related to drug clearance and is not well understood [6]. It is seen in all types of critically ill patients, but is most common in those

| Withdrawal symptom | Treatment | Note |
|---|---|---|
| Insomnia | Sleep hygiene, melatonin, quetiapine or temazepam at bedtime | Use the lowest possible dose and consider simultaneous psychiatric diagnoses |
| Nausea/Vomiting | Metoclopramide, prochlorperazine, ondansetron | |
| Diarrhea | Loperamide, atropine/diphenoxylate | |
| Headaches/Joint Pains | Ibuprofen, acetaminophen | Use appropriate dosing in patients with HCV cirrhosis |
| Agitation/Anxiety | Diazepam | Avoid short acting benzodiazepines and do not use if concurrent benzodiazepine withdrawal |
| Hypertension and Hyperalgesia | Clonidine | In sedated patients, dexmedetomidine may be of use |

**Fig. 5.3** Potential treatment options for symptoms of opioid withdrawal

with major trauma and in children or patients who are mechanically ventilated or exposed to opioids for prolonged periods [6, 10].

*Incidence:* Opioid tolerance can readily occur in the acute ICU setting, there is no set time frame of administration or dose at which this predictably happens. It is not uncommon for patients to require drastically increasing opioid dosing for efficacious pain relief over weeks to months, but acute tolerance has been demonstrated in animal models in minutes to hours with unknown clinical significance [15]. Tolerance is worsened in the ICU setting as cytokine release can reduce blood-brain barrier penetration and reduce opioid efficacy [6].

*Diagnosis:* Tolerance is defined by a patient's efficacious opioid dose needing to be increased over time. Different opioids may also confer tolerance at different rates and cross tolerance may be incomplete between different drugs [10].

*Management*: As in physiologic dependence, the best treatment for tolerance is prevention. Opioids should be used in the minimum necessary dosing and a multimodal pain regimen employed whenever possible. Continuous infusions of opioids should be avoided as a means of sedation when possible. Intermittent opioids will produce less tolerance than continuous. When opioids cannot be avoided, they may be rotated to avoid-drug specific tolerance. This is specifically done between drugs that have active metabolites which may impair analgesia (morphine and hydromorphone) and those that do not (fentanyl) [6].

## *Hyperalgesia*

*Description:* This condition is characterized by increased pain sensitivity, even in the face of increasing opioid use. It is believed to be related to the effect of opioid metabolites, such as morphine-3-glucuronide [10]. These metabolites are thought to induce GABA neuron apoptosis leading to changes in neurologic response and act as NMDA receptor agonists [10].

*Incidence:* Hyperalgesia may occur with opioid use and is associated with chronic pain in almost half of ICU survivors evaluated up to a year after discharge [16].

*Diagnosis*: This condition is characterized by increased pain sensitivity, even in the face of increasing opioid use. The diagnosis is a clinical one. Patients with chronic opioid therapy may exhibit pain out of proportion to that expected for a given stimulus, also demonstrating marked temperature intolerance in some cases.

*Management*: Treatment of hyperalgesia is geared toward appropriate analgesic therapy. Avoidance of certain opioids may be useful. Remifentanil in particular has been implicated in hyperalgesia in post-operative patients, though it is not commonly used in the ICU setting [16]. Clonidine and dexmedetomidine, alpha-2-adrenergic agonists, may be useful in symptomatic relief [6]. The use of calcium channel blockers such as amlodipine has been helpful and ketamine, methadone, and magnesium may also aid in therapy through NMDA receptor antagonism [10].

## *Delirium*

*Description*: Delirium is an acute change in mental status characterized by disorientation or confusion. It may be hypoactive (somnolence) or hyperactive (agitation). It is characterized by its eb and flow with the symptoms appearing to come and go with time. Both benzodiazepines and opioids have been implicated in increasing the incidence of delirium in the critically ill and this is especially true in the elderly.

*Incidence*: Delirium is a common phenomenon in the intensive care unit, affecting 60–80% of patients who are mechanically ventilated and anywhere from 20% to 50% of those who are not [17, 18].

*Diagnosis:* The diagnosis of delirium is clinical and will, in this case, be related to the timing of administration of an opioid. Other causes of confusion and agitation should be considered, such as infection, stroke, or head trauma.

*Management*: Opioids should be avoided as possible and/or given at the lowest therapeutic dose. While their use can worsen delirium if the intent of their use is sedation, opioids used first confer lower delirium rates when utilized to address pain [13, 17–19]. This is ultimately related to the fact that untreated pain itself may cause delirium [6]. High-quality studies comparing specific opioids and their relation to

delirium is currently lacking, although meperidine has been deemed causative in several studies and should be avoided [13, 20]. Standard approaches to delirium management outside of opioid titration include sleep hygiene optimization and frequent reorientation.

## *Seizures*

*Description:* Seizures are classically defined by a sudden cerebral electrical disturbance. This may manifest itself as anything from an *absence* seizure to a generalized tonic-clonic seizure. Opioids are known to cause neuroinflammation and even direct neurotoxicity [6]. In many cases, it is the metabolites of opioids that cause these significant neurologic complications.

*Incidence:* Opioid-related seizures are uncommon unless an overdose has occurred. Specific rates are not well known. Normeperidine, a metabolite of meperidine, has a particularly long half-life and can accumulate in the body. It is not reversible and can lead to seizures and delirium [13]. Morphine-3-glucuronide, a neurotoxic metabolite of morphine, has also been implicated in seizure activity and its effects are most significant in the setting of renal failure when it cannot be adequately cleared [21]. Hydromorphone-3-glucuronide, a metabolite of hydromorphone, has theoretically similar complications but does not significantly accumulate in the setting of renal failure [16, 13, 21, 22]. Tramadol, in extreme doses, can also decrease seizure threshold. Fentanyl, which is quite commonly used in the ICU, has no active metabolites and has notably not been associated with seizures [16].

*Diagnosis*: Diagnosis is typically made based on a witness report of seizure activity alone. Additional diagnoses such as brain lesions or hemorrhagic strokes are typically ruled out utilizing brain imaging. If the diagnosis remains unclear, electroencephalogram (EEG) may be utilized.

*Management:* In the short term, seizures should be treated with intravenous benzodiazepine to stop the active seizing. Prevention of seizures involves appropriate opioid dosing and avoidance of extremely high opioid levels including tramadol, morphine, hydromorphone, and meperidine, which are not commonly administered in the ICU.

## *Sleep and Sedation*

*Description*: Sleep and sedation are related in that both involve a diminished mental status. Sedation can be a goal of opioid use in the ICU, but it can also be an adverse effect. Opioid sedation is thought to be related to anticholinergic activity and is dose and tolerance dependent [10, 23].

*Incidence*: Sleep impairment and sedation from opioid use are thought to be nearly ubiquitous and have been demonstrated in randomized trials. Impacts are

dose dependent. While many opioids, such as fentanyl, have a fairly short half-life with bolus administration and no metabolites, their use as a continuous infusion can lead to drug accumulation. Bolus dosing of fentanyl in particular has a short half-life, but this is due to its rapid re-distribution into different body compartments given its highly lipophilic nature rather than rapid clearance [24]. After discontinuation of an infusion, fentanyl deposited in peripheral adipose tissue is re-distributed into the plasma again and sedation may continue for quite some time [13, 24]. Ultimately, the "true" half-life of the drug is more related to its volume of distribution than its clearance and long-term infusions in the ICU can confer a longer than anticipated duration of action. This concept is known as a context-sensitive half time [13, 24].

While opioids may be sedating and induce sleep, they do not improve sleep quality. The caveat, of course, is that untreated pain can also be deleterious to sleep, but certainly a balance must be achieved. Opioids are associated with worsened sleep duration and quality, a reduction in REM and delta sleep, and an increased number of sleep-wake cycles [10, 25]. This finding has been replicated in healthy volunteers and is thought to be impactful in both acute and chronic opioid use settings [10, 25, 26].

Diagnosis: The diagnosis of these conditions is again a clinical one. Sedation from opioids can mimic hypoactive delirium but resolves with naloxone administration. Sleep disturbance and sedation can be best mitigated by using the lowest efficacious dose of the medications and avoiding opioids that lack active metabolites. Continuous fentanyl infusions should ideally be limited in favor of intermittent boluses.

## Cardiovascular Side Effects

*Description:* Cardiac side effects range from bradycardia and hypotension to life-threatening arrhythmias. Methadone, which may be used to treat acute pain in the ICU, is a particular risk for cardiovascular complications, specifically *torsades de pointes* due to QT prolongation. Morphine is known to induce vasodilation and hypotension in response to histamine release at levels beyond other opioids, particularly as compared to fentanyl, which lacks any histaminic activity [16, 6, 10]. This can often be interpreted as an anaphylactic response although it is not. While given in myocardial ischemia to increase coronary perfusion through vasodilation and reduction in myocardial oxygen consumption, opioids do have deleterious cardiovascular effects [13]. Bradycardia and systemic hypotension may be caused by opioids through blunting of the stress response release of catecholamines [16, 27]. In particular, sympathetic nervous system control of the cardiovascular system is disrupted through opioid interactions with adrenergic receptors [1].

*Incidence*: The incidence of most cardiac complications related to opioids are not well chronicled, but they do exist. Methadone is the second most common drug-induced cause of ventricular arrhythmias [28]. It is associated with QT prolongation

and may lead to *torsades de pointes*, conferring a mortality rate of almost 20% [16, 10]. Hypotension is thought to have an incidence of less than 5% [29].

*Diagnosis*: Identifying cardiovascular impacts of opioids often requires significant clinical suspicion and is largely based on the relation of the clinical change and drug administration. Electrocardiograms (ECGs) are useful in identifying a prolonged QT interval associated with methadone. When *torsades de pointes* occurs, the prior ECG pattern tends to be pathognomonic for a lengthened QT which is often drug related.

*Management:* Limit therapy to the lowest efficacious dose of medication. Some tolerance for a given dose may develop with time. For reversal of some cardiac effects, naloxone can be trialed and has been shown to increase peripheral vascular resistance and improve cardiac function in anesthetized swine and primate hemorrhage models [1]. Intravenous fluid administration or vasopressor support may be needed in extreme cases. With regard to *torsades de pointes*, ventricular tachycardia, and cardiac arrest, advanced cardiac life support (ACLS) measures should be undertaken immediately and prompt defibrillation is key. Serial ECGs should be done when using methadone to monitor for QTi elongation and the drug stopped if this develops. Other QT-altering drugs should be avoided as concurrent therapy and electrolytes should be routinely repleted, especially potassium and magnesium. A list of common drugs that may increase the QT interval is included in Fig. 5.4 [30]. There are many drugs not necessarily included here which may have similar effects. These drugs include some anti-emetics (ondansetron), antipsychotics (haloperidol and atypical antipsychotics), some antibiotics (fluoroquinolones and azole antifungals), and tricyclic antidepressants among numerous others [30].

| Drug Types Causing QT Interval Elongation | Specific Medications |
|---|---|
| Anti-psychotics | Haloperidol, olanzapine, risperidone, thioridazine, ziprasidone |
| Antiarrhythmics | Amiodarone, dofetilide, flecainide, procainamide, quinidine, sotalol |
| Antibiotics | Macrolide and fluoroquinolone classes, azole antifungals, terbinafine |
| Antivirals | Atazanavir, darunavir, indinavir, fosamprenavir, nelfinavir, saquinavir, tiprinavir |
| Antidepressants | Amitriptyline, bupropion, citalopram, duloxetine, escitalopram, imipramine, paroxetine |
| Antiemetics | Droperidol, ondansetron, cisapride |
| Other | Cilostazol, donepezil, methadone, sumatriptan |

**Fig. 5.4** A list of common medications that may cause elongation of the QT interval and should be avoided with methadone use. (Data from Li et al. [21])

## Pulmonary Side Effects

*Description:* Respiratory consequences of opioid use are among the most familiar to physicians and the public alike. Respiratory depression ranging from a decreased respiratory rate to total apnea leading to respiratory arrest and anoxic brain injury is a well-known consequence of opioid use in any setting, and this includes in the ICU [6, 10, 13]. Additional adverse pulmonary events include bronchospasm, though the incidence is not well defined [16, 6]. This is most associated with morphine administration. A reduction in functional residual capacity (FRC) and forced vital capacity (FVC) from opioid use may also impair clearance of secretions and contribute to pneumonia [13]. Conversely, inadequately controlled pain can cause abdominal muscle tensing and similarly decreased FRC and FVC with the same clinical outcome [13]. Additionally, there are reports of chest wall rigidity impairing mechanical ventilation with intravenous pushes of fentanyl [31].

*Incidence:* The incidence of respiratory depression with opioid analgesia is not well defined. This is primarily because of the varied end points that may be used to demonstrate hypoventilation. Studies may use variable definitions of hypoventilation: pulse oximetry of varying threshold levels, varying respiratory rates to define hypoventilation, levels for hypercapnia, or more vaguely any administration of naloxone. A meta-analysis of post-operative analgesia with differing administration techniques concluded that 0.3% of patients require naloxone, 1.1% have hypoventilation, 3.3% become hypercapneic, and 17% display some degree of oxygen desaturation [29]. Additional pulmonary effects are not well studied and their incidence is not well described.

*Diagnosis:* As described above, the definition of hypoventilation is not well circumscribed. A relative drop in pulse oximetry, an increase in end-tidal carbon dioxide, or a drop in respiratory rate may all be identified. In general, an attempt should be made to maintain end-tidal carbon dioxide within a normal range of 35–45 mmHg. Measurement of this is usually accomplished using a nasal prong and is often part of patient-controlled analgesia. Pulse oximetry can be an effective means of monitoring patients for oxygen desaturation and, in general, should be maintained above 92%.

*Management:* Quick recognition of hypoventilation is important. Pulse oximetry and end-tidal $CO_2$ monitoring are useful clinical adjuncts. Oxygen desaturation with otherwise adequate ventilation can be managed with supplemental oxygen administration in an otherwise arousable patient. Patients with hypercarbia or a diminished mental status from hypoventilation may require naloxone administration and those who are apneic or have significant respiratory compromise should receive immediate assistance with the use of a bag valve mask and intubation if the airway remains unsecured.

## Gastrointestinal Side Effects

*Description:* Like the respiratory impacts of opioids, the gastrointestinal maladies are among the most common and well known. Constipation, ileus, Ogilvie's syndrome, nausea, and vomiting are the most common side effects of opioid therapy [6,

10]. Opioids are known to stimulate chemoreceptor trigger zones, acting to increase vestibular sensitivity and inducing nausea, vomiting, and decreased gastric motility [13]. Gastric emptying can be similarly impacted with slowed transit times and increased non-propulsing contractions [10]. Unlike many opioid side effects, constipation typically does not improve over time and can be a major source of morbidity and hospitalization length of stay [10].

*Incidence:* Constipation, mediated by mu receptor-controlled motility in the gastrointestinal tract, effects anywhere from 25 to 95% of opioid users [16, 6, 7, 10, 13]. Nausea and vomiting occur in about a quarter of patients using opioids [13]. Other side effects are not as well described.

*Diagnosis*: The diagnosis of gastrointestinal side effects is primarily a clinical one based upon the timing of symptoms and medication administration. Ileus and Ogilvie's may be diagnosed with abdominal X-rays or CT imaging if the X-ray is unclear.

*Management:* Gastric emptying can be improved with prokinetic agents for symptomatic relief and nausea and vomiting largely managed with anti-emetics. Both can be improved with dose reductions or multimodal pain regimens avoiding opioids as much as possible. Such multimodal therapy may include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX-2) inhibitors, local or regional anesthetics, and other adjunctive therapies. The same can be said for constipation and ileus, although it is especially hard to manage. Bowel regimens are often utilized. In patients who are opioid naïve and about to undergo major surgery that will necessitate opioid use, preoperative methylnaltrexone and alvimopan (mu receptor antagonists which inhibit peripheral but not central opioid activity) have shown some promise [10]. Patients with ileus may require gastric decompression until the ileus resolves, and patients with Ogilvie's may require neostigmine administration which can itself be life threatening.

## Genitourinary Side Effects

*Description:* Genitourinary effects of opioids may include urinary retention and difficulty voiding. Opioids may impair detrusor contractility and block the urge to void. The feeling of bladder fullness and the urinary reflex are also inhibited [10]. This has specifically been demonstrated in study of morphine [10]. Regardless, the primary genitourinary impact of opioids may well be that existing renal dysfunction may decrease opioid clearance and enhance their other side effects [13, 21]. The extent of this is primarily related to metabolite accumulation and the level of renal failure [21].

*Incidence:* The genitourinary impacts of opioids are less common than their gastrointestinal counterparts, but may be clinically relevant as well. Anywhere from 3.8 to 18.1% of patients may get urinary retention believed to be related to opioids [6, 10]. Epidural morphine has a higher incidence of voiding dysfunction than other means of administration [10]. However, it is not always clear that this is due to the opioids themselves and this is not well delineated.

*Diagnosis:* The diagnosis of genitourinary effects is clinical and may be difficult to differentiate from other causes of voiding dysfunction.

*Management:* Genitourinary complications are best avoided through use of the minimum efficacious opioid dose. Naloxone is known to reverse opioid effects on the bladder, but will reverse many favorable effects of the opioids as well. Significant urinary retention should be treated with bladder catheterization until symptoms resolve.

## Endocrine Side Effects

*Description*: Numerous endocrine impacts of opioids have been documented with varying clinical importance. Opioids are known to decrease serum levels of testosterone, estrogen, luteinizing hormone (LH), gonadotropin releasing hormone (GRH), corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and dehydroepiandrosterone (DHEA) [10, 1]. Many of these effects act to mediate vascular and cardiac responses in stress [27]. Clinically, decreased testosterone and estrogen from opioid-induced hypogonadism is associated with decreased energy and increased depression, and these may be the most readily identifiable symptoms. While clinical symptoms may vary, some endocrine effects are evident in laboratory study within as little as 1 hour after administration and return to normal within 1 day after cessation [10]. In a rodent study, opioids increased catabolism and worsen hyperglycemia [1].

*Incidence:* Hormonal effects are thought to be frequent, but the incidence is not well characterized as most effects are clinically silent. Testosterone has been somewhat better studied and is known to acutely drop within four hours of opioid use. This effect is mitigated within a day of cessation of the drug [10].

*Diagnosis:* The diagnosis of endocrine dysfunction related to opioid use is typically clinical. It is often difficult to identify opioids as the specific cause. Hormonal levels can be assessed, but this is typically more relevant in the setting of chronic opioid use.

*Management:* Most hormonal effects are thought to be dose dependent. Dose reduction or cessation of use are the best treatment modalities for mitigating endocrine effects. However, acute untreated pain can cause much the same dysregulation and risks and benefits of therapy should be carefully considered [6].

## Hematologic Side Effects

*Description:* Hematologic consequences of opioid therapy are poorly studied. It is known that drugs such as heroin impact levels of trace elements in the body, including iron [32]. The timing of this effect is largely unknown, however, as most studies utilized chronic opioid users [32]. Much data is extrapolated from populations of

heroin and opium users, limiting clinical application. Chronic heroin users, when controlled to healthy individuals, have overall higher mean corpuscular volume, red cell distribution width, mean corpuscular hemoglobin, and iron-binding capacity [32, 33]. However, hemoglobin, hematocrit, platelet counts, and serum iron levels were significantly lower [32]. Increases in hemoglobin from their baseline during active heroin use were also found 1 month after withdrawal [33]. Most findings did relate to the route of administration of the drug with intravenous administration having the biggest effect. It is difficult to separate this from other lifestyle and dietary confounders in the studied populations.

*Incidence*: The incidence of hematologic changes from clinically used opioids is unknown.

*Diagnosis:* Any accomplished diagnosis would be difficult to pinpoint to opioid therapy and no certain conclusions could be made in a critically ill patient.

*Management*: As always, opioid therapy should be limited to the minimum efficacious dose and multimodal opioid-sparing techniques utilized whenever possible.

## Immunologic Side Effects

*Description:* Opioids have been implicated in immunologic dysfunction and poor wound healing, beginning as early as the late 1800s [10, 21]. It was long ago discovered that the cellular immune response was impaired in an animal model treated with morphine [10]. Opioids may inhibit both innate and adaptive immune responses and specifically inhibit T-cells, B-cells, intestinal barrier integrity, natural killer cells, neutrophils, mast cells, cytokine expression, and phagocytosis [6, 10, 1, 2], (Fig. 5.5). Exposure to morphine may also result in TH-1 cell death but TH-2 cell differentiation [2]. Though immune cells do express opioid receptors, some immune

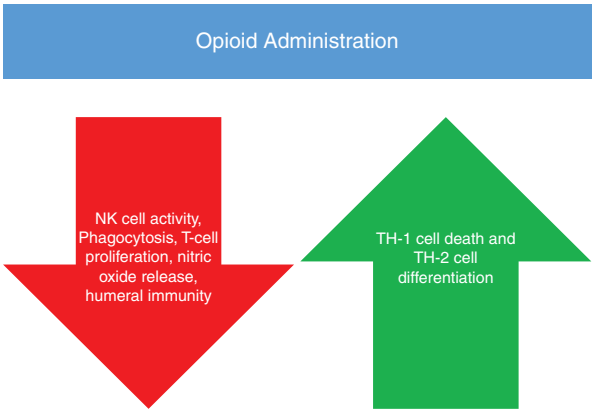


**Fig. 5.5** Some of the wide ranging effects of morphine administration on the innate and adaptive immune systems. Most immunologic impacts have been catalogued in animal models; clinically significant effects on humans are not well studied. (Data from Benyamin et al. [10])

effects are actually mediated by opioid modulation of receptors in the central nervous system and hypothalamic-pituitary-adrenal (HPA) axis [1]. This pathway ultimately involves the cleavage of POMC to ACTH, alpha MSH, and beta endorphin, which specifically impacts immune cells [1]. The clinical importance of this is not well defined and much of the study is limited to animal models. Limited study in humans has also suggested immune modulation by opioids, including infection in ventilator-associated conditions [1, 34]. As in many of the impacts of opioids, untreated pain may have much the same immunologic impairment through stress response and similar interaction with the HPA [6].

*Incidence*: Effects on immune function are variable and the effect of opioids may be related to the underlying health of the host, the mode of drug administration, and the medication given [1]. Effects can be immediate and may last for up to a day after administration. Unpredictably, some study has actually shown an increase in cytotoxicity in NK cells of healthy hosts given fentanyl [1]. In short, clinical relevance is not well understood.

*Diagnosis*: As the clinical impacts of opioid therapy on the immune system are not well understood, a diagnosis is not easily achieved. Far more study is required to better understand which patients, if any, may clinically benefit from opioid reduction or cessation for immunomodulating purposes.

*Management:* There is no specific treatment related to immunomodulation due to opioids. Avoidance and discontinuation are the only known interventions, though again the clinical relevance is not well known.

## Summary

The effects of opioids are wide ranging and impact almost every physiologic system. While some effects may be clinically silent or of unclear importance with contemporary research, others are well known and quickly lethal. Genitourinary, endocrine, immunologic, and hematologic effects in particular can be of unclear clinical relevance in the intensive care setting. A high level of caregiver vigilance and clinical suspicion is necessary to identify such outcomes, which may be mostly theoretical. Neurologic, respiratory, and cardiovascular effects are both rampant in clinical medicine and potentially life threatening. Opioid use disorder is a major source of morbidity and mortality in modern America and across the globe. Patients should always be monitored for physiologic dependence, tolerance, over-sedation, hypoventilation, and cardiovascular compromise from opioid therapy. Many, if not all, of the adverse effects of opioid therapy are best managed with avoidance. The minimum efficacious dose should always be pursued, continuous infusions avoided, and multimodal pain regimens that spare opioids initiated.

**Conflicts of Interest** No author has a relevant conflict of interest or financial disclosure necessary.

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