Opioid Complications and Side Effects

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Medications which bind to opioid receptors are increasingly being prescribed for the treatment of multiple and diverse chronic painful conditions. Their use for acute pain or terminal pain is well accepted. Their role in the long-term treatment of chronic noncancer pain is, however, controversial for many reasons. One of the primary reasons is the well-known phenomenon of psychological addiction that can occur with the use of these medications. Abuse and diversion of these medications is a growing problem as the availability of these medications increases and this public health issue confounds their clinical utility. Also, the extent of their efficacy in the treatment of pain when utilized on a chronic basis has not been definitively proven. Lastly, the role of opioids in the treatment of chronic pain is also influenced by the fact that these potent analgesics are associated with a significant number of side effects and complications. It is these phenomena that are the focus of this review.

Common side effects of opioid administration include sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression. Physical dependence and addiction are clinical concerns that may prevent proper prescribing and in turn inadequate pain management. Less common side effects may include delayed gastric emptying, hyperalgesia, immunologic and hormonal dysfunction, muscle rigidity, and myoclonus. The most common side effects of opioid usage are constipation (which has a very high incidence) and nausea. These 2 side effects can be difficult to manage and frequently tolerance to them does not develop; this is especially true for constipation. They may be severe enough to require opioid discontinuation, and contribute to under-dosing and inadequate analgesia. Several clinical trials are underway to identify adjunct therapies that may mitigate these side effects. Switching opioids and/or routes of administration may also provide benefits for patients. Proper patient screening, education, and preemptive treatment of potential side effects may aid in maximizing effectiveness while reducing the severity of side effects and adverse events. Opioids can be considered broad spectrum analgesic agents, affecting a wide number of organ systems and influencing a large number of body functions.

Key words: Opioids, morphine, methadone, fentsnyl, oxycodone, hydrocodone, xymorphone, codeine, adverse events, narcotics, side effects, constipation, sedation, hearing loss, tolerance, addiction, hyperalgesia

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O pioids have been used for thousands of years for the treatment of acute and chronic pain. Around 3400 B.C., the opium poppy was cultivated in lower Mesopotamia by Sumerians who referred to it as *Hul Gil*, the "joy plant." The Sumerians passed along the plant and its euphoric effects to the Assyrians and Babylonians who in turn would pass their knowledge onto the Egyptians. Ancient Egyptian papyrus records mention opium as a treatment for pain (1), and in 1170, the first book of western surgery described using sponges soaked in opium held over the patient's nose for surgical procedures (2). Their use in America has waxed and waned based on multiple and disparate factors including availability, the introduction of new methods of administration, regulatory efforts, and physician and societal attitudes. Currently, the prescribing of opioids has escalated dramatically for a variety of reasons in the United States. Unfortunately, but not unexpectedly, this has also been accompanied by a concomitant and dramatic rise in the incidence of diversion and abuse of these medications as well as the incidence of complications including overdosage and death.

Currently, statistics show that approximately 90% of patients with chronic pain receive opioids (3-26), and 90% of patients presenting to an interventional pain management center are already on opioids (27). It is estimated that the prevalence of a substance abuse disorder is 8.1% in the general population (28) and even higher in the population of patients with chronic pain (20-26). These facts explain the dramatic rise in prescription drug abuse and in complications secondary to controlled substances. One study showed that 16% of active pain patients were found to be abusing their medications (21). In another study, Manchikanti et al (22) reviewed the records of almost 5,500 patients, and found 91 deaths, of which 18 were drug poisoning deaths. Of those, 12 were felt to be partially or significantly due to prescription drugs.

Other side effects, such as constipation, nausea and vomiting, respiratory depression, and sedation often limit the dosing and effectiveness of opioids, leading to early discontinuation, under-dosing, and inadequate analgesia. Appropriate identification and management of these side effects would be expected to improve patient compliance and medication efficacy and reduce complications.

For many years, the use of opioids for noncancer pain was limited but this has changed secondary to recent efforts to address the lack of recognition and under-treatment of chronic pain by the medical professionals. These efforts include the regulatory requirement of hospitals to evaluate and address "pain," education by advocacy pain organizations, and aggressive marketing by prescription opioid manufacturers to physicians of all specialties. The confluence of these efforts has contributed to a recent dramatic increase in opioid prescribing.

Although the following clinical statement may be intuitive to most physicians, its importance cannot be overstated when utilizing opioids for the treatment of chronic noncancer pain. Opioids should be prescribed at the lowest dose possible to provide adequate analgesia for improvement in the quality of the patient's life and for improvement in function. Complete pain relief may occur but this is uncommon and cannot be considered a treatment goal. The patient must be educated regarding these goals and continually reminded during the course of treatment. Opioids should not be used in isolation to treat pain and the goals of treatment will commonly require additional medications such as anticonvulsants, antidepressants, NSAIDs, and other adjuvant treatments as well as nonpharmacologic strategies. While advocacy for appropriate opioid usage in chronic pain continues, it is well known that prolonged use of opioids may result in adverse consequences, including tolerance, hyperalgesia, hormonal effects, and immunosuppression.

OPIOID TOLERANCE AND PHYSICAL DEPENDENCE

Tolerance, a loss of analgesic potency, is one of the common complications of opioid treatment, leading to ever-increasing dose requirements and decreasing effectiveness over time. Physical dependence is the development of an altered physiological state that is revealed by an opioid withdrawal syndrome involving autonomic and somatic hyperactivity. There are 2 types of tolerance: innate (which is genetically determined and would be present from the initial dose of the opioid) and acquired (pharmacokinetic, pharmacodynamic, and learned) (29). Pharmacokinetic tolerance results from changes in the metabolism of a drug after repeated administration, such as the induction of an enzyme by the administration of the drug itself (as seen with initiation of methadone treatment). Pharmacodynamic tolerance is represented by the classic decreased effectiveness of an opioid over time, related to up-regulation of receptors. Learned toler-

ance, on the other hand, results in a decrease in efficacy as compensatory mechanisms are incorporated or learned. For instance, a patient in a setting where he or she usually consumes the drug typically expects the drug to be less effective; however, if the same person takes the same amount of drug in a nonstandard setting, he or she will likely feel a greater effect (30).

One concern when starting a patient on long-term opioids has to be whether efficacy can be maintained over time. Both acute and chronic administration of opioids may produce tolerance as indicated by the lowering analgesic effects of the same dose over time. Since the initial studies by Light and Torrance in the 1920s, the major focus on research for tolerance has been its relationship to physical and psychological dependence (31). Since tolerance was considered to be the driving force to support the street addicts' abuse of opioids, there was a notion that it would occur in a similar way if opioids were used on a chronic basis in patients with chronic pain. Physicians were reluctant to use opioids and preferred to use them in a restrictive manner to preserve their efficacy for a situation when they were really needed. However, there are no studies to support this point of view. Interestingly, it seems that tolerance develops at a different rate depending on the specific opioid prescribed.

Although short-term studies have shown opioid efficacy for 4 to 32 weeks, it is not ethically possible to do placebo controlled randomized opioid trials, so the only knowledge of long-term analgesia comes from surveys, case series, open-label studies, and epidemiologic studies (32). When prescribing opioids, clinicians should be aware of the lack of complete cross tolerance. That is, the development of tolerance to one particular opioid doesn't necessarily confer tolerance to another. The clinical significance of this fact is paramount, as prescription of a new opioid at equianalgesic doses may lead to overdose.

Recent evidence suggests that spinal adaptations leading to increased activity of sensory neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance *P*, and their downstream signaling messengers derived from metabolism of arachidonic acid such as prostaglandins (PG), lipoxygenase (LOX) metabolites, and endocannabinoids, play an important role in the tolerance phenomenon (33).

In mice, NMDA receptor antagonists block the development of tolerance to morphine, but not fentanyl or a pure delta opioid receptor agonist; few similar studies in humans have been performed. It is

also striking that patients on chronic opioids such as methadone have dramatically decreased tolerance to experimental pain (such as a cold pressor test) compared to patients on no opioids (20 seconds compared to 1 minute), despite additional high doses of morphine (34).

In conclusion, although tolerance is a well known physiologic phenomena, its clinical relevance is unknown. Further studies to determine appropriate methods to decrease its development and to determine its relevance are warranted.

OPIOID-INDUCED IMMUNOLOGIC EFFECTS

The immunomodulatory effects of opioids were initially demonstrated in the 1890s when Cantacuzene showed cellular immune suppression and decreased resistance to bacterial infection in guinea pigs treated with morphine. Opioids have been implicated in the increased incidence of infections in heroin addicts and as a cofactor in the pathogenesis of human immunodeficiency virus. Interestingly, although exogenous opioids may generate immunosuppression, their endogenous counterparts (e.g., endorphins), induce immunoactivation. It is known that acute and chronic opioid administration can cause inhibitory effects on antibody and cellular immune responses, natural killer cell activity, cytokine expression, and phagocytic activity. The immunologic effects of opioids are mediated by central and peripheral mechanisms. The potential mechanism by which central opioid receptors mediate peripheral immunosuppression may involve the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. Interestingly, peripheral immune cells under the influence of cytokines, may release endogenous opioids modulating analgesia and inflammatory responses. Moreover, the same cells can express opioid receptors, creating a bi-directional system whereby opioids, immune cells, and cytokines dynamically interact (35-37).

The role of different central opioid receptors in the modulation of the immune response is variable (Table 1). Activation of KOR (kappa opioid receptor) and DOR (delta opioid receptor) may activate the cellular immune response (38,39), while effects of MOR (mu opioid receptor) may be more related to natural killer (NK) cell activity, cytokine secretion, and macrophage phagocytosis. Probably related to the affinity of different opioids to a particular receptor is the finding that mice injected with morphine had a biphasic immune response (40) with an increase in polymorpho-

Table 1. *Central immunologic effects of opioids.*

Receptor	Effect
MOR	Decreases NK cell activity (central) Macrophage phagocytosis (central) Inhibits T-cell proliferation (central) Nitric oxide release (peripheral)
DOR	Increases NK cell activity (central) Potentiates humoral immune response (MOR dependent) Decreases PFC response
DOR antagonist	At low dose inhibits DHR
KOR	Pronounced suppression of humoral immunity
KOR antagonist	Increases PFC Suppression of humoral immune response (MOR dependent)

PFC=plaque forming cells; DHR=delayed hypersensitivity reaction; NK=natural killer

Table 2. *Opioid-induced hormonal changes.*

Hormone	Opioid Effect	Potential symptom linkage
Testosterone	decrease	decreased libido erectile dysfunction reduced energy
Estrogen	decrease	sexual dysfunction reduced bone mineral density osteoporosis
Cortisol	decrease	secondary hormonal alterations
Luetenizing hormone	decrease	secondary reduced androgen hormone levels amenorrhea hypomenorrhea
Gonadotropin releasing hormone	decrease	secondary reduced androgen hormone levels

nuclear phagocytosis, followed by a marked decrease 24 hours later. Methadone, however, in an equianalgesic dose did not affect the tested immunoparameters. In clinical practice, not all opioids have similar effects on the immune system. Particular reference needs to be made to tramadol, which enhances NK cell activity, lymphocyte proliferation, and IL-2 release compared to morphine, while buprenorphine, with its mu agonist and kappa antagonist effects, doesn't show any effects on the immune response compared to morphine. It is important to remark that severe pain by itself has a significant immunosuppressive effect and although the use of certain opioids may potentially increase the risk of infection, the clinical significance of this relationship between pain, analgesia, and opioid-induced immunosuppression has not been clarified.

OPIOID-INDUCED HORMONAL CHANGES

The effects of opioid compounds on hormonal function is now fairly well understood and has been termed opioid endocrinopathy (OE) (Table 2) or, in the case of androgen hormones, opioid-induced androgen deficiency (OPIAD) (41-43). The hormonal effects of opioid usage affect both men and women and have been documented during oral consumption (41,43-47) as well as transdermal (4,44-48), intravenous (49-52), and intrathecal (53,54) administration. OE has also been documented in illicit drug users where serum hormone levels return to normal following withdrawal from the drug (45,49,55,56). Various studies have demonstrated opioid effects on a variety of hormones including but not limited to testosterone (both total

and free) (41,47), estrogen (estradiol, etc.) (42,45-53), luteinizing hormone (LH) (42,53), gonadotrophin releasing hormone (GnRH) (51,57,58), dehydroepi-androsterone (DHEA) and dehydroepiandrosterone sulfates (DHEAS) (43), adrenocorticotropin (ACTH) and corticotropin-releasing hormone (CRH) (48,59), and cortisol (48,59). The majority of work has focused on the androgen hormones because of their linkage to many symptomatic side effects of opioid usage.

Many men who are taking prescribed or illicit opioids suffer from several side effects including sexual dysfunction (i.e., erectile dysfunction, decreased libido, etc.), depression, and decreased energy level. These unwanted side effects have been correlated to hypogonadism and likely hypogonadotrophic hypogonadism (43,44,60,61). Testosterone levels are typically lowered 1 – 4 hours after acute administration of opioids (45) and return to normal levels within 24 hours of stopping the opioid (62). Chronic administration of opioids for nonmalignant pain result in tonic decreases in both total (TT) and free (FT) testosterone levels in an apparent dose-dependent fashion (41,47). It should be noted, however, that not all men show decreased TT levels and several physiological (e.g., Basal Metabolic Index) and behavioral measures (e.g., smoking) may predispose individuals to hormonal side effects of opioids (41). Also, it is not entirely clear that reduced testosterone directly contributes to sexual dysfunction. Through multivariate analyses Hallinan and colleagues concluded that testosterone levels contributed little variance in measures of sexual dysfunction (63). However, it should be noted that these

data were obtained from addicts on methadone or buprenorphine maintenance treatment and may not entirely apply to patient populations taking opioids for nonmalignant chronic pain. Studies examining potential adjuvant therapies treating potential hormonally mediated side effects are rare. Daniell and colleagues (44) performed an open-label trial of testosterone replacement therapy in men taking opioids for chronic noncancer related pain. Although many men showed improvement in indexes of sexual function, mood, and well-being, the effects were generally incompletely resolved (44). Interestingly, the effects of opioids on testosterone may be dependent on the specific opioid utilized. Bliesener and colleagues (47) studied the hormonal effects of opioid maintenance and found that individuals taking buprenorphine had significantly higher plasma testosterone levels and showed less sexual dysfunction compared to patients receiving methadone.

Again, it is unclear if these results can be extrapolated to pain patient populations, but it underscores the importance of a potential for medication dependent hormonal side effects. Apart from circulating testosterone levels, adrenal androgens are also reduced in men on prescribed opioids (42,45,53). These latter findings suggest that opioids may not only affect hypothamic-pituitary-gonadal function but also hypothalamic-pituitary-adrenal function as well.

Women also experience similar hormonally linked side effects of opioids including depression, dysmenorrhea, sexual dysfunction, and, potentially, reduced bone mineral density. Several studies have demonstrated reduced estrogen levels in women on methadone maintenance (42).

Reduced LH is also observed and appears to be more pronounced in postmenopausal women. Interestingly, testosterone levels also appear to be reduced in women taking prescribed opioids and may be related to body mass index and estrogen replacement therapy (64). The direct consequences of reduced LH and progesterone levels on dysmenorrhea are currently unclear.

The reductions in estrogen may have implications for osteoporosis and fractures in the older population. Ensrud and colleagues (64) found that, in a cohort of 8,127 older women, patients that were taking opioids had a greater risk for any nonspinal fracture. Some have suggested that, in part, this relative increase in risk of fracture may be due to an androgen-based reduction in bone density (65-67). While this is a plausible hypothesis, there is a lack of causal data connecting the hormonal ef-

fects of opioids to reduced bone mineral density. Moreover, while estrogen replacement therapy may be useful in some women to restore menses or maintain bone mineral density in younger women, there have been no controlled studies weighing the benefits of such therapy against the well publicized risks associated with estrogen replacement therapy.

OPIOID-INDUCED HYPERALGESIA

Hyperalgesia (also referred to as hyperalgia) is a relatively new recognized adverse effect, and is generally defined as an increased pain sensitivity (68). This sensitization presents as increasing pain despite increasing doses of opioids (69). Long-term use and high doses of opioids may be associated with the development of hyperalgesia, which may be related to opioid metabolites, such as morphine 3-gluceronide (M3G). Opioid-induced cell apoptosis may also be associated with hyperalgesia. The loss of GABA neurons to apoptosis may result in changes in spinal neuronal circuits (70). NMDA receptor agonism also has a major role in the development of hyperalgesia, as does glycine, an inhibitory neurotransmitter that mediates the postsynaptic inhibition of spinal neurons (71). At least in mice, the use of an L-type calcium channel blocker (amlodipine) prevented the hyperalgesia and tolerance of chronic morphine administration (72). This is consistent with the concept that morphine-induced abnormal pain and antinociceptive tolerance may be mediated by enhanced release of excitatory neurotransmitters (73). There are limited treatment options for the hyperalgesia and tolerance; in rats, ketamine (a NMDA antagonist) prevented fentanyl-induced hyperalgesia (74). Recent studies in opioid addicts have helped to confirm the clinical impression that chronic opioid use results in an abnormal pain perception, consistent with hyperalgesia (75).

OPIOID-INDUCED SEDATION

The sedating effects of opioids in opioid naïve patients are fairly well known (76). Opioid-induced sedation and drowsiness are thought to be caused by the anticholinergic activity of opioids. Although tolerance to these side effects often develops, dose initiation and rapid dose escalation may result in sedation and consequently lead to noncompliance and/or reduced quality of life. The suggested treatments are opioid dose reduction, opioid rotation, and use of psychosomatic stimulants.

Psychostimulants may improve psychomotor performance scores and subjective drowsiness (77). Methylphenidate is the most common medication investigated to treat opioid-induced sedation. In a double-blind randomized study of cancer patients receiving continuous subcutaneous opioids, a daily dose of 10 mg methylphenidate significantly improved the mean baseline drowsiness scores by 35% compared with 8% in the placebo group (78). In another double-blind, randomized study in cancer patients, 15 mg of daily methylphenidate use led to a 61% improvement in drowsiness score, with only 25% improvement in the placebo group; at the same time, there was an associated decreased pain and decreased number of opioid doses (79). A 15 mg daily dose of methylphenidate was studied in a double-blind randomized fashion in 32 cancer patients maintained on a steady dose of oral opioids (80). The treatment group had a 61% improvement in drowsiness score, which was significantly greater than 25% improvement in the placebo group. Methylphenidate was also associated with decreased pain and rescue opioid doses. Multiple uncontrolled studies have also demonstrated positive results with methylphenidate. Although other options like dextroamphetamine, donepezil, modafinil, and caffeine are also available, methylphenidate is the most widely studied agent, and in absence of side effects and abuse potential it should be considered as first line therapy (81).

Opioid-induced Sleep Disturbances

Sleep disturbance is common in cancer patients (82). It is usually attributed to insomnia or pain, but there is little evidence to support this. Arousal from sleep or disturbed sleep from pain has been reported but there is some evidence that patients in pain do not suffer from disturbed sleep more than those not in pain. In addition, no correlation has been found between pain severity and sleep disturbance. The effect of opioids on sleep in palliative care patients has not been well studied. Opioids are generally believed to enhance sleep but again, there is little evidence to support this belief.

Opioids increase the number of shifts in sleep-waking states (83), and decrease total sleep time, sleep efficiency (84), delta sleep, and REM sleep (85). However, in these studies, it is difficult to differentiate the effects of the opioid medication from the effects of the underlying disorders (e.g., cancer, addiction/dependence, postoperative pain). A study of 7 healthy volunteers treated with IV morphine showed reductions in slow wave sleep and a mild decrease in REM, but no increase in awakenings or arousals (86). A randomized, double-blind study (87) involving 42 healthy volunteers given 5 mg methadone or 15 mg sustained release morphine, showed that both opioids increased the percentage of time spent in light sleep and substantially decreased (30% to 50%) the percentage of time in deep sleep (stages 3 and 4). No drug effects were seen on sleep efficiency, total sleep time, wake after sleep onset, or subjective measures of mood or fatigue. Both cortical arousal and the sleep-wake cycles are regulated by converging inputs from the brainstem and pontinecholinergic projections (88). Sleep and waking is regulated by many neurotransmitters, including noradrenaline, serotonin, acetylcholine, dopamine, histamine, gamma-aminobutyric acid (GABA), the pituitary hormones, and the neurohormone melatonin. Any drugs that alter the balance of these neurotransmitters, as opioids do, can potentially affect sleep. Although the exact mechanism by which opioids disrupt sleep is unclear, morphine has been shown to reduce REM sleep perhaps in part by modulating GABAergic signaling via inhibition of acetylcholine release in the medial pontine reticular formation. The resultant disruption of sleep architecture affects the states of arousal during wakefulness (89). In animals, REM suppression is associated with mu, but not kappa or delta opioid receptor agonists.

Psychomotor Performance in Opioid Therapy

The negative effects of opioids on psychomotor/driving performance in opioid naïve patients remains controversial in the minds of clinicians — multiple studies support the notion that for many patients it is reasonable to drive on a stable dose of opioids (76,90-92). When opioids are initially added to the management of pain, patients' abilities to operate heavy equipment may be diminished and so they should not be allowed to drive automobiles; however, once a stable opioid analgesic regimen is reached, patients with no significant cognitive/psychomotor impairments should be allowed to drive — as they would be allowed to drive with any medication which can potentially cause central nervous system depression (e.g., antidepressants). In contrast, others believe that patients on stable doses of opioid medications should be allowed to drive vehicles (93). Direct evidence provided in a subset of patients with chronic pain on a stable opioid analgesic regimen (76)

showed that these patients were capable of operating automobiles safely during daytime, in normal climate weather. A structured, evidence-based review by Fishbain et al (94) suggested that in opioid-dependent/tolerant patients on stable doses of opioids, no impairment of psychomotor abilities are observed even immediately after a dose of opioid.

OPIOID-INDUCED CONSTIPATION

Constipation is a common problem, occurring in 40% to 95% of patients treated with opioids and can occur even with a single dose of morphine (95). Although often dismissed as a trivial side effect, the long-term consequences of constipation can result in significant morbidity and mortality, with an adverse effect on patient quality of life. Severe constipation can force patients to reduce the dose of the opioid, resulting in decreased analgesia. Chronic constipation can result in hemorrhoid formation, rectal pain and burning, bowel obstruction, and potential bowel rupture and death. Opioids activate mu receptors in the gastrointestinal tract responsible for gut motility (84) from a vascular distribution as well as local application to the gut (96). Reported rates of constipation with spinal administration of opioids vary, but in general it is thought that spinal opioid receptors do not affect intestinal motility and transit in humans (61,97). It is unclear whether opioid-induced constipation in humans is predominantly centrally mediated or peripherally mediated. Morphine may act within the CNS to alter autonomic outflow to the gut (98). Peripherally it affects intestinal motility by a direct stimulation of opioid receptors in the enteric nervous system (99). Loperamide, an opioid receptor agonist with limited ability to cross the blood brain barrier, is used clinically to treat diarrhea, suggesting that opioids have a more direct local constipating effect.

Unlike many of the other side effects of opioids (respiratory depression, nausea, sedation), constipation is unlikely to improve over time, and therefore must be anticipated, monitored, and addressed throughout the opioid treatment course (100) (Table 3). It is suggested that tolerance may be linked to certain subtypes of mu receptors that mediate various pharmacological actions (99). Tolerance develops more readily to mu-1-dependent actions than to non-mu-1-dependent actions. Another hypothesis suggests that development of tolerance requires P-glycoprotein up-regulation. Morphine induces P-glycoprotein

up-regulation in the brain, but it does not up-regulate intestinal P-glycoprotein (101).

Assessment of constipation can be difficult; a questionnaire (Patient Assessment of Constipation) that measures symptom severity (PAC-SYM) and quality of life (PAC-QOL) can be used (102). The questionnaire was validated in chronic low back pain patients and found to be a reliable, valid, and responsive measure of the presence and severity of opioid-induced constipation symptoms.

There is a need for effective treatment of opiate-induced constipation. It is partially attenuated by using different types of opioid compounds or routes of administration or combining opioids with other medications. However, refractory constipation may still develop and opioid antagonists may play an important therapeutic role in this respect. Antagonizing the gastrointestinal mu receptors is the basis for many current investigational medications to treat opioid-induced constipation.

A novel approach to management of opioid-induced constipation involves blocking peripheral opioid receptors in the gut with opioid receptor antagonists with prokinetic activity. Two recently developed mu receptor antagonists, methylnaltrexone and alvimopan, are currently under review (103). Methylnaltrexone is a quaternary derivative of naltrexone with strong mu receptor affinity but no intrinsic agonist activity; it blocks the peripheral actions of opioids while sparing central analgesic effects and reverses the gut-slowing action of morphine. It is currently under late-stage clinical investigation for the treatment of opioid-induced constipation in patients with advanced illness. Alvimopan, a selective, competitive mu receptor antagonist with limited oral bioavailability, has been used to reduce the length of postoperative ileus. A systematic review of available data shows proof of concept but does not conclusively demonstrate the efficacy of peripherally acting mu opioid antagonists in managing opiate-related constipation (103).

OPIOID-INDUCED BLADDER DYSFUNCTION

The risk of opioid-induced bladder dysfunction (i.e., difficulty voiding or frank urinary retention) is a significant problem in postoperative patients, but the incidence has been difficult to estimate because many other factors can play a role. Two studies reported urinary retention in 3.8% and 18.1% of patients receiving opioids in the postoperative period (104,105). Urinary

Table 3. *Medications for treatment of chronic constipation.*

Agent	Formula/strength	Adult dosage	Side effects/complications
Bulk laxatives			
Methylcellulose (Citrucel)	Powder: 2 g (mix with 8 oz liquid) Tablets: 500 mg (take with 8 oz liquid)	One to 3 times daily 2 tablets up to 6 times daily	Bulk mass may predispose inactive patients to obstruction. Most common side effect is increased intestinal gas.
Polycarbophil (Fibercon)	Tablets: 625 mg	2 tablets 1 to 4 times daily	Bulk mass may predispose inactive patients to obstruction. Most common side effect is increased intestinal gas.
Psyllium (Metamucil)	Powder: 3.4 g (mix with 8 oz liquid)	1 to 4 times daily	Bulk mass may predispose inactive patients to obstruction. Most common side effect is increased intestinal gas.
Stool softeners			
Docusate calcium (Surfak)	Capsules: 240 mg	Once daily	Ineffective unless adequate fluid intake. Ineffective as sole agent in patients with decreased bowel motility. Contra-indicated with mineral oil laxatives.
Docusate sodium (Colace)	Capsules: 50 or 100 mg Liquid: 150 mg per 15 mL Syrup: 60 mg per 15 mL	50 to 300 mg	Ineffective unless adequate fluid intake. Ineffective as sole agent in patients with decreased bowel motility. Contraindicated with mineral oil laxatives.
Osmotic laxatives			
Lactulose	Liquid: 10 g per 15 mL	15 to 60 mL daily	Possible side effects include flatulence, abdominal cramps, diarrhea, or nausea or vomiting. Use with caution in diabetics.
Magnesium citrate	Liquid: 296 mL per bottle	0.5 to 1 bottle per day	Possible side effects include diarrhea and electrolyte imbalances. Rarely considered first-line therapy due to their undesirably strong and quick laxative activity. Use with caution in patients with decreased renal function. Excess magnesium can cause CNS depression, muscle weakness, and EKG changes.
Magnesium hydroxide (Milk of Magnesia)	Liquid: 400 mg per 5 mL	30 to 60 mL once daily	Possible side effects include diarrhea and electrolyte imbalances. Rarely considered first-line therapy due to their undesirably strong and quick laxative activity. Use with caution in patients with decreased renal function. Excess magnesium can cause CNS depression, muscle weakness, and EKG changes.
Polyethylene glycol 3350 (Miralax)	Powder: 17 g (mix with 8 oz liquid)	Once daily	Side effects include abdominal pain, bloating, cramping, and increased intestinal gas. More severe side effects include diarrhea and hives.
Sodium biphosphate (Phospho-Soda)	Liquid: 45 mL, 90 mL (mix with 4 oz water, then follow with 8 oz water)	20 to 45 mL daily	Use with caution in patients on sodium restricted diets. Use with caution in patients with decreased renal function.
Sorbitol	Liquid: 480 mL	30 to 150 mL daily	Side effects may include nausea, gas, diarrhea, stomach cramps, or anal irritation.
Stimulant laxatives			
Bisacodyl (Dulcolax)	Tablets: 5 mg	5 to 15 mg daily	Side effects may include stomach ache, cramping, weakness, sweating, irritation of the rectal area, diarrhea, or dizziness. Do not use in presence of nausea, vomiting, or other symptoms of bowel obstruction.

Table 3. *Continued*.

Agent	Formula/strength	Adult dosage	Side effects/complications
Cascara sagrada	Liquid: 120 mL Tablets: 325 mg	5 mL once daily 1 tablet daily	Side effects may include strong cramping in the abdomen, electrolyte imbalance (loss of potassium), loss of body fluids, and dark pigmentation in the colon, called melanosis coli. Long-term use has been linked to the development of colorectal growths (adenomas) and cancer. Interaction may occur with cardiac glycosides, such as digitalis. Do not use in presence of nausea, vomiting, or other symptoms of bowel obstruction.
Castor oil	Liquid: 60 mL	15 to 60 mL once daily	Side effects can include abdominal pain or cramping, colic, nausea, vomiting, and diarrhea. Long-term use of castor oil can lead to fluid and electrolyte loss. Do not use in presence of nausea, vomiting, or other symptoms of bowel obstruction. Contraindicated in pregnancy or during breastfeeding.
Senna (Senokot)	Tablets: 8.6 mg	2 or 4 tablets once or twice daily	Side effects may include strong cramping and abdominal pain, electrolyte imbalance (loss of potassium), loss of body fluids, nausea, rash, swelling of the fingertips, weight loss, and dark pigmentation in the colon, called melanosis coli. Long-term use has been linked to the development of colorectal growths (adenomas) and cancer. May interact with calcium channel blockers and Indocin. It has been linked to liver toxicity.
Prokinetic Agents			
Tegaserod (Zelnorm)	Tablets: 2 mg, 6 mg	2 times daily‡	In March 2007, the FDA asked Novartis to stop sales of Zelnorm in the U.S. effective immediately. The FDA's action was the result of a new analysis of 29 clinical studies of Zelnorm that showed an increased risk of heart attack, stroke, and angina (chest pain) in patients who took Zelnorm. Side effects include headache, abdominal pain, and diarrhea. Other side effects include rectal bleeding, bloody diarrhea, or new or worsening abdominal pain that may be symptoms of intestinal ischemia.

retention is much more likely to occur after epidural injection of morphine rather than intravenous or intramuscular injection (106). The mechanism of urinary retention is still not completely understood. Opioids are well known to decrease detrusor tone and the force of contraction, decrease the sensation of fullness and urge to void, and inhibit the voiding reflex. They probably do not increase sphincter tone (107). These effects are naloxone reversible. Animal and human studies suggest a significant centrally mediated effect on the brain and spinal cord, although peripheral effects at the bladder may also play a role. Rosow and colleagues (108) demonstrated that opioid-induced changes in bladder function are due, in part, to a peripheral opioid effect and can be reversed by methylnaltrexone, a peripheral opioid antagonist indicating that peripheral mechanisms may play a role.

CARDIAC EFFECTS OF OPIOIDS

The cardiac side effects of opioids are not very common. Morphine has been associated with histamine release and consequent vasodilation and hypotension (109). This adverse effect is partially blocked by H1 antagonism but completely reversed by naloxone. Parasympathetic stimulation may also contribute to bradycardia. Recently, a syndrome of QT prolongation and torsade des pointes (Tdp) has drawn some attention partially due to an increase in use of methadone for treatment of chronic pain (110,111). Mortality rate due to Tdp could be as much as 17% (112) and therefore it is prudent to monitor the EKG for presence of QT prolongation in patients receiving methadone.

Methadone can block the human ether-a-go-go-related-gene (hERG) channel causing QT prolongation and torsades de pointes ventricular tachycardia (113-

115). The incidence of tachycardia-corrected QT pro-longation (QTc) of greater than 500 milliseconds was found to be 16% among heroin addicts treated with methadone, and TdP occurred in 3.6% of that same group (116). The absolute QTc value of 500 ms has been known as a definite risk factor to develop Tdp. But, some have suggested that a QT prolongation of more than 30 ms from the baseline should be considered clinically significant, and more than 60 ms prolongation beyond baseline is a risk factor to develop Tdp (117,118). The QTc prolongation by methadone has been attributed to its (R)-enantiomer which has 50 times more analgesic potency than its (S)-enantiomer (119). Clinically significant QTc prolongation has been mostly observed in patients taking total daily doses of more than 40 mg methadone (120). But in a recent retrospective review, lower daily doses of 30 mg methadone were found to cause QTc prolongation, and Tdp was observed in patients receiving daily doses of 40–200 mg methadone. Significant correlation was observed between QTc prolongation and patients receiving methadone and CYP3A4 inhibitors like fluoxetine, clarithromycin, fluconazole, and valproate (116). The same report also identified hypokalemia and diminished liver function as other risk factors for developing QTc prolongation. Previously in separate reports, other medications like cocaine, tricyclic antidepressants, quinine, haloperidol, droperidol, chlorpromazine, and erythromycin had been implicated to cause QTc prolongation (Table 4). An updated list of medications causing Tdp-VT can be found at www.qtdrugs.org.

The serious consequence of QTc prolongation has prompted some to recommend repeated surface EKGs during the course of treatment with methadone, especially when raising the dose and adding other medications like CYP3A4 inhibitors and also when hypokalemia and diminished liver function are present (121).

Table 4. *Factors correlated with QT prolongation in methadone use.*

- CYP3A4 inhibitors (e.g. fluoxetine, clarithromycin, fluconazole and valproate)
- Hypokalemia
- Diminished liver function
- Cocaine
- Tricyclic antidepressants
- Haloperidol
- Droperidol

Adverse Effects of Specific Opioids

This section explores both common and uncommon specific complications of the administration of several medications including codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone, morphine, and fentanyl.

Codeine is commonly used in the postpartum period for pain associated with episiotomy and cesarean section. As most mothers initiate breastfeeding, the safety of codeine and its pharmacologically active metabolite, morphine, amongst breastfed infants is of primary concern. The American Academy of Pediatrics lists codeine as compatible with breastfeeding. However, Koren et al (83) published a case of a full-term, breastfed infant who died in a manner consistent with morphine overdose. An explanation proposed was that if the mother is an ultrarapid metabolizer of cytochrome P450 2D6, she produces much more morphine when taking codeine than most people do. Options to reduce the risk include discontinuing codeine after 2 – 3 days of use and being aware of symptoms of potential opioid toxicity in both mothers and newborns.

Hydrocodone/acetaminophen is one of the most commonly prescribed medications for both acute and chronic pain relief in the United States, and is effective as both an antitussive and opioid analgesic. Common adverse reactions to this medication combination include dizziness, nausea, vomiting, drowsiness, and euphoria. Respiratory depression and mood disturbance are rare. As with all opioids, hydrocodone may lead to physical and psychological dependence. Hearing loss is an infrequently recognized side effect of hydrocodone use, with only a few case reports to date. Friedman et al (122) described 12 patients with profound hearing loss attributed to hydrocodone (4 were initially unilateral); none noted relief after high dose steroids, and 7 of the 8 who underwent cochlear implantation had good early response. Ho et al (123) described the clinical characteristics of 5 patients who presented with progressive sensorineural hearing loss, suspected to be due to chronic hydrocodone/acetaminophen use. The admitted hydrocodone dose ranged from 10 to 300 mg per day. None responded to high dose steroids, and all responded to cochlear implant. The authors felt that genetic polymorphisms of the drug metabolizing enzymes CYP2D6 or CYP3D4 or associated comorbidities such as hepatitis C may predispose certain individuals to adverse reactions to the drug. It is unclear whether the hearing loss is due to the hydrocodone or the associated acetaminophen.

OROS hydromorphone is a controlled-release formulation that uses an active osmotic system to deliver consistent levels of hydromorphone over 24 hours and achieve rapid steady state concentrations. Wallace at el (124) investigated the safety and efficacy of once-daily OROS hydromorphone in patients with moderate-to-severe chronic low back pain. The study involved 209 patients randomized to receive treatment in 15 North American study centers. The most common side effects included constipation (20.9%), nausea (19.8%), vomiting (9.7%), headache (14.0%), and somnolence (14.0%). Long-acting opioids usually cause similar adverse event profiles to short-acting agents, with the most frequent effects on the gastrointestinal and nervous systems.

Oxymorphone is an opioid specific for the mu receptor and is approved to treat both acute and chronic pain. Chamberlin et al (125) described the pharmacology, safety, efficacy, and usage of oral oxymorphone for pain management. Unlike oxycodone, it does not bind the kappa opioid receptor. This medication undergoes extensive hepatic metabolism and it is contraindicated in patients with moderate to severe liver impairment. However, there is no report of significant CYP3A4, 2C9, or 2D6 drug interactions. The absence of CYP2D6 metabolism limits its potential to cause some of the more common drug interactions via the CYP450 system. The elderly can experience a 40% increase in plasma concentrations while renally impaired patients may have a 57 – 65% increase in bioavailability. Food can also increase the rate of absorption by as much as 50%, necessitating dosing either 1 hour before or 2 hours after a meal. Primary adverse side effects include nausea, vomiting, pruritus, pyrexia, and constipation. Notably, the manufacturer lists nausea and pyrexia as the most common (defined as >10%). Caution is also warranted with using oxymorphone with other CNS depressants including opioids, general anesthetics, antidepressants, phenothiazines, sedatives, and hypnotics. The manufacturer also warns of confusion, disorientation, respiratory depression, apnea, and seizures when oxymorphone is given with cimetidine. However, no cause and effect relationship is known or given for this warning. Mixed agonist/antagonist analgesics (e.g., butorphanol, buprenorphine) can also reduce the medication's efficacy and precipitate withdrawal symptoms in patients who take oxymorphone. Respiratory depression is also a concern and the medication is prescribed with caution in patients with hypoxia, hypercapnia, or decreased respiratory reserve.

Further, this medication may aggravate seizures in patients with seizure disorders, as all opioids can potentially lower the seizure threshold. Additionally, since opioids may cause sphincter of Oddi spasm, plasma amylase and lipase levels may unexpectedly increase. Caution is warranted in patients with biliary tract disease such as acute pancreatitis or cholelithiasis.

Oxycodone CR is a long-acting opioid used for the treatment of noncancer pain. Portenoy et al (126) performed an open-label, uncontrolled, prospective longitudinal investigation of outcomes associated with use of Oxycodone CR. The study provides evidence that the greatest need for dose titration occurs during the first 3 months for most patients, after which further dose escalation is minimal. During the 3 year study, the most common adverse events included constipation (15%) and nausea (12%). Other adverse events included somnolence (8%), vomiting (7%), and depression (2%). After the first 3 months, the incidence of all the common adverse events except depression declined substantially. The most serious adverse events included chest pain and accidental injury. All patients with chest pain had cardiac risk factors at the time of study entry and the accidental injuries reported were mostly fractures.

Morphine is used for the treatment of noncancer pain. Osteoarthritis is often treated with opioids as NSAIDS may cause gastrointestinal injury as well as renal compromise. The efficacy and safety of several branded sustained release morphine medications has been studied in randomized trials to be comparable to generic sustained release morphine (127). Constipation is one of the primary reasons for adverse event related patient withdrawal in this study.

Fentanyl is also used for the treatment of chronic low back pain. The delivery systems include transdermal, buccal tablet, and oral transmucosal preparations. Allan et al (128) studied the use of transdermal fentanyl (TDF) in strong opioid naïve patients with chronic low back pain in an open, randomized, parallel group multicenter study. This study looked at the efficacy and safety of TDF and sustained release morphine (SRM) in strong opioid naïve patients with chronic low back pain. Data from 680 patients studied over 13 months showed similar pain relief with both medications but TDF caused significantly less constipation. Another study by Portenoy et al (129) studied the fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain with a randomized, placebo-controlled study.

FBT is a new formulation of fentanyl that enhances transbuccal drug delivery via an effervescent reaction. Currently it is FDA approved for cancer related breakthrough pain. Adverse events were reported in 65% of patients including nausea (19%), dizziness (13%), somnolence (9%), dysgeusia (8%), vomiting (6%), and dry mouth (5%). Two patients experienced serious adverse events during the study including diabetic gastroparesis and accidental overdose resulting in loss of consciousness. This patient took 4 of the 600 mcg tablets without explanation. He fully recovered after resuscitation with oxygen and admission to the hospital. This is an untoward opioid-related effect, which may make this medication seem less attractive for breakthrough back pain. The study did show FBT is generally well tolerated at doses of 100 – 800 mcg and provides evidence that a rapid-onset opioid is useful for pain not associated with cancer.

Discussion

Adverse events related to the opioids discussed above appear similar except for a few exceptions. In general, they appear to fall into 2 broad categories: nonlife-threatening and life-threatening. Hydrocodone may cause sensorineural hearing loss due to possible genetic polymorphisms. Constipation and nausea are the most common adverse effects and also lead to dropouts in controlled trials. Both constipation and nausea occurred more often with opioid therapy compared to treatment with tricyclic antidepressants in the only study that compared these 2 treatments with placebo in postherpetic neuralgia (130). Dellemijn et al (131) reported high incidence of sweating, anorexia, and clouded vision. Their study also assessed the severity of adverse effects and found that the mean intensity of adverse effects, particularly that of sedation, decreased gradually over 2 – 3 months. Tolerance may not develop to the constipating effects of opioids, and so constipation should be treated early and effectively. Two RCTs on oral opioids (132,133) reported withdrawal symptoms that occurred in 1 – 2% of patients. After the treatment period, drug craving was reported by 8.7% of patients on morphine compared with 4.3%

on placebo (134). The Cochrane review of opioids for neuropathic pain (135) reported a majority of adverse events and withdrawals from 8 intermediate term placebo controlled trials (130,136-141). Analysis of 4 studies reviewed by the authors of the Cochrane review (136,137,139,141) revealed that 23 (11%) of 212 patients withdrew because of adverse events during opioid therapy versus 9 (4%) of 202 receiving placebo. Another study (142) reported adverse events on a VAS, precluding determination of the numbers of affected participants. The most common adverse events were nausea (33% opioid versus 9% control) and constipation (33% opioid versus 10% control), followed by drowsiness (29% opioid versus 6% control), and vomiting (15% opioid versus 3% control).

With all opioids, respiratory depression and death are the most feared complications. From 1979 to 1990, unintentional drug poisoning death rates were on average 5.3% per year; however, from 1990 to 2002, the rate increased to 18.1% per year. In that same time period, the number of opioid analgesic poisonings on death certificates increased 91.2%, while heroin deaths increased only 12.4% and cocaine deaths 22.8%. The increase in deaths generally matched the increase in sales for each type of opioid.

Drug deaths from opioids are a serious and increasing issue. Effective patient compliance with appropriate medical treatment programs are needed to prevent rare but life-threatening adverse events.

Conclusion

There is evidence that opioid medications can be effective in treating a variety of chronic pain conditions but, like most pharmaceutical based therapies, their use can be potentially accompanied by side effects and complications. Despite the rise in serious adverse events involving the use of opioids, including death, these medications continue to be widely prescribed in the majority of patients suffering from chronic pain. Proper prescribing practices as well as physician and patient education can help manage tolerance issues, adverse events, as well as common and uncommon side effects.

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