Palliative Care Review

Opioid Therapy in the Seriously Ill: Managing Opioid Side Effects

The goal of long-term opioid treatment is to provide clinically meaningful pain relief with tolerable side effects and overall benefit to quality of life. This presentation is about best practices for minimizing the risks associated with opioid side effects during long-term treatment.

Persistent and troubling side effects occur in about one-third of patients during long-term therapy. They are highly diverse, and variation is noted across patients, across drugs in the same patient, and over time. Overall, the most common side effects are gastrointestinal and neurological.

Opioid-Induced Nausea

Opioids cause an array of upper GI symptoms, including nausea, pyrosis and early satiety. The mechanisms are presumably both central and peripheral. Nausea may occur through direct activation of brainstem receptors mediated by multiple opioid receptor subtypes, sensitization of the labrynthine-vestibular system, gastroparesis and slowed peristalsis, or reflux from a lax GE sphincter. Management of nausea may involve a switch to an alternative opioid (opioid rotation) or various non-pharmacologic interventions, such as acupuncture, cognitive therapy or dietary changes. In the absence of data that define the most effective approach, the clinician usually selects from among a group of first-line anti-emetics.

These include anti-dopaminergic drugs (e.g., metoclopramide, proclorperazine or haloperidol), serotonin receptor antagonists (e.g., ondansetron or granisetron), or atypical antipsychotic agents (e.g., olanzapine). Alternatively, pharmacotherapy can be initiated by targeting the mechanism suggested by symptoms. Vertigo suggests sensitization of labrynthine-vestibular system, which may be treated with an antihistamine or anticholinergic drug. Meclizine often is tried. Early satiety suggests gastroparesis, which may be addressed by a prokinetic drug such as metoclopramide.

Pyrosis suggests reflux from a lax GE sphincter, and may be treated with a PPI or H2 blocker.

Opioid-Induced Constipation

The prevalence of constipation in the medically ill is inexact because multiple causes are often present. Estimates vary from 15% to 90%. The mechanisms of constipation include both central effects mediated by multiple brainstem receptors and peripheral effects mediated by μ and other receptors in the gut wall.

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The peripheral effects predominate. The impact on the gut includes increased non-propulsive motility, decreased peristalsis, and decreased secretions.

The management of opioid-induced constipation involves the treatment of contributing factors, rotation at times (the transdermal route is believed to be less constipating than the oral route), non-pharmacologic interventions (e.g., improved hydration and dietary changes), and laxative therapy. The routine use of laxatives is generally recommended, and drug selection is usually based on conventional practice, availability, and cost. There is no data on dose finding, combination therapy, or laxative rotation. Conventional first-line therapies include bulk laxatives (fiber and others), which should not be given in debilitated or dehydrated patients, and osmotic (e.g., lactulose and polyethylene glycol) and stimulant (e.g., senna) laxative.

There are new therapies now available for opioid-induced constipation. These include 1) probiotics; 2) peripherally-acting μ opioid receptor antagonists (methylnaltrexone [Relistor®], naloxegol [Movantik®], and oral naloxone, alone or in an opioid combination drug); 3) chloride channel stimulants (linaclotide [Linzess®], which acts via agonism at guanylate cyclase C; 4) lubiprostone (Amitiza®), which acts via activation of a prostaglandin receptor; and 5) prokinetics like metoclopramide. In development are 5-HT4 receptor modulators, guanylate cyclase C agonists, and bile acid transporter inhibitors.

Opioid-Induced Somnolence/Mental Clouding

One study in cancer patients suggests that as many as one-third of medically ill patients receiving chronic opioid therapy will experience persistent cognitive dysfunction. Somnolence and mental clouding are part of a spectrum, which may include problems with cognition, attention, mood, or perception. Any or a combination of these effects may occur in patterns that are highly variable across individuals, drugs, and time.

Opioid-induced somnolence/mental clouding often occurs transiently after dosing is initiated or increased. Acute management may involve treatment of contributing factors, opioid dose reduction and possibly rotation, and non-pharmacologic interventions such as cognitive-behavioral strategies. For persistent problems, drug therapy sometimes is considered. Psychostimulants have been used for many years. Methylphenidate is most studied and has yielded positive results in randomized trials. Modafinil (Provigil®) is supported by very limited data, but may be better tolerated. One open-label trial also suggested that somnolence/mental clouding may be ameliorated by using cholinesterase inhibitors, such as donepezil (Aricept®).

Opioid-Induced Neuroendocrine Effects

Opioids inhibit GnRH, LHRH, FSH and LH and produce both hypogonadism and hyperprolactinemia. Potential effects include sexual dysfunction, infertility, galactorrhea, fatigue, depressed mood, hot flashes, and night sweats. Worsening of osteoporosis or sarcopenia also is possible. The risk-to-benefit of treatment depends on context, and clinicians should assess patients for the symptoms associated with hypogonadism. If these are present in a male, and the clinical situation is such that replacement therapy would be initiated, testosterone should be measured. If low, treatment may help the symptoms. The decision to measure estradiol in the symptomatic pre-menopausal woman is similar. If low, a trial of estrogen replacement may be considered.

Opioid-Induced Itch

Although the prevalence of itch is probably low—2%-10%—opioid therapy may worsen itch from other factors, such as dermatological disorders common in chronic illness, renal failure, cholestasis, drug effects, or paraneoplastic disorder. To manage itch, the clinician should focus on skin care, treatment of contributing factors, and the potential value of opioid rotation. Opioid-related itch does respond to low-dose opioid antagonist therapy, e.g., naltrexone, but this is difficult to use when the opioid is being taken for pain. Other drugs may be tried based on limited evidence and use

in other forms of itch. These include H1 antagonists (e.g., diphenhydramine), H2 antagonists (e.g., ranitidine), 5-HT3 antagonists (e.g., ondansetron), an SSRI antidepressant (e.g., paroxetine or sertraline), an atypical antidepressant (e.g., mirtazapine), and a gabapentinoid (e.g., gabapentin or pregabalin). Other treatment trials are used specifically for cholestatic itch (e.g., rifampicin).

Opioid-Induced Urinary Retention

The prevalence of urinary retention caused by an opioid is unknown and the mechanisms are poorly understood. They presumably involve decreased detrusor muscle tone and contraction and impairment of the voiding reflex. Management may start with consideration of opioid rotation. Like itch, opioid antagonists work but are difficult to use. Empirically, alpha 1 adrenergic blockers, e.g., tamsulosin, often are tried.

Opioid-Induced Sleep-Disordered Breathing

Opioid therapy is associated with an increased risk of symptoms related to sleep apnea syndrome. Both an exacerbation of previously diagnosed disorders and precipitation of new syndrome occur in dose-dependent fashion. Limited data suggest that this risk is more likely when methadone is used or when benzodiazepines are co-administered with an opioid. Management includes efforts to treat the risk factors for sleep apnea and avoidance of methadone and benzodiazepine co-therapy. Standard treatment of sleep apnea also is employed, at times guided by the results of polysomnography.

Opioid-Induced QTc Prolongation

QTc prolongation is a dose-dependent effect of methadone. Patients may be predisposed by the use of other drugs with similar effects, intrinsic heart disease, or hypokalemia. In most cases, the decision to select methadone for a trial involves a check of a baseline ECG. With rare exceptions, methadone should not be prescribed if the QTc is >500 ms. An alternative drug or interventions to manage concomitant risk factors should be considered if the QTc is >450 ms and <500 ms. If methadone is prescribed, it is reasonable to repeat the ECG after 2 weeks or after increasing the dose to above 100 mg per day.

Opioid-Induced Hyperalgesia (OIH)

OIH is an increase in sensitivity to noxious stimuli caused by exposure to the opioid. It can be readily demonstrated in animal models and has a complex biology involving neuroplastic changes in the peripheral and central nervous systems. The potential for OIH in humans has been confirmed in volunteer studies and some short-term clinical studies. Anecdotes suggest that OIH may occur in some patients receiving chronic therapy, but the salience of this phenomenon is controversial. It is reasonable for clinicians to consider OIH when analgesia wanes in the absence of disease progression, particularly if unexplained pain or sensitivity to stimuli are occurring. If OIH is suspected, interventions include strategies to lower the dose, opioid rotation, and empirical trials of anticonvulsants, sedative-hypnotics, or NMDA antagonists.

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