



Adverse Effects of Opioids CME Module

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Adverse Effects of Opioids CME Module

Course Description and Learning Objectives

Course Description: Opioids are commonly prescribed for patients with serious illnesses such as advanced cancer or organ failure to manage symptoms such as pain or dyspnea. Unfortunately, adverse effects from opioids are common and it is estimated that 10-30% of patients treated with opioids do not have successful outcomes because of either excessive adverse effects, inadequate analgesia, or a combination of both. The management of opioid adverse effects remains to be challenging for clinicians considering the paucity of robust medical studies and management guidelines to define best practices. In this module, users can attain 1.0 hours of CME credit after successful completion of the following:

A. Content review of ten *Fast Facts and Concepts* covering the following topics:

- a. Opioid induced nausea.
- b. Opioid induced pruritus
- c. Neuroexcitatory effects of opioids (part 1 and 2)
- d. Opioid allergies
- e. Hyperalgesia from opioids
- f. Opioid androgen syndrome
- g. Urinary retention from opioids
- h. Opioid induced constipation (part 1 and 2)

B. Score of 70% or higher on a 10 question quiz covering this content

C. Completion of a course evaluation.

Learning Objectives: After completion of this course, the learner will be able to:

1. Describe diagnostic and treatment approaches to 8 common opioid adverse effects.
2. Differentiate two different types of reactions commonly described as opioids allergies.
3. Describe a comprehensive treatment approach to the prevention and management of opioid constipation.

FAST FACTS AND CONCEPTS #25

OPIOIDS AND NAUSEA

David E Weissman MD

Background Why do patients get nauseated and vomit after receiving an opioid? Commonly described as an “allergy”, opioid-induced nausea/vomiting is not an allergic reaction. In fact, rather than indicating a pathologic reaction, nausea indicates normal functioning of the brain. Opioid-induced nausea occurs through the following mechanisms:

- At the base of the 4th ventricle lies the chemoreceptor trigger zone (CTZ), a “sampling port”, to detect substances that do not belong in the blood. Adjacent to the CTZ lies the medullary vomiting center which controls the complex muscular sequence of vomiting. When the CTZ detects a noxious chemical in the blood, a signal is sent to the VC and the vomiting reflex is initiated. Of note, this is the same mechanism when patients vomit after receiving chemotherapy.
- Opioids can directly stimulate the vestibular apparatus—patients note a spinning sensation with their nausea.
- Opioids cause constipation which can lead to nausea via stimulation of afferent cholinergic pathways.

Do all opioids produce the same degree of nausea? There is little research data on this topic. In clinical practice, morphine and codeine are often mentioned as the worst offenders. Some clinical studies along with preclinical data in rats suggest that the transdermal fentanyl patch may have less nausea and constipation than morphine.

Why are some patients more sensitive to the emetic effects of opioids than others? Unknown

What is the natural history of opioid-induced nausea? Most patients develop tolerance to the emetic effects, so that within 3-7 days, at a constant opioid dose, the emetic effect will abate.

What are management approaches?

- Dose adjustment—if good pain relief is achieved but associated with nausea, it may be possible to lower the opioid dose, still retain good analgesia, but eliminate the nausea.
- Switching opioids—there is variability in emetic reaction to different opioids. Note: since tolerance to nausea develops, one never knows if a reduction in nausea is from the change of drug or tolerance.
- Anti-emetics—Whenever possible, choose a drug directed at the most likely cause of nausea (see *Fast Fact* # 5). There are little published data to guide physicians in specific choice of anti-emetic for opioid-induced nausea.
- Start with low-cost dopamine antagonists (e.g. prochlorperazine, haloperidol, or metoclopramide) or anti-cholinergics (e.g. scopolamine);
- Anti-histamines may be helpful for patients who note a spinning sensation.
- 5HT₃ antagonists (e.g. ondansetron) can be used for more refractory cases. Two multi-center randomized trials have examined control of emesis associated with opioids not used for anesthesia. In one, 16 mg of ondansetron was more effective than 8 mg or placebo. In the other trial, stopped early due to lack of patient accrual, 24 mg ondansetron was no better than placebo or metoclopramide.
- Non-pharmacological approaches: there is little evidence to support non-pharmacological treatments for nausea outside of chemotherapy associated nausea; suggested approaches include acupressure and behavioral treatments.

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FAST FACTS AND CONCEPTS #37**PRURITUS****Charles von Gunten MD and Frank Ferris MD****Background**

Pruritus (itching) is a common and often distressing symptom near the end of life. The itch sensation may arise from stimulation of the skin itch receptor via unmyelinated C fibers, or itch may arise as a central phenomenon without skin involvement (e.g. opioid induced pruritus). Although histamine causes pruritus, many patients with pruritus show no signs of histamine release. Besides histamine, serotonin, prostaglandins, kinins, proteases and physical stimuli have all been implicated as mediators of pruritus.

Common Causes

- Dermatological (dryness, wetness, irritation, eczema, psoriasis)
- Metabolic (hepatic failure, renal failure, hypothyroidism)
- Hematologic (iron deficiency, polycythemia, thrombocytosis, leukemia, lymphoma)
- Drugs (opioids, aspirin, drug reactions)
- Infectious (scabies, lice, candida)
- Allergy (urticaria, contact dermatitis, drug reactions)
- Psychogenic

Management Management of pruritus involves eliminating the cause when possible. Symptomatic strategies include:

- **Moisturizers:** Dryness (xerosis) is very common and may exacerbate other causes. The mainstay of treatment is skin hydration. Note: Most OTC preparations only have small amounts of moisturizer—they are mostly water. Serious dryness requires emollients and moisturizers (such as petroleum jelly) that patients find oily or greasy. Nevertheless, they may be applied after bathing, over damp skin, with a superficial covering.
- **Cooling agents** (e.g. Calamine and/or Menthol in aqueous cream, 0.5%-2%) are mildly antipruritic. They may act as a counterirritant or anesthetic. A more direct way to anesthetize the skin is with the eutectic mixture of local anesthetics lidocaine and prilocaine (EMLA cream).
- **Antihistamines** may be helpful in relieving itch when associated with histamine release. Morphine causes non-immune mediated histamine release from mast cells. Although there is not much supporting research, many report benefits of combining H1 and H2 receptor subtype antihistamines. These may have central effects as well as peripheral antihistaminergic effects. Doxepin (10-30 mg PO at bedtime), a tricyclic antidepressant, is a very potent antihistamine and may help in more refractory cases.
- **Topical steroids** may be helpful in the presence of skin inflammation. These are best applied in ointment rather than cream formulations to alleviate dryness. Systemic steroids have been used in refractory cases.
- **Newer Generation Antidepressants** There are accounts of paroxetine being used successfully to treat pruritus associated with a paraneoplastic process, opioids or cholestasis. Also mirtazapine has been shown to improve pruritus at low doses of 15 mg/day in small case reports; this is likely due to its known antihistamine effects and its blockage of post-synaptic 5HT₂ and 5HT₃ receptors.
- **Opioid Antagonists** Low dose, continuous infusions of IV naloxone has the largest body of data supporting its use in adult and pediatric patients with opioid induced pruritus. There are smaller studies suggest oral naloxone may have less favorable results. Small studies suggest a potential role for methylnaltrexone in opioid induced pruritus.
- **Other:** An old-fashioned but effective remedy is immersion in an oatmeal bath (e.g. Aveeno). More recent pharmacological treatments include cholestyramine for cholestatic pruritus; ondansetron for patients with cholestatic, opioid-induced, or renally-induced pruritus. Since the

pain sensing neurological system seems to be responsible for pruritis, agents like gabapentin have also been reported to be helpful.

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FAST FACTS AND CONCEPTS #57
NEUROEXCITATORY EFFECTS OF OPIOIDS: PATIENT ASSESSMENT

Robin K Wilson MD, PhD, David E Weissman MD

Background Everyone recognizes the common opioid side effects: constipation, nausea, pruritis, and urinary retention. Less well appreciated are the neuroexcitatory effects, commonly seen among patients on chronic opioids. Among these, myoclonus is typically the herald symptom. This *Fast Fact* will discuss risk factors and patient assessment of the neuroexcitatory opioid side effects, particularly myoclonus; *Fast Fact* #58 will discuss treatment options.

Physiology and Risk Factors Myoclonus can occur in patients on chronic therapy with most opioids including morphine, hydromorphone, fentanyl, meperidine, and sufentanil. Higher doses more frequently result in myoclonus, but the dose relationship is variable. Myoclonus can occur with all routes of administration. Current research implicates the 3-glucuronide opioid metabolites as one likely cause of neuroexcitatory side effects with some suggestion that symptoms may not develop until a neurotoxic threshold is surpassed, although current understanding is limited. Co-morbid factors including renal failure, electrolyte disturbances, and dehydration can also contribute to myoclonus development.

Clinical Scenarios Myoclonus – the uncontrollable twitching and jerking of muscles or muscle groups – usually occurs in the extremities, starting with only an occasional random jerking movement. A patient's spouse may be the first to recognize this symptom. With continued administration, the jerking may increase in frequency; at the extreme, there is constant jerking of random muscle groups in all extremities. As myoclonus worsens, patients may develop other neuroexcitatory signs: hyperalgesia (increased sensitivity to noxious stimuli), delirium with hallucinations, and eventually grand mal seizures. Well meaning clinicians may misinterpret the hyperalgesia as increasing pain, leading to a vicious cycle of increasing dose, increasing hyperalgesia, increasing dose, worsening delirium, and finally seizures. After identifying a patient with possible opioid toxicity, the clinician should complete a physical examination and chart review.

Physical Examination

- Assess frequency of myoclonic jerks. Stand at the bedside and observe a patient for 30-60 seconds. Watch for and count the number of uncontrolled jerking movements.
- Determine if there is evidence of a new or worsening delirium. Complete a bedside mini-mental assessment.
- Assess hydration status.
- Estimate prognosis: hours, days, weeks, months or years? A longer prognosis demands a more definitive change in treatment.

Chart review

- Review the recent opioid analgesic history. What is the current drug and dose? How has the dose changed over the past few days and weeks?
- Review the medication list for potentially exacerbating drugs. (e.g. haloperidol, phenothiazines)
- Review recent laboratory studies if available. Check renal and liver function, and for low magnesium, glucose or sodium.

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FAST FACTS AND CONCEPTS #58

NEUROEXCITATORY EFFECTS OF OPIOIDS: TREATMENT

Robin K Wilson PhD and David E Weissman MD

Background *Fast Fact #57* reviewed the pharmacology and patient assessment aspects of opioid induced neurotoxicity, notably myoclonus. This *Fast Fact* discusses treatment.

General Approach Decisions about the most appropriate treatment approach need to take into account features of the physical examination (the frequency and intensity of symptoms, hydration status, and estimated prognosis) and information from the medical record (temporal pattern of opioid use and dose escalation, other medications, the presence of electrolyte abnormalities and major organ dysfunction). Whenever medically appropriate, easily treatable causes or exacerbating factors should be corrected (e.g. correct hypomagnesemia).

Treatment Strategies The range of options for management of pain and direct opioid neurotoxic effects divides into strategies to treat the myoclonus and strategies to reduce the offending opioid.

1. **Observation.** Mild myoclonus may trouble family members more than the patient. If the patient is satisfied with current therapy, explaining the cause/progression of symptoms may be all that is necessary.
2. **Opioid dose reduction.** Seeing that some observational studies suggest that neuroexcitatory symptoms from opioid may not develop until a certain neuroexcitatory threshold of 3-glucoronide metabolites is surpassed, myoclonus may resolve over a few days with a decrease in opioid dose. However, make sure you are not reducing the opioid dose solely to control myoclonus at the expense of good pain control.
3. **Rotate to a dissimilar opioid.** Rotating to a lower dosage of a structurally dissimilar opioid will often reduce myoclonus and other neuroexcitatory effects within 24 hours, while achieving comparable pain control (*Fast Fact #175* discusses opioid structural classes.) Rotation is especially important in patients with opioid-induced hyperalgesia. As a general rule, decrease the morphine equianalgesic dose by at least 50% when switching to a new medication (see *Fast Fact # 36*). For patients on very high doses, rotate to a new opioid at 20-25% of the morphine equianalgesic dose. Historically, methadone and fentanyl have been considered to be better opioids to rotate to as they have no active metabolites (which are implicated in the neuroexcitatory effects of other opioids). This observation is empiric, and has not been evaluated in clinical trials; clinicians should be cautious of using methadone without familiarity with its pharmacology (see *Fast Facts #75, 86*).
4. **Adjuvant and other analgesic therapy.** Adjuvant analgesics (e.g. anticonvulsants, antidepressants, corticosteroids) or non-drug therapies (e.g. acupuncture, TENS, heat, cold) may allow for opioid reduction, with preservation of analgesia.
5. **Benzodiazepines and other drugs to reduce myoclonus.** The addition of a benzodiazepine can reduce myoclonus without alteration of the opioid dose, although increasing sedation may be an unwanted side effect. Start with clonazepam 0.5-1 mg at night or 0.5 mg 2-3 times a day. Alternative agents include lorazepam orally or sublingually, starting at 1-2 mg q8 hours. A continuous infusion of midazolam is an expensive but effective option. Alternatives to benzodiazepines include baclofen, gabapentin, and nifedipine. Start baclofen at 5 mg 3 times a day and increase as needed/tolerated to 20 mg 3 times a day. Start gabapentin at 100 mg 3 times a day and increase as needed to 900-3600 mg total a day. Nifedipine (10 mg 3 times a day) can also be used.

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FAST FACTS AND CONCEPTS #142
OPIOID-INDUCED HYPERALGESIA**Winifred G Teuteberg MD**

Background Opioid-induced hyperalgesia is a clinical phenomenon, characterized by increasing in pain in patients who are receiving increasing doses of opioids. This *Fast Fact* reviews the clinical findings and treatment options. See also *Fast Fact* #215 on opioid poorly-responsive pain.

Clinical features of opioid hyperalgesia:

- *History*
 - Increasing sensitivity to pain stimuli (hyperalgesia).
 - Worsening pain despite increasing doses of opioids.
 - Pain that becomes more diffuse, extending beyond the distribution of pre-existing pain.
 - Can occur at any dose of opioid, but more commonly with high parenteral doses of morphine or hydromorphone and/or in the setting of renal failure.
- *Physical Examination*
 - Pain elicited from ordinarily non-painful stimuli, such as stroking skin with cotton (*allodynia*)
 - Presence of other opioid hyperexcitability effects: myoclonus, delirium or seizures (see *Fast Facts* #57,58).

Proposed mechanisms:

- Toxic effect of opioid metabolites (e.g. morphine-3-glucuronide or hydromorphone-3-glucuronide).
- Central sensitization as a result of opioid-related activation of N-methyl-D-aspartate (NMDA) receptors in the central nervous system.
- Increase in spinal dynorphin activity.
- Enhanced descending facilitation from the rostral ventromedial medulla.
- Activation of intracellular protein kinase C.

Therapies:

- Reduce or discontinue the current opioid.
- Change opioid to one with less risk of neurotoxic effects: fentanyl or methadone (see *Fast Fact* #75).
- Add an infusion of a non-opioid NMDA receptor antagonist such as ketamine (see *Fast Fact* #132).
- Add a non-opioid adjuvant such as gabapentin, baclofen, acetaminophen or an NSAID.
- Initiate epidural, intrathecal, regional or local anesthesia and taper/discontinue systemic opioids.
- Increase hydration if clinically appropriate.

Conclusion Opioids can lead to a paradoxical increase in pain. Opioid-induced hyperalgesia should be considered in any patient with increasing pain that is not responding to increasing opioids. Referral to pain/palliative care professionals is appropriate to help develop a management strategy.

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FAST FACTS AND CONCEPTS #175
OPIOID ALLERGIC REACTIONS

Hunter E Woodall MD, Asriani Chiu MD, and David E Weissman MD

Background Patient reports of opioid “allergies” are common, most often due to symptoms of nausea, vomiting, itching, hypotension, or constipation. This *Fast Fact* will review signs, symptoms, and management options of opioid allergies and pseudo-allergies.

Pathophysiology Allergies can be defined as an *exaggerated immune reaction to an antigen*. There are different types of allergic, or hypersensitivity, reactions (immediate, cytotoxic, immune complex, or delayed), but the common feature is that all such reactions are *mediated by the immune system*. In contrast, the vast majority of opioid side effects are not immune related. Opioid side effects can be divided into three categories: those that have no element of an immune reaction, those that mimic an immune reaction, and those that are immune mediated.

Side effects with no immune mechanism: these include nausea/vomiting, constipation, sedation, delirium, respiratory depression, and urinary retention.

Side effects that mimic immune reactions: common signs/symptoms include mild itching, urticaria, bronchospasm, or hypotension. **Note:** if all these occur soon after an opioid dose, and the patient appears acutely ill, this may represent an anaphylactoid reaction (see below). For most patients, these symptoms are mild and self-limited. The etiology most commonly involves direct mast cell degranulation with histamine release, unrelated to a true immune-mediated reaction. Such reactions to opioids are usually idiosyncratic and may or may not recur with re-challenge of the same opioid; they are not a contraindication to continued opioid use, since an alternative opioid may be well tolerated. Hypotension can also occur due to arterial and venous vasodilation, thus, hypotension is more common in a volume depleted patient. Opioids can also have negative inotropic effects and induce a vagally-mediated bradycardia leading to hypotension – again, not a true allergic reaction.

Immune mediated reactions:

- **Allergic dermatitis** in response to opioids has been described. It is characterized as erythroderma, scarlatina, eczema, or exudative vesicular eruptions; these may represent a Type IV (delayed) hypersensitivity reaction. Patients can undergo diagnostic patch testing for confirmation.
- **Anaphylaxis/Anaphylactoid Reactions.** Anaphylaxis is a systemic IgE mediated reaction resulting in the immediate release of potent mediators; anaphylactoid reactions are clinically the same, but not IgE mediated. Early symptoms include nasal congestion, flushing, pruritus, angioedema; if the process worsens, patients can develop nausea, diarrhea, urinary urgency, bronchospasm, hypotension, and death. Opioids can lead to an anaphylactoid reaction, but such events are very rare.

Management True allergic reactions appear to be rare. If you suspect an immune-mediated skin rash you should consult a dermatologist or allergist to establish a definitive diagnosis and determine the need for desensitization or appropriate alternatives. Anaphylactoid reactions require emergent management with epinephrine and histamine blockers. For milder histamine-related symptoms, common practice is to rotate to an opioid in a different pharmacologic class (see below) along with use of anti-histamines or steroids. Anecdotal reports suggest that methadone and fentanyl cause fewer instances of itching.

Opioid Class	Drugs
Phenanthrenes	morphine; codeine; hydrocodone; oxycodone; oxymorphone; hydromorphone; levorphanol.
Phenylpiperadines	fentanyl; meperidine; sufentanil; remifentanyl
Diphenylheptanes	methadone; propoxyphene

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FAST FACTS AND CONCEPTS #284
OPIOID-INDUCED ANDROGEN DEFICIENCY

Sara Healy MD, Amber Hartman PharmD, Jillian Gustin MD

Introduction Opioid-induced androgen deficiency (OPIAD) is a common, yet under-diagnosed consequence of prolonged opioid therapy; this *Fast Fact* will review OPIAD.

Demographics Biochemical and clinical hypogonadism have been observed in patients receiving intrathecal, transdermal, and sustained-release opioids [1]. Hypothalamic-pituitary-gonadal axis (HPA) suppression has been demonstrated within hours of methadone exposure, but risk appears to increase with increasing doses for extended durations. Some studies have found a dose-response effect with increased testosterone suppression at higher opioid doses [2, 3]. As many as 50-100% of patients receiving daily opioid doses equivalent to 100-200 mg oral morphine for more than one month will have some degree of OPIAD [4, 5]. In one observational study, 89% had biochemical evidence of hypogonadism, and 87% reported severe erectile dysfunction or diminished libido after starting opioids despite normal erectile dysfunction before using opioids [6]. One study found that men may have higher prevalence of hypogonadism than women [7]. Teenage patients have not been studied.

Physiology OPIAD results primarily from suppression of the HPA and is a form of secondary (hypogonadotropic) hypogonadism. Opioids inhibit secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus, leading to decreased sex hormone secretion [4, 5]. Opioids may also decrease adrenal androgen synthesis and directly inhibit testicular testosterone synthesis [4, 6].

Symptoms and Signs Hypogonadism can cause decreased libido, erectile dysfunction, decreased fertility, fatigue, irregular menstrual cycle, weight gain, depression, osteoporosis, or hot flashes [4, 5]. Physical findings include decreased facial and body hair, reduced muscle mass, increased body fat, and small or shrinking testes [5, 8].

Diagnosis Because the incidence is high and data about dosing thresholds is unknown, OPIAD should be considered in any patient on opioids with signs or symptoms of hypogonadism [5]. Measurable improvements in depressed mood and energy have been documented after 12 weeks of testosterone therapy [9, 10]. However, many of the symptoms of OPIAD are also caused by advanced illnesses, making it difficult to attribute them appropriately. There are no data to guide decision-making about OPIAD in advanced illness. It is reasonable to limit clinical evaluation of OPIAD to patients whose prognoses are judged to be sufficiently long enough to benefit from OPIAD treatment [9].

- **Men:** Test the total serum testosterone drawn at 8 am (normal range in most laboratories is 300 to 800 ng/dl). If abnormal or borderline, repeat the test at 8 am once more (as levels may fluctuate day to day). Obesity and older age reduce hormone binding proteins and can interfere with results. Additional confirmatory testing can include free testosterone, serum hormone binding globulin, LH, FSH, and prolactin. [4, 8] Men with diagnostic uncertainty should be seen by an endocrinologist.
- **Women:** There are currently no established diagnostic criteria in women. Women with symptoms of OPIAD should be referred to an endocrinologist.

Management There is no direct evidence as to whether OPIAD improves with opioid rotation or dose reduction (short of cessation). Since improvement of other opioid side effects vary among patients with opioid rotation or dose reduction, these may be attempted [2]. If this is unsuccessful, hormone replacement may be considered.

Testosterone Replacement Cessation of opioid therapy can lead to recovery of normal serum testosterone levels within days of discontinuation [5]. Testosterone replacement therapy for women is not FDA approved, but may be appropriate for some patients [5, 11]. Management of OPIAD in women who need to remain on opioid therapy is not established and is best managed by an endocrinologist.

For men who need to remain on opioid therapy, testosterone replacement is the mainstay. It may be administered by intramuscular injections, buccal tablets, or transdermal patches, gels, or creams [4, 5]. Doses and frequencies vary by route and dosage form.

Precautions: Testosterone treatment is not recommended in patients with breast or prostate cancer, a palpable prostate nodule, or PSA greater than 4 ng/ml or greater than 3 ng/ml in patients at high risk for prostate cancer [8]. Adverse Effects: Increased hemoglobin and hematocrit, decreased HDL, hypoglycemia, hypercalcemia, edema, acne, gynecomastia, headache, mood swings, BPH. Recent retrospective studies [12, 13] have found an association between testosterone therapy and increased mortality, MI, and stroke. These studies are controversial and prospective data is needed. The FDA also recently added a warning about potential risk of venous blood clots unrelated to polycythemia [14].

Monitoring: Effects of testosterone therapy typically occur within the first three to six months of treatment [9]. Therefore, serum testosterone levels should be measured 3-6 months after starting testosterone therapy and then annually. Measure the level midway between injections in men receiving IM injections. The total testosterone level should be in the mid-normal range, 400-700 ng/dL [8]. Practice guidelines recommend men age 40 and older who have baseline PSA > 0.6 ng/ml should have DRE and PSA measurement before initiating therapy, at 3-6 months, then in accordance with normal screening guidelines. Urological consultation is recommended if there is an increase in serum PSA concentration > 1.4 ng/ml within any 12-month period of testosterone treatment [8]. Hematocrit should be measured before starting therapy, after three to six months, and then yearly to screen for erythrocytosis [8].

Conclusion OPIAD is an under-diagnosed consequence of prolonged opioid therapy, and untreated patients may have reduced quality of life [5]. Men who are diagnosed with OPIAD may be treated with testosterone therapy with appropriate monitoring. Diagnosis and treatment of OPIAD in women is not well established and should be referred to an endocrinologist.

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FAST FACTS AND CONCEPTS #287
DRUG-INDUCED ACUTE URINARY RETENTION**Winifred Teuteberg MD**

Background A variety of medications used for symptom management can cause urinary retention. This *Fast Fact* will review which drugs contribute to acute urinary retention and offer management strategies.

Clinical features and evaluation Acute urinary retention is defined as sudden onset of impaired bladder emptying which results in a post-void residual (PVR) urine volume greater than 50 mL. This can be uncomfortable, impair quality of life, and can cause kidney injury (1). Signs and symptoms of acute urinary retention include bladder/suprapubic pain and tenderness, lack of voiding, and new onset overflow incontinence. The presence of acute urinary retention should be assessed in older patients who develop delirium, particularly if they have underlying dementia. Medications are a common cause of urinary retention. Common non-drug etiologies include benign prostatic hypertrophy, malignancy (e.g., epidural spinal cord compression), neurogenic bladder, and fecal impaction. There are little data on the incidence of urinary retention in palliative care. However, a small observational study showed that 15% of patients admitted to a large palliative care program had urinary retention (2). In contrast to acute urinary retention, chronic urinary retention is difficult to define as urine volumes vary greatly between patients. Chronic urinary retention is often the result of chronic neurologic condition or benign prostatic hypertrophy. A key difference between acute and chronic urinary retention is that chronic urinary retention is often asymptomatic and rarely painful due to gradual distention of the bladder over time. Common symptoms of chronic urinary retention include frequency, hesitancy and decreased force of urine stream (3). This article pertains to acute urinary retention due to medications.

Medications associated with acute urinary retention Medications that commonly lead to urinary retention include those with anticholinergic properties (e.g., antipsychotics antihistamines and many anti-emetics and antidepressants) as well as opioids and anesthetics. Other drugs associated with urinary retention include alpha-agonists, benzodiazepines, NSAIDs, detrusor relaxants (e.g., oxybutynin), and calcium channel antagonists. Elderly patients are more at risk for urinary retention due to increased prevalence of benign prostatic hypertrophy (BPH) and polypharmacy.

- Selective serotonin reuptake inhibitors (SSRI's) are an under-recognized cause of retention. One prospective study found that urinary retention occurred in about 10% of patients prescribed SSRI's and the symptom often leads to the discontinuation of the medication (4).
- Opioids causing urinary retention has long been recognized, and is most studied in post-operative adult patients where its incidence is approximately 25% (5). All opioids can cause urinary retention due to mu-opioid receptor agonism.

Patient Assessment On physical exam, a distended bladder is palpable as a tender suprapubic mass once it has reached a urine volume of 150 mL. Bladders with volumes in excess of 500 mL can manifest as a visible suprapubic mass in thin patients. Because a normal bladder volume is less than 50 mL, acute urinary retention can be missed on physical exam, particularly in obese patients. PVR can also be assessed by bedside bladder ultrasound or by catheterization.

Clinical Management Acute urinary retention is a medical emergency. All patients with acute urinary retention and a PVR greater than 50 mL by bladder ultrasound should be catheterized to relieve bladder distension. Depending on the age of the patient and the volume of the PVR, patients should be treated with either catheterization (in-and-out) followed by a trial of spontaneous voiding or be sent home with an indwelling bladder catheter for several days to a week. Patients older than 75 years and those with PVRs greater than 1000 mL are less likely to have successful voiding after a one-time catheterization. Medications should be reviewed and offending agents should be stopped or dose-limited. If BPH is a contributing factor, the addition or up-titration of BPH drugs, such as 5- α reductase inhibitors and α -

antagonists, can help improve urine flow (5). If a spontaneous voiding trial fails after adjustment of medication and several days of catheterization, a referral to urology is warranted (6).

For patients with a limited life expectancy for whom causative medications cannot be adjusted, life-long indwelling catheterization or intermittent catheterization are reasonable options. Although many clinicians may consider catheterization to be burdensome, a recent study which surveyed patients with neurogenic bladders using long-term indwelling or intermittent self-catheterization found that the majority of patients felt that the use of catheterization positively impacted quality of life when compared to not using catheterization (7).

Novel Pharmacologic Management Strategies If the offending pharmacotherapy cannot be stopped, certain targeted pharmacotherapies may be able to counteract urinary retention. The use of opioid antagonists such as naloxone and methylnaltrexone to block opioid receptors and allow for normal urination is supported in the literature by a case reports and a single, human, pre-clinical (healthy adult) controlled trial (8,9). In addition, one case report describes the reversal of citalopram-related urinary retention by the addition of mirtazapine (10). Given the lack of evidence, these approaches should be considered investigational.

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FAST FACTS AND CONCEPTS #294
OPIOID INDUCED CONSTIPATION PART 1: ESTABLISHED MANAGEMENT STRATEGIES

Andrew Badke MD and Drew A Rosielle MD

Background Opioid induced constipation (OIC) affects 45-90% of patients (1, 2) and can cause significant morbidity. It is the most common reason patients avoid and/or discontinue opioids (3, 4) and can often result in an increase in hospital length of stay (5) and overall healthcare costs (6). This *Fast Fact* will describe the physiology of OIC and describe established treatment strategies. *Fast Fact # 295* will discuss newer management strategies.

Physiology OIC is mediated through several different mechanisms including ineffective GI motility, inhibition of mucosal transport of electrolytes and fluids, and interference with the defecation reflex (7). The greatest risk factor for developing OIC is duration of opioid therapy. Route of delivery or increased opioid dosing does not appear to affect the risk of developing OIC (2). While patients usually develop tolerance to most other side effects from opioids, they do not develop tolerance to OIC (1).

Non-pharmacologic Therapies Physical activity, scheduled toileting, fiber, and adequate fluid intake have been traditional non-pharmacologic mainstays for preserving GI regularity in constipation (8). However, there is no specific evidence in favor for any of these interventions to treat OIC and adherence may be challenging for chronically ill patients.

Pharmacologic Therapies In general, patients with regular opioid exposure will require pharmacologic therapy to appropriately manage OIC. Both stimulant and osmotic laxatives have shown to be effective in treating OIC and are considered the cornerstone of treatment. Failure of oral pharmacologic therapy usually requires more invasive rectal based interventions or one of the newer treatment modalities (see *Fast Fact #295*).

- **Stimulant Laxatives:** Senna and bisacodyl are the main stimulant laxatives available in the US and work by increasing enteric muscle contraction and GI motility. The onset of action for oral senna and bisacodyl is around 6-12 hours. Starting dose for senna is two 8.6 mg tabs; bisacodyl is one 10mg tab. However, higher doses are usually needed for OIC. Senna can be safely dosed up to 12 tabs daily and bisacodyl up to 30 mg (9). Both medications are relatively inexpensive. Because stimulant laxatives cause intestinal contractions their use can be limited by abdominal cramps and pain. This can sometimes be avoided by dividing the total dose into smaller more frequent doses (9).
- **Osmotic Laxatives:** These include non-absorbable sugar molecules such as polyethylene glycol (PEG), lactulose, and sorbitol, as well as poorly absorbed salt-based molecules like milk of magnesia and magnesium citrate. Osmotic laxatives have limited intestinal absorption leading to an increase in colonic intraluminal water through oncotic pressure. With increased intraluminal volume and distension, reflex peristalsis subsequently occurs. Additionally, the increase in intraluminal water also leads to softer stool and allows for easier intestinal transit. The starting daily dose for PEG is 17 g, for lactulose is 15 ml, and 30 ml for 70% sorbitol solution. Osmotic laxatives will have a linear effect on bowel function with dose increases; the maximum effective daily dose of PEG is 68 g (10), lactulose is 60 ml, and for sorbitol is 150 ml. The onset of action for osmotic laxatives tends to be variable ranging from 12 to 48 hours, but when used regularly patients will have a more consistent effect. Osmotic laxatives generally do not lead to a loss of fluids or electrolytes as they only bind to orally taken fluid. With this, PEG requires 125 ml of fluid per 17 g dose (11) and similarly ~200 ml is recommended with every 30 ml of lactulose (12). Major side effects from osmotic laxatives include abdominal cramping, pain, and flatulence. Lactulose and sorbitol tend to have more of these side effects than PEG (11). While sorbitol and lactulose have shown similar efficacy, sorbitol tends to be more cost effective (13). Magnesium based compounds (milk of magnesia and magnesium citrate) are also effective, but the magnesium load can be dangerous for patients with renal insufficiency.
- **Rectal Based Laxatives:** Unfortunately, there is a lack of clinical research to support rectal based laxatives, but anecdotally they are often used for refractory constipation. Stimulant suppositories such

as bisacodyl and rectal vault lubricants such as glycerin are inexpensive. Their onset is usually within 10-15 minutes and can be dosed daily (9). Warm tap water and milk of molasses enemas (12) can be dosed more frequently (up to every two hours). They work by causing rectal distension and reflex defecation. Other enema formulations, such as phosphate or saline enemas, should be used with caution in renal insufficiency due to concern for electrolyte shifts.

- **Manual Evacuation:** Digital stimulation and manual disimpaction may be necessary if fecal impaction is suspected. Due to the discomfort associated with manual evacuations, these are often interventions of last resort and may require pre-medication with pain medications and/or anxiolytics.
- **Ineffective Therapies:** Docusate sodium not demonstrated efficacy in randomized controlled studies for OIC compared with placebo (14). Bulk forming laxatives (psyllium or fiber) require at least 1.5 L of water to be effective and can actually lead to worsened constipation with inadequate fluid intake. Consequently, most guidelines do not routinely recommend their use (11,15,16).

Practical Advice A consistent bowel regimen is essential in preventing constipation in patients on chronic opioid therapy. Providers should educate their patients about the signs and symptoms of OIC and seek appropriate consultation in a timely manner. A scheduled stimulant laxative regimen such as Senna 2 tabs twice daily should be prescribed at the onset of regular opioid use regardless of opioid dosing. The goal for the bowel regimen should be an unforced bowel movement at least every other day. If a patient has not had a bowel movement in 48 hours, increasing stimulant laxative dose and/or adding an osmotic laxative is appropriate. Failure of oral laxative therapy usually requires rectal based interventions and/or one of the newer treatment modalities (see *Fast Fact #295*).

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FAST FACTS AND CONCEPTS #295
OPIOID INDUCED CONSTIPATION PART II: NEWER THERAPIES

Andrew Badke MD and Drew A Rosielle MD

Background *Fast Fact #294* introduces OIC and discusses well-established treatments. This *Fast Fact* discusses emerging management approaches. In general, these agents are used for refractory OIC, which implies persistent and distressing symptoms despite exposure to typically effective doses of stimulant and osmotic laxatives. When exactly to use these emerging therapies remains largely empiric.

Opioid Antagonists Since the majority of symptoms associated with OIC are secondary to stimulation of μ -opioid receptors in the gut, opioid antagonists offer an attractive pharmacologic rationale for OIC (1).

Naloxone: Until recently, naloxone was the only available opioid antagonist for OIC treatment. Typically, patients orally ingest the contents of IV ampules. Naloxone has a high first pass metabolism, so it is possible for patients who take it orally to have peripheral μ -opioid receptor antagonism *without* significant impact on central receptors which could lead to opioid withdrawal and loss of analgesia (2). In a small, non-controlled study, 80% of chronic opioid users had bowel evacuation in 1-4 hours after naloxone administration. Unfortunately, over two-thirds reported a 10-15% loss of analgesia and nearly one-third had withdrawal symptoms (3). Therefore, if used, it is recommended to start at a low dose of 0.8 mg twice daily. Effective doses typically need to be at least 10% of equivalent daily morphine dose, so naloxone usually requires slow up-titration with max dosing of 12 mg daily (2).

Methylnaltrexone bromide: Methylnaltrexone is a peripherally-acting μ -opioid receptor antagonist. It is a methylated form of naltrexone and formulated as a subcutaneous injection. It is less able to cross the blood brain barrier, reducing the risk of altering analgesia or inducing central opioid withdrawal. An industry-funded randomized controlled trial of chronic opioid users showed that weight based methylnaltrexone dosing led to laxation in nearly half of subjects within 4 hours as opposed to 15% of placebo (4). A subsequent meta-analysis of 6 separate trials with methylnaltrexone demonstrated the number needed to treat (NNT) is 3 for OIC patients that have failed to respond to standard laxative therapy (5). Its use is limited by cost which averages \$55 per dose, and it is also contraindicated when bowel obstruction is suspected or for patients with compromised bowel integrity. The most common side effects are nausea, diarrhea, and cramping – which can be severely painful.

Naloxegol: Two oral peripheral acting μ -opioid receptor antagonists are available in the US: alvimopam, which is only approved for post-operative ileus, and naloxegol (pegylated naloxone), which has recently been approved for OIC in non-cancer patients. Two separate phase-three clinical trials showed an increase from 1 to >3 bowel movements per week in non-cancer patients on chronic opioids with daily dosed naloxegol compared to placebo. There was also a significant improvement in a subset of patients who had failed traditional laxative therapy as well (7). Both 12.5 mg and 25 mg have been studied; the 25 mg dose has a higher success rate but is associated with more abdominal pain, nausea, vomiting and diarrhea (7). Its current price is approximately \$300 for 30 pills.

Other Agents

- **Lubiprostone:** Lubiprostone is a selective chloride channel-2 activator that acts locally on the small intestine to increase fluid secretion and GI motility. It is FDA approved for OIC. Two randomized controlled trials in non-cancer chronic opioid users demonstrated an increase in frequency of spontaneous bowel movements by week 8. Moreover, approximately 40% of subjects had a bowel movement at 24 hours, 60% within 48 hours, and 27% of subjects had > 3 bowel movements per week (8,9). The most studied dose is 24 mcg orally twice per day. Common side effects included nausea, diarrhea and abdominal distension. Curiously, lubiprostone does not appear to be effective for methadone induced constipation (10).

- Linaclootide has a different mechanism than lubiprostone, but is also a small intestinal secretagogue. It currently is approved for irritable bowel syndrome. Though there is interest in its efficacy in OIC, it has yet to be specifically studied in this population.
- Prucalopride is a serotonin receptor type-4 agonist which is available in Canada and parts of Europe and Asia to treat chronic constipation. It is a prokinetic agent which has shown promise for treating OIC in a phase 2 study (5). It is unclear if or when it will be released in the US.

Practical Advice Traditional oral and rectal laxatives have been the mainstay of treatment in OIC for many years. However, recent development of novel approaches to treat OIC show promise for the future. Of the pharmacologic interventions described above, methylnaltrexone has been the best studied and shown to be the most efficacious. It is reasonable to give methylnaltrexone after failure of oral laxatives (see *Fast Facts* #294) in OIC, and potentially can be used prior to using more invasive rectal based interventions. With time and more clinical trials, other oral formulations targeting OIC may become more standard of care. Patient and caregiver education about the importance of adherence to recommended therapy and guidance about signs and symptoms of OIC is essential to ensure effective treatment.

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