Management of Opioid Tolerability and Related Adverse Effects

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Abstract

Opioid analgesics are effective but are not always well tolerated by patients. Adverse effects of opioids range from the common ones (constipation, nausea) to the less common (hiccups, lower leg edema), from the relatively mild (dry skin, runny nose) to the severe (respiratory depression). Adverse effects associated with opioid use can be treatment limiting, but a variety of management strategies and tactics exists. The adverse effects of opioids may be classed into inhibitory and excitatory, although they sometimes occur simultaneously. Ultra-low doses of opioid antagonists can reduce excitatory effects, which, in turn, can heighten the inhibitory response (and possibly potentiate analgesia). Patients on opioid therapy may benefit from a change in drugs (ideally to a non-opioid altogether, but possibly to a lower dose or different opioid) or combination therapy. Specific medications or therapies have been shown to be effective in managing some adverse effects of opioid therapy and are discussed here, but there is considerable intra-patient variability. Opioid therapy confers analgesic benefits to well selected patients, but adverse effects of this therapy are common and may require physician management.

Key Words: Opioids, opioid adverse effects, opioid antagonists, opioid adverse events

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Introduction

Opioids are powerful and widely prescribed analgesics associated with a wide range of adverse effects ranging from the familiar and serious (constipation, nausea, respiratory depression) to the less frequent (lower leg edema, petechiae, hiccups). Complicating the picture are matters of tolerance and antagonism. Opioid tolerance can be defined as the need to take increasing amounts of the opioid agent in order to effectively maintain the same level of analgesic relief;[1] the relationship between opioid tolerance and addictive mechanisms is unknown. Patients with increasing tolerance to a particular opioid require dose escalations to maintain pain relief, but many side effects are dose dependent. Thus, increases in tolerance may increase side effects as the patient requires larger and larger doses. Very small doses of opioid antagonists, such as naloxone and naltrexone, have been shown to reduce tolerance, allowing patients to obtain adequate analgesia at comparatively lower doses, which, in turn, reduce adverse effects. Thus, the prescribing physician must balance effective analgesia against adverse effects in an effort to find adequate pain relief with minimal and tolerable side effects for the patient. While opioid rotation can often be useful to strike this appropriate balance, the adverse effects of different opioids may create new or worsened side effects in a patient otherwise achieving adequate analgesia. Opioid rotation can be limited by the fact that there is not always sufficient evidence available to guide equianalgesic ratios.[2]

The most straightforward approach to management of opioid-related side effects starts with dose reduction, followed by changing to a different opioid or route of administration, and managing symptoms using other compounds.[3,4] However, many adverse effects (AEs) are systemic and central in nature, so opi-

Table 1
Major Subtypes of Opioid Receptor Sites with those Particular Events and Associations Linked to Each of the Major Subtypes

Receptor	Events	Associations
Mu	Analgesia; euphoria; respiratory depression; sedation; suppression of hypothalamo-pituitary-adrenal axis; dopamine and acetylcholine release[9]	Dependence
Kappa	Dysphoria; decrease in gastrointestinal motility; appetite suppression; psychotic symptoms; depression; diuresis;[9] orthostatic hypotension[10]	Not associated with respiratory depression
Delta	Hormonal changes; appetite suppression; dopamine release[11]	Minimal potential for dependence;[12] may counteract respiratory depression[13] and constipation[14]

oid rotation may not abate the symptoms; changing routes of administration may be impractical. Thus, prescribing additional medications to manage side effects has become common, although it often leads to patient inconvenience and potentially hazardous polypharmacy. This article offers a comprehensive review of the range of adverse effects of opioids and their classifications with recommendations for their clinical management.

Opioid Classifications

Opioids bind to the brain at receptor sites; opioid receptors are groups of G-protein coupled receptors with opioids as ligans. There are 3 major types of opioid receptors with multiple subtypes of each. Opioid analgesics are often defined, in part, by the receptor sites to which they bind (Table 1). The analgesic effect of opioids is exerted primarily on the cortex and brain stem[5-7] where an abundance of opioid receptors can be found in the rostral parts of the anterior cingulated cortex and mid-anterior insula. Opioid receptors also can be found in peripheral tissues.[8]

Opioids also can be classified as hydrophilic or lipophilic. The more lipid-soluble the opioid, the greater is its extent of receptor occupancy and its relative strength. The most hydrophilic opioid is propoxyphene. Increasing in lipophilicity, in this order, are codeine, morphine, oxycodone, hydrocodone, hydromorphone, methadone, fentanyl, buprenorphine, sufentanil, carfentanyl, and lofentanyl.

Classification of Opioid Adverse Effects

Opioid AEs may be categorized as excitatory or inhibitory, although it is unclear whether these two properties are possessed by a single receptor or a pair of receptors (Table 2). Note that excitatory and inhibitory effects may occur simultaneously, producing bimodal action.[15]

Ultra-low doses of opioid antagonists block the excitatory effects, such as hyperalgesia, while potentiating the inhibitory effects, such as analgesia, and may improve the side-effect profile.[16,17] These ultra-low doses of antagonists, such as naloxone or naltrexone, appear to enhance analgesic benefit by minimizing tolerance, although much of this information comes from animal studies.[18,19] A recent study of low-dose nalbuphine and morphine in humans (n = 174) found that low-dose nalbuphine with morphine in patient-controlled anesthesia reduced the rate of nausea without adversely affecting analgesic benefit.[20] In the aforementioned study, 1 mg nalbuphine was added to 100 mg preservative-free morphine and saline to make a total volume of 100 mL solution for patient-controlled analgesia. Another human study of analgesia (n = 112) combined 100 ng (1 mL) of naloxone with 100 µg of fentanyl and 34 mL of lidocaine 1.5% for the active agent arm of the study, finding that the addition of low-dose naloxone prolonged axillary brachial plexus blockade—that is, time to first postoperative pain—in patients undergoing elective forearm surgery.[21] These minute doses of opioid antagonists have a predilection for excitatory receptors and inhibit them before binding to inhibitory receptors. The decrease in excitation allows the inhibitory function to be more clinically expressed. Hence, potentiated analgesia occurs in the presence of micro doses of opioid antagonists.[16] These excitatory and inhibitory central nervous system effects are described in Table 3.

Morphine[22] and fentanyl[23] are known to increase extracellular dopamine in nucleus accumbens, but the exact relationship of dopamine to exogenous opioids remains unclear.[24] Systemic opioids increase dopamine turnover in the nucleus accumbens.[25] Dopamine has been speculated to be associated with gratification. Dopamine must be present in sufficiently high levels in the prefrontal cortex of the brain and sufficiently low enough in the subcortical region of the brain for appropriate, balanced psychiatric function. Dopamine blockers (antipsychotic agents) may decrease the euphoric effects of opioids, possibly lessening abuse potential. Morphine abstinence decreases dopamine in the same area of the brain, which could trigger craving. However, dopamine in the prefrontal cortex increases with morphine abstinence but not morphine exposure.[22] Thus, morphine is not associated with dopamine-based cognitive sharpening, which could explain the cognitive improvement typically exhibited upon discontinuation of morphine.

Managing Opioid-Related Adverse Effects

A number of approaches can be used to counteract the inhibitory and excitatory effects of commonly prescribed opioids (Table

4). The preferred course of action for patients who require strong analgesia but have adverse effects with opioids is to switch to a non-opioid pain reliever, if possible. Multimodal pain relief strategies may be important here, such as using analgesics as well as diet and lifestyle changes, the use of massage or occupational therapy, complementary and alternative medicine, and so on. Combination therapy involves concomitant drug therapy with an opioid and another pain reliever; some combination drug products are available in a single formulation, eg, oxycodone and acetaminophen, reducing the pill burden. Combination therapy may reduce the amount of opioid the patient has to take to achieve relief. For opioid patients dealing with adverse effects, occasionally changing the drug regimen, in particular to lower doses or non-opioid analgesics, should be attempted periodically to determine the patient's response. Opioid rotation is based on the insight that individual patients may have variable responses to specific opioids and transitioning to different opioids may provide more effective analgesia at lower doses,[26] although there is a paucity of evidence in the literature to help guide these prescribing choices.[27] Opioids should always be prescribed judiciously, but patients with a personal or family history of substance abuse require strict monitoring. Many patients who take opioid pain relievers take other medications as well; care should be exercised to avoid potential drug-drug interactions. In fact, the prescribing physician should review all medications taken by a patient who receives opioids. Many patients who take opioids may discontinue them and restart. Tolerance to opioids can build quickly, but it is also lost quickly. When prescribing opioids to a patient who has taken them previously but not recently, it is prudent to treat such patients as opioid-naïve.

In many clinical presentations, it is not always reasonable or possible to discontinue opioid analgesics; therefore, it is important to understand how certain AEs may be managed.

Opioid-Related Adverse Effects

Respiratory AEs. Respiratory AEs are so important that they belong in a special category. Respiratory depression is a central nervous system effect based on the direct action of the opioid on brain stem respiratory centers. This action decreases the brain stem's response to CO_2 and directly affects the cough center in the medulla, even at subanalgesic levels. While cough suppression is often a beneficial effect of certain opioid formulations (such as cough medicine containing codeine), opioid antagonism of mu-opioid receptors (MOR)-2 in the medulla lowers ventilation by reducing sensitivity of medullary receptors to hypercapnea[28] and thus depresses the ventilation response to hypoxia. This cascade reduces the patient's stimulus to breathe.[29] Although the incidence of respiratory depression with opioid agents is about 0.5%, it can be fatal.[30] Morphine and fentanyl have higher rates of respiratory depression than buprenorphine, which in one study was found to exhibit a plateau effect with respect to respiratory depression.[30] Doubling the dose of

Table 2
Inhibitory Versus Excitatory Effects of Opioids

Receptor	Inhibitory Properties	Excitatory Properties
Mu	Analgesia; respiratory depression; sedation; mental slowness; fatigue; weight gain; constipation; weakness; miosis; dry skin; xerostemia; hypotension; cough suppression; hormonal suppression; sedation	Hyperalgesia; increased tolerance; euphoria; agitation; psychosis; hallucinations; irritability; insomnia; edema; muscle twitching; sweating; rash; nausea; headaches; pruritus; gastrointestinal spasm; urinary retention
Kappa	Constipation; gastroparesis; appetite suppression; depression; orthostatic hypotension	Dysphoria; diuresis
Delta	Appetite suppression; hormonal suppression	Psychosis; irritability; offset of respiratory depression; offset of constipation

Table 3
Central Nervous System Effects of Opioids

Inhibitory	Excitatory
Pain control	Hyperalgesia
Sedation	Seizures
Fatigue	Hallucinations
Confusion	Paranoia
Decrease in concentration	Delirium
Shortness of breath	Agitation
Short-term memory impairment	Anxiety
	Dysphoria
Personality changes	Dissociative symptoms
Loss of affect	Pleasure
Poor concentration	Euphoria
Decreased creativity	Insomnia
Mental slowing	Irritability
Memory impairment	Anger
Loss of interest	Confusion
Impaired judgment	Decreased consciousness
Impaired insight	Fever
Decreased consciousness	Toxic encephalopathy (delirium)

Table 4
Management of Opioid-Related Adverse Effects

1. If possible, use non-opioids.
2. Use combination therapy (opioid and a non-opioid pain reliever) rather than increasing the dose of the single opioid.
3. Periodically convert to non-opioids, decrease and/or discontinue opioids to see if the patient tolerates the change.
4. Consider opioid rotation (changing from one opioid to another opioid) if you are unable to circumvent side effects.
5. Consider social and family history in relation to opioids.
6. Exercise caution when combining opioids with other CNS depressants.
7. If opioids are decreased or discontinued and then re-introduced, slow titration is preferred to give the body time to adjust. Opioid tolerance disappears rapidly when medication is discontinued, so re-introduction is safest when opioid-naïve doses are used initially.
8. Watch for CYP P-450 medications interactions.

Table 5
Respiratory Adverse Effects

Inhibitory	Excitatory
Respiratory depression	Runny nose
Cough suppression	Bronchial spasm
Hoarseness	

Table 6
Intracranial Adverse Effects

Inhibitory	Excitatory
Headache	Headache
	CSF pressure elevation

buprenorphine increased analgesia but did not increase the rate of respiratory depression.

Inhibitory respiratory effects include respiratory depression and hoarseness. General principles of airway management and managing inhibitory symptoms may be utilized including naloxone 0.4 mg to 2 mg intravenously in emergencies. Excitatory upper respiratory effects include runny nose, which may be managed with judiciously chosen anticholinergic medications or micro-doses of naltrexone or both. Anticholinergic medications have the potential of increasing CNS depression or provoking other adverse events, such as constipation or urinary retention. Their use must be weighed carefully in this context (Table 5).

Intracranial AEs. Headaches are a common AE with opioids. All opioids, particularly short-acting opioids, are known to induce headaches in chronic headache patients. Opioid agonists elevate cerebrospinal fluid (CSF) pressure and retain CO_2 due to respiratory depression. Headaches may occur due to the opioids' inhibitory effects (respiratory depression and CO_2 retention) or excitatory effects (CSF pressure elevation) (Table 6). A severe headache induced immediately after opioid initiation usually subsides spontaneously and may respond, at least partially, to acetaminophen and nonsteroidal anti-inflammatory drugs. Severe headaches may require discontinuation of the opioid.

Musculoskeletal AEs. Musculoskeletal AEs are mainly excitatory and may be a part of opioid-induced hyperalgesia (Table 7). They include muscle twitching, arthralgia, myalgia, and bone pain. Muscle weakness with a decrease in deep tendon reflexes may be a result of opioid-induced central nervous system inhibition. Such complaints may be treated with the previously described general AE approaches, including micro doses of naltrexone, which is particularly effective. Muscle relaxants in usual doses can be used; antispasmodic medications, including alpha blockade from tizanidine, can be beneficial in treating muscle twitching and myalgia. Dopaminergic anti-Parkinson medications, such as pramipexole dihydrochloride and ropinirole extended release, may be beneficial but must be used with caution because of their potential to depress the central nervous system. Primidone, an anticonvulsant containing phenobarbital, should only be used with extreme care, in that while it may decrease blood levels of P450 metabolized opioids, it also can increase the risk of respiratory depression.

Other approaches to musculoskeletal AEs include oxygen therapy, progressive relaxation, massage, transcutaneous electrical nerve stimulation units, and physical exercise. Buprenorphine has less excitatory effects on the muscles than other similar agents.

Cutaneous AEs. Cutaneous AEs are mostly excitatory in nature and include itching, flushing, sweating, rash, ecchymosis, petechiae, and facial wrinkles. In the authors' observations, the latter three occur more frequently with the use of methadone than other opioids. Inhibitory cutaneous AEs include dry skin as well as brittle hair and nails. Hypoventilation is associated with pallor or grayish skin color and is a direct sign of developing hypoxia and encephalopathy (Table 8).

Some cutaneous adverse effects are related to the release of histamine and may diminish over time in chronic opioid therapy. Common practice for histamine-related symptoms involves the use of antihistamines, steroids, or opioid rotation.[31,32]

Sweating may be treated with a variety of measures: hydroxyzine 25 mg to 100 mg every 6 to 8 hours; terazosin 2 mg to 4 mg

orally per day; scopolamine patch and atropine; aluminum chloride 20% topically; calcium supplementation; and micro-doses of naltrexone. Anticholinergic biperiden also may be used,[33] but care must be taken since anticholinergic agents may increase constipation, urinary retention, or other adverse effects. It has been reported that rotating to an opioid other than morphine (which has significant histamine-releasing properties) may be a useful measure in such cases where flushing, itching, and sweating are tolerability concerns.[34]

For inhibitory AEs, simple measures, such as 3 g to 6 g a day of Omega III fatty acids (fish oil, flaxseed oil) and liberal use of creams and topical ointments, may suffice. Mild hyberbaric oxygenation can be helpful in rash, ecchymosis, and petechiae treatment.

Pale or grayish skin color caused by subcutaneous vasoconstriction has been associated with both high doses and long-term use of opioids but typically disappears quickly when opioids are discontinued. Heroin abusers develop a characteristic look including wrinkled, dry, pale skin, droopy eyelids, downward pointed sides of the mouth, deep nasolabial folds, bags under the eyes, and a lack of subcutaneous tissue; however, many of these signs may owe more to malnutrition than opioid use. For patients with such characteristics, a switch to buprenorphine and naloxone combination may provide a dramatic cosmetic improvement even before better nutrition can play a role. It has been suggested by this phenomenon that opioids have a direct effect on the patient's cosmetic appearance. Anecdotally, buprenorphine alone (without naloxone) does not produce such marked improvement in appearance, which suggests that minute doses of naloxone may eliminate the excitatory effects of the opioids and improve cutaneous appearance and health.

Naloxone and naltrexone are opioid antagonists, which reduce opioid tolerance.[19] Chronic morphine has been shown to cause the mu opioid receptor to switch its coupling from Gi/o to Gs, provoking excitatory signaling, but ultra-low doses of naloxone prevent this switch, which is thought to attenuate the addictive properties of morphine and allow for lower effective doses.[35,36] Ultra-low doses of these opioid antagonists may allow for effective analgesia at lower doses, which, in turn, may result in fewer or mitigated side effects.

Circulatory AEs. The inhibitory AEs associated with opioids on the circulatory system include orthostatic hypotension due to vasodilatation; a decrease in cardiac output; bradycardia or tachycardia; and QT-segment prolongation on the electrocardiogram. The excitatory AE is mainly peripheral edema, especially lower leg edema due to histamine release and cAMP induction. Such cellulitis is usually caused by tissue compression of the lower extremities caused by exudate or cellulite (Table 9).

For inhibitory AEs, vasoconstrictors and hydration can be used. For excitatory AEs, diuretics and terazosin 1 mg to 10 mg by mouth at bedtime can be considered. Compression stockings and sequential circulation may be used in cases of lymphedema. Anecdotally, the authors have observed dramatic decreases in lower leg edema within the first 3 days after adding micro-doses of naltrexone.

Table 7
Musculoskeletal Adverse Effects

Inhibitory	Excitatory
Muscle weakness	Muscle twitching
Deep tendon reflexes decrease	Muscle rigidity
Improvement in restless leg syndrome	Periodic limb movement disorder
	Myalgia
	Arthralgia
	Bone pain

Table 8
Cutaneous Adverse Effects

Inhibitory	Excitatory
Dry skin	Itching
Brittle hair	Sweating
Brittle nails	Flushing
	Wrinkle formation
	Rash
	Ecchymosis
	Petechiae
	Photosensitivity

Table 9
Circulatory Adverse Effects

Inhibitory	Excitatory
Orthostatic hypotension	Peripheral edema
Vasodilatation	Secondary cellulitis
Decrease in cardiac output	Tachycardia
Bradycardia	Pulmonary edema
QT segment prolongation	
Other cardiac arrhythmias	

Visual AEs. Blurred vision is a commonly reported adverse effect in opioid patients.[37] The mechanism behind visual problems is not clearly understood, but one suggestion is that MOR-3 activation releases nitric oxide, which, in turn, causes intraocular hypertension and miosis, resulting in blurred vision.[37,38] Another theory proposes

Table 10
Visual Adverse Effects

Inhibitory	Excitatory
Mydriasis (hypoxia induced)	Miosis
Intraocular hypotension	Intraocular hypertension
Blurry vision	Decrease in night vision
Increase in light sensitivity	Red eyes
	Tearing

Table 11
Gastrointestinal Adverse Effects

Inhibitory	Excitatory
Constipation	Gastrointestinal spasm
Bloating	Abdominal cramps
Dry mouth	Spasm of sphincter of Oddi and duodenum
Tooth decay	Obstruction of the common bile duct
Drooling (due to esophageal dysregulation)	Nausea
	Vomiting
	Hiccups
	Gastroesophageal reflux disease

Table 12
Endocrine Adverse Effects

Inhibitory	Excitatory
Decrease in testosterone, estrogen, LH	Prolactinemia
Decrease in sexual drive	Gynecomastia
Infertility	THS elevation independent of thyroid function
Hypothyroidism	
Hypoadrenalism	
Weight gain	
Osteoporosis	

that kappa receptor stimulation causes endogenous kappa ligands (dynorphins) to lower intraocular pressure by lowering the aqueous flow rate, thus producing mydriasis antagonism.[39,40] Finally, it is known that morphine increases the firing of the neurons that constrict the pupil, which increases the sensitivity of photoreflexes.[29,41]

Both miosis (constricted pupil) and mydriasis (lack of pupil's response to penlight exam) can occur in opioid patients. Patients with miosis often accommodate to the condition over time, but even opioid-tolerant patients may have miosis with sudden or marked increases in dose. Mydriasis is more likely to occur in patients with opioid-induced hypoventilation and hypoxia. Pulsating pupils under penlight exam suggest adrenal fatigue. Visual disturbances, like other side effects, may be dose related.

Histamine released into the sclera by mast cells can cause red eyes, which can be managed by antihistamines, a change of opioid, or the use of micro-doses of naltrexone. Tearing of the eyes is an excitatory AE based on the same mechanisms as a runny nose and can be treated with anticholinergic medications, micro-doses of naltrexone, or both. Note that anticholinergic medications must be used with care, as they can induce other adverse effects and may even contribute to visual disturbances (Table 10).

Gastrointestinal AEs. Gastrointestinal (GI) AEs are both common and complex and can be caused by a number of different mechanisms, including:

- Increase in smooth muscle of the stomach and duodenum
- Spasm of the sphincter of Oddi
- Inhibition of gut propulsion
- Increase in colon tone and colonic spasms
- Reduction of gastric, biliary, and pancreatic secretions.

The GI tract is innervated by the enteric nervous system, which synthesizes endogenous opioid peptides and their transmitters. Three opioid receptor types have been identified in the enteric nervous system: mu, kappa, and delta.[42] When these endogenous opioids inhibit enteric nerve activity, an inhibitory effect on the propulsion and secretion actions of the GI tract can be observed.[43,44] Under normal conditions, endogenous opioids mediate the contractile process and suppress intestinal motility when appropriate (such as during stress).[45] Current thinking is that mu opioid receptors are the main coordinators of opioid effects on the GI tract[46] and when exogenous opioids bind to these receptors, it interrupts the rhythmic contractions necessary for intestinal motility and inhibits mucosal secretions.[47,48]

Sphincter of Oddi dysfunctions relate to the obstruction of the flow of bile or pancreatic juice through the pancreaticobiliary junction (sphincter of Oddi) and may be structural or the result of a motor abnormality.[49] Although it had long been thought that meperidine was a useful alternative analgesic for patients with sphincter of Oddi dysfunction, recent anecdotal evidence contradicts this belief.[50] Meperidine is an opioid analgesic associated with certain safety issues related to the drug's active metabolite, normeperidine, which is neurotoxic.

The inhibitory GI AEs include constipation, bloating, dry mouth, and tooth decay, while the excitatory AEs include nausea, vomiting, and hiccups (Table 11).

Stool softeners are commonly used to treat opioid-induced constipation, but this is not usually as effective as a laxative or laxa-

tive-stool softener combination, since opioid-induced constipation is caused by poor gut motility. Patients who had GI spasm prior to opioid therapy will likely find their abdominal pain exacerbated by opioids. In chronic pancreatitis patients who are treated with opioids, pancreatic secretions accumulate rather than drain properly, leading to more pain. Abdominal pain from chronic pancreatitis or biliary spasms may be treated with rapid-onset, short-acting opioids rather than maintenance or extended-release opioids to avoid prolonged interference with the sphincter of Oddi that can interfere with pancreatic drainage as well as promote biliary spasms.

Opioid-induced abdominal bloating can be due to the decrease in GI propulsion and the concomitant increase in bacterial growth in the gut. Relieving the constipation often improves the bloating.

Increased tooth decay may be secondary to dry mouth, bacterial overgrowth in the oral cavity, vascular changes, and changes in the gums.

Hiccups (singultus) occur when esophageal propulsion gets out of sync with the diaphragm. Opioid-induced diaphragmatic contraction can occur because the neuroexcitatory metabolites acting as agonists of the MOR-2 receptors in the medulla activate the inspiratory muscles (diaphragm and intercostal muscles), causing hiccups to occur.[51] The literature suggests that when opioids interact with certain cancer drugs, they cause abnormal opioid metabolism and encourage hiccups.[52]

Myoclonus, a brief involuntary twitching of a muscle including but not limited to hiccups, is a familiar but not very well studied phenomenon. The hiccup is thought to be an involuntary medullary reflex that is independent of the respiratory center but influenced by it.[53] In a study of cancer patients on opioid analgesic therapy, the incidence of myoclonus had a dose-dependent relationship observed with hydromorphone.[54] It was suggested in this study that when continuous parenteral hydromorphone accumulates beyond a neurotoxic threshold, neuroexcitatory symptoms, including myoclonus, occur, but it appears to be the result of the metabolites of hydromorphone (morphine-3-glucuronide or hydromorphone-3-glucuronide) rather than the parent compound. Myoclonus in this case does not reverse with naloxone.[55] There is also an opinion that opioids influence the dorsal horn of the spinal cord via glycine and the excitation of the diaphragm through the activation of NMDA receptors, producing asynchronous diaphragmatic-esophageal contraction, resulting in hiccups.[55] Drooling, associated with inhibited movement of the esophagus, can occur and may lead to aspiration pneumonia.

To manage excitatory GI AEs, decrease opioid dose and consider the use of promethazine, prochlorperazine, and ondansetron. Micro-doses of naltrexone can be considered as well. Inhibitory AEs, specifically constipation, are treated by laxatives (possibly in combination with a stool softener) as well as metoclopramide and dicyclomine. Methylnaltrexone can block opioid-inhibitory GI AEs in the gut. The usual dose of methylnaltrexone is 12 mg by subcutaneous injection. A bowel movement typically occurs in the first half-hour post-injection. While useful, long-term use of methylnaltrexone can diminish its effectiveness. Alvimopan, a peripheral mu-opioid antagonist, is indicated for inpatients following partial bowel resection but is not practical in the outpatient setting. Alvimopan is recommended only for short-term use, as it is associated with an elevated risk for myocardial infarction and is the subject of a Risk Evaluation and Mitigation Strategy (REMS) document from the Food and Drug Administration.[56] Rarely, patients suffering from severe impaction or intestinal obstruction may require mechanical or surgical intervention.

Table 13
Sexual Adverse Effects

Inhibitory	Excitatory
Decrease in sexual desire	Spontaneous orgasms and erections on opioid withdrawal
Erectile disorder	
Unorgasmia	

Table 14
Immune System Adverse Effects

Inhibitory	Excitatory
Increase in infectious diseases due to immune suppression	Angiogenesis
	Tumor growth

Table 15
Urinary Adverse Effects

Inhibitory	Excitatory
Prostatic hypertrophy	Urinary retention
	Urinary incontinence

Constipation is one of the most common AEs in opioid therapy and one that most patients find particularly disagreeable. Among opioids, fentanyl is probably least likely to cause constipation, but there is considerable variation among patients; therefore, opioid rotation may be considered for refractory constipation.

Endocrine AEs. There is a dose-dependent relationship with respect to opioids and AEs involving the endocrine system, typically manifesting as decreased testosterone, estrogen, luteiniz-

ing hormone, decreased libido, increased infertility, and hypogonadism. Curiously, there are no reports in the literature of decreases in follicular-stimulating hormones and prolactin blood levels as AEs of opioids.[57] Hypothyroidism has been associated with opioid therapy and can contribute to problems with thermoregulation as well as dry skin, fatigue, edema, and weight gain, blurring the line between primary AEs and secondary effects. Thyroid-stimulating hormone (TSH) may be suppressed or stimulated by opioids and can mask hypothyroid symptoms. Hypoadrenalism is related to suppression of adrenocorticotropic hormone (ACTH), and some opioid patients may require steroid supplementation because of cortisol suppression and clinical Addison's disease (Table 12).

Opioids do not appear to suppress prolactin; on the contrary, prolactinemia has been reported, including gynecomastia, weight gain, and infertility. The use of bromocriptine 5 mg to 7.5 mg by mouth every day may be used to treat prolactinemia along with decreasing the opioid dose or changing the opioid used. Hormonal supplementation may be considered to address any of these endocrinal AEs after a careful risk/benefit analysis of their long-term risk.

Sexual AEs. The inhibitory function of opioids may result in decreased sexual desire and inhibited erection and orgasm. It is thought that these AEs are not solely produced by the endocrine system but also involve suppression of sympathetic and parasympathetic systems. Spontaneous erections and orgasms have been described by patients going through opioid withdrawal, attributed to the possible effects of nitric oxide. Sexual AEs are clinically managed in opioid patients the same way they would be managed in non-opioid patients (Table 13).

Immune system AEs. The high prevalence of infectious diseases among opioid abusers has led to speculation that chronic opioid use in the absence of pain depresses the immune system,[58] but lifestyle factors may also play a role. Chronic morphine use stimulates COX-II receptors and promotes angiogenesis and tumor growth as well as metastasis and reduced survival in mice.[58] For that reason, consideration can be given to co-administration of COX-II inhibitors or nonsteroidal anti-inflammatory drugs, which may possibly prevent these AEs and may improve analgesia as well.

The paradox is that pain itself inhibits the immune system, meaning that reducing pain (through opioid use) should improve rather than inhibit the immune system.[58] Opioid receptors are present on multiple distinct peripheral targets, including a variety of immune cells.[59] These receptors can modulate such functions as chemotaxis, superoxide production, and mast cell degranulation. These immunomodulatory actions can be stimulatory as well as inhibitory. At present, it is unknown how they relate to antinociception[8] (Table 14). The literature remains sparse on dealing with immune system effects associated with opioids. The common sense strategy would be a healthful lifestyle and avoidance of immunosuppressive medications in such patients.

Urinary AEs. Urinary AEs are primarily excitatory and involve urinary retention caused by an increase in the sphincter's tonus (Table 15). There is a higher prevalence of hypogonadism in male opioid patients than in females,[60] which has led to the speculation that prostatic hypertrophy may owe to inhibitory effects of opioids suppressing more testosterone than estrogen. Although the link between long-term opioid use and hypertrophic prostatic disorder remains speculative, the Merck manual recommends discontinuing all opioids in the presence of benign prostatic hyperplasia.[61]

Clinical management of urinary AEs may include conservative approaches with hydration or one of the pharmacological measures, such as dicyclomine 10 mg to 20 mg up to 4 times daily, oral bethanechol 10 mg to 30 mg 2 to 4 times daily, 1 mg to 10 mg oral terazosin at bedtime, or 0.5 mg oral dulasteride daily.

Meperidine, in particular, should not be used in patients where renal toxicity might be an issue.

Conclusion

Opioids represent a challenge in clinical practice due to their wide-ranging clinical, side effect, and end-organ effects. The complex properties of opioid analgesics and their potential interactions with other medications present a significant clinical challenge to even seasoned pain specialists. The AEs associated with opioids are comprehensive, complex, and can limit treatment. It is not unheard of that chronic opioid patients choose to discontinue opioid therapy (and give up pain relief) rather than endure intolerable adverse effects. Nevertheless, opioid analgesia offers tremendous benefits to well selected chronic pain patients when resulting AEs can be managed. In addition to the previously described strategies, further research needs to be carried out to address specific opioid AE management strategies that will optimize analgesia while lessening concerns about tolerability, serious adverse events, and chronic end-organ concerns.

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