PALLIATIVE CARE NETWORK OF WISCONSIN

Fast Facts Core Curriculum

Opioid Toxicity

PALLIATIVE CARE NETWORK OF WISCONSIN

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 metoclopromide) or anti-cholinergics (e.g. scopolamine);
  - Anti-histamines may be helpful for patients who note a spinning sensation.
  - $5HT_3$ 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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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #39
USING NALOXNE

Colleen J Dunwoody MS, RN and Robert Arnold MD

Background Naloxone (Narcan®), a semisynthetic opioid antagonist, is indicated for the complete or partial reversal of life-threatening CNS/respiratory depression induced by opioids. Naloxone is often inappropriately used in the hospital setting, administered as a full ampule (0.4 mg) in response to physiologically normal opioid-induced decrease in respiratory rate or mild sedation. This probably comes from application of principles of use in the Emergency Department to other settings. Of note, it is normal to have a lower respiratory rate during sleep, especially on opioids. Mild bradypnea, which is not associated with physiologic consequences like hypoxemia, should be closely monitored.

Depending on the dose administered, naloxone administration to a patient physically dependent on opioids will cause the abrupt return of pain and can precipitate an abstinence (withdrawal) syndrome, with symptoms ranging from mild anxiety, irritability and muscle aches to life-threatening tachycardia and hypertension. Once thought to be devoid of side effects, naloxone can cause cardiovascular collapse and pulmonary edema, probably through abrupt increase in sympathetic nervous system activity associated with opioid reversal.

Key Teaching Points

1. Review treatment goals; naloxone administration is not indicated for patients on opioids who are dying (see *Fast Fact* #3), as all dying patients will at some point have an altered mentation and respiratory changes. It may be necessary to write specific orders **not** to administer naloxone.
2. Patients should meet all of the following criteria before naloxone is administered:
    a) Depressed mental status: difficult to arouse or unarousable (if the patient wakes to voice or light shake, the diagnosis is sleeping, not opioid overdose).
    b) Shallow respirations or rate less than 8/minute, associated with evidence of inadequate ventilation (e.g. low oxygen saturation, hypotension). Note: some people breathe at 6-8 per minute when they sleep yet are well ventilated.
3. Stop opioid administration.
4. Dilute 0.4 mg naloxone (one ampule) with normal saline to a total volume of 10 ml (1 ml = 0.04 mg naloxone).
5. Remind the patient to breathe; though narcotized, patients report hearing concerned staff and being unable to open their eyes or respond. Reminders to “take a deep breath” are often followed.
6. Administer 1 ml IV (0.04 mg) q1min until the patient is responsive. A typical response is noted after 2-4 ml with deeper breathing and greater level of arousal. Gradual naloxone administration should prevent acute opioid withdrawal.
7. If the patient does not respond to a total of 0.8 mg naloxone (2 amps), consider other causes of sedation and respiratory depression (e.g. benzodiazepines, stroke).
8. The duration of action of naloxone is considerably shorter than the duration of action of most short-acting opioids. A repeat dose of naloxone, or even a continuous naloxone infusion, may be needed.
9. Wait until there is sustained improvement in consciousness before restarting opioids at a lower dose.

Final notes: After the patient is stable, review events leading up to the patient requiring naloxone and address oversights and errors which lead to this complication of opioid therapy. Review your institution's policy on naloxone administration. Is it appropriate? If not, write one; see (2) for a recommended nursing protocol.

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PALLIATIVE CARE NETWORK OF WISCONSIN

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

Robin K Wilson PhD and 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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PALLIATIVE CARE NETWORK OF WISCONSIN

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-glucronide).
- Central sensitization as a result of opioid-related activation of N-methyl-D-asparate (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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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #161
OPIOID USE IN RENAL FAILURE

Robert Arnold MD, Peg Verrico RPh, Sara N Davison MD

Background Chronic pain is common in chronic kidney disease impacting 50% of hemodialysis patients, 82% of whom experience moderate to severe pain. The absorption, metabolism, and renal clearance of opioids are complex in renal failure. However, with the appropriate selection and titration of opioids, patients with renal failure can achieve analgesia with minimal risk of adverse effects. This *Fast Fact* reviews recommendations for opioid use in the setting of renal failure and in patients receiving chronic dialysis.

Not Recommended for Use:

- **Meperidine** is not recommended in renal failure due to accumulation of normeperidine, which may cause seizures.
- **Codeine** has been reported to cause profound toxicity which can be delayed and may occur after trivial doses. We recommend that codeine be avoided in patients with a Glomerular Filtration Rate (GFR) <30 mL/min.
- **Dextropropoxyphene** is associated with central nervous system (CNS) and cardiac toxicity and is not recommended for use in patients with renal failure.
- **Morphine** is not recommended for chronic use in renal insufficiency (GFR <30 mL/min) due to the rapid accumulation of active, nondialyzable metabolites that are neurotoxic. If morphine must be used, avoid long-acting preparations and monitor closely for toxicity (see *Fast Facts* #57, 58).

Use with Caution:

- **Oxycodone** is metabolized in the liver with 19% excreted unchanged in the urine. There are reports of accumulation of both the parent compound and metabolites in renal failure resulting in CNS toxicity and sedation.
- **Hydromorphone**, as the parent drug, does not substantially accumulate in hemodialysis patients. Conversely, an active metabolite, hydromorphone-3-glucuronide, quickly accumulates between dialysis treatments but appears to be effectively removed during hemodialysis. With careful monitoring, hydromorphone may be used safely in dialysis patients. However, it should be used with caution in patients with a GFR < 30mL/min who have yet to start dialysis or who have withdrawn from dialysis.

Safest in Renal Insufficiency:

- **Fentanyl** is considered relatively safe in renal failure as it has no active metabolites. However, very little pharmacokinetic data exist regarding fentanyl in end stage renal disease. While some studies have shown decreased clearance in renal failure, most studies do not show drug accumulation. Fentanyl is not dialyzable due to high protein binding and a high volume of distribution.
- **Methadone** is considered relatively safe in renal failure. It has no active metabolites and limited plasma accumulation in renal failure due to enhanced elimination in the feces. However, precautions regarding the use of methadone exist (See *Fast Facts* # 75, 86). It does not appear to be removed by dialysis.

Opioid Dosing Given the lack of pharmacokinetic and pharmacodynamic data of opioids in renal failure, it is difficult to advocate for specific analgesic treatment algorithms. However, the following guide has been proposed (Broadbent 2003) for the *initial* dosing of the safer opioids in renal impairment and renal failure.

- Creatinine Clearance > 50 mL/min: normal dosing.
- Creatinine Clearance of 10-50 mL/min: 75% of normal.
- Creatining Clearance < 10 mL/min: 50% of normal.

The “normal opioid dose” for any given patient is the dose that adequately relieves pain without unacceptable adverse effects (see *Fast Fact* #20). Rarely, do opioids need to be adjusted when GFR is > 50 mL/min. While opioids can be used when GFR is <50, they require closer monitoring

and constant reassessment to ensure that accumulation of active metabolites does not result in toxicity. This should not preclude the effective use of opioids in these patients.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #175
OPIOID ALLERGIC REACTIONS

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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, uticaria, brochospasm, 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, brochospasm, 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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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #248
COUNSELING PATIENTS ON SIDE EFFECTS AND DRIVING WHEN STARTING OPIOIDS

Randall E Schisler MD, Hunter Groninger MD, and Drew A Rosielle MD

Background Opioids have side effects which can limit their acceptability to patients. This *Fast Fact* gives expert opinion recommendations about patient counseling when initiating opioid therapy. See *Fast Fact* #83 for a discussion of patient fear of opioids, including addiction and tolerance.

Key Symptoms *Patients should be reassured that most opioid side effects are short-lived or otherwise manageable, and they should seek help immediately for intolerable side effects.*

- **Constipation**
  - *Background for clinicians:* Very common, reported by 23-84% of patients in various studies. It does not diminish over time, even on a steady dose. Opioids delay gastric emptying, decrease peristalsis, decrease secretions, and slow small bowel transit time.
  - *Key counseling points:*
    - Most patients need an ongoing bowel regimen involving stimulant laxatives (stool softeners such as docusate or bulking agents like fiber are ineffective), which should be used as maintenance therapy to *prevent* constipation, not just rescue therapy to *treat* it after it has developed (1). See *Fast Facts* #294 and #295 for more information.
    - Patients should aim for an unstrained bowel movement at least every other day. *"If you have not had a bowel movement in 4 days, call me for advice."*
- **Nausea**
  - *Background for clinicians:* Nausea occurs in ~25% of patients given opioids (2). There are many effective strategies to prevent and ameliorate opioid-induced nausea – see *Fast Fact* #25 for more details. Make sure patients have access to your anti-emetic of choice. There is no consensus as to whether anti-emetics should be given *prophylactically* when initiating or increasing opioids.
  - *Key counseling points:*
    - Nausea is usually transient and resolves in several days on a stable dose (3).
    - Patients should use their prescribed anti-emetic if nausea develops, but should contact you immediately if ineffective and/or vomiting occurs so you can prescribe alternative agents.
- **Sedation** (See also the section on driving below.)
  - *Background for clinicians:* Sedation occurs in 20-60% of patients (2), usually during opioid initiation or around the time of dose increases. Mild-to-moderate sedation usually resolves in a few days; if persistent, it may improve with drug therapy (4). Moderate-to-severe sedation responds to dose reduction, but may also necessitate opioid rotation.
  - *Key counseling points:*
    - Reassure patients that mild-to-moderate sedation usually resolves in a few days.
    - Encourage patients to accept mild sedation (e.g. noticeable drowsiness, falling asleep unintentionally during relaxing activities such as watching TV or reading) for a few days as long as they are in a safe environment. Moderate (falling asleep during stimulating activities such as eating or having a conversation) or severe sedation should prompt a call to you immediately to discuss next steps.

Less Common Symptoms

- **Pruritus** is rare and does not require extensive pre-emptive counseling. *"If you feel itchy it might go away after a few days. If it's really bothering you or not going away, call me and we can make some changes."* See *Fast Fact* #37.
- **Urinary retention** is rare but potentially an emergency. Counsel patients to seek medical care immediately if they lose the ability to urinate. See *Fast Fact* #287 for further information.

Driving Safety There are no large, randomized studies directly examining the risk of driving while on opioids (6). Opioids can slow reaction time, cause drowsiness, or cloud judgment when they are first started or increased (7). Most experts agree that driving or operating heavy machinery is unsafe and should be avoided until a stable dose has been reached (8). Multiple smaller studies suggest that many patients on chronic opioids (defined as no dose change within the last week) have no increased risk of motor vehicle collisions compared to the general population and no reduction in concentration or perception compared to controls(9). According to one study, which videotaped patients while actually driving, those on chronic opioid therapy versus healthy controls displayed neither a difference in driving errors in community or obstacle course driving nor in tests of attention (10). **Counseling bottom line:** patients who have been on a stable dose for a week, who feel no cognitive changes (drowsiness, 'fuzziness,' difficulties in concentrating) can drive.

For **commercial driving**, the Federal Motor Carriers Safety Administration generally prohibits opioid use, but with the caveat that these rules "do not apply to the possession or use of a substance administered to a driver by or under the instructions of a licensed medical practitioner…who has advised the driver that the substance will not affect the driver's ability to safely operate a motor vehicle" (11). Individual states, employers, and insurance agencies may have further restrictions, and patients should be advised to investigate these prior to driving commercially.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #260
OPIOID USE IN LIVER FAILURE

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Background Most opioids are at least partially metabolized by the liver, complicating their use in liver failure. This *Fast Fact* discusses the use of opioids in patients with liver failure (see also *Fast Facts* #161 about opioid use in renal failure, #176 and #177 about managing ascites and #189 about prognostication in end-stage liver disease). **Note:** while there are plenty of pharmacokinetic data about opioids & liver failure, all the clinical recommendations below are empiric and not based on clinical outcomes research.

Hepatic Opioid Metabolism There are two different types of chemical reactions involved in hepatic drug metabolism. The first, *oxidation/reduction reactions*, occurs through the cytochrome (CYP) P450 enzyme system. The CYP450 enzymes most relevant in palliative medicine include CYP1A2, 2D6, 2C9, 2C19, 3A3 and 3A4; most opioids are metabolized by these enzymes. In hepatic failure, opioid clearance is reduced and drug bioavailability is increased. These changes can be secondary to reduced hepatic blood flow (limiting first-pass metabolism) or decreased CYP450 enzyme levels in these patients. *Conjugation and glucuronidation* comprise the second group of chemical reactions in the liver. These reactions are less affected in hepatic disease due to glucuronidation enzyme preservation and also because of extrahepatic glucuronidation processes. Glucuronidated opioid metabolites are generally renally excreted. Changes such as decreased serum albumin and ascites can also alter opioid volume of distribution which can lead to either increased or decreased drug concentrations, although there is no practical way to 'test' for or predict this apart from close clinical observation.

Morphine Morphine is metabolized by glucuronidation to two major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G is an active analgesic that is more potent than morphine, while M3G has no analgesic effect but contributes to neurotoxic side effects such as confusion. Morphine accumulation has been reported in liver disease which can result from decreased plasma clearance and/or increased elimination half-life of the parent drug. In patients with early liver disease, initial lower doses should be used, but at normal dosing intervals. However, as the disease progresses to advanced hepatic failure, longer dosing intervals may be necessary.

Oxycodone Oxycodone is metabolized to two different metabolites by CYP2D6 and 3A4. However, neither metabolite contributes significantly to analgesia. In advanced liver failure, oxycodone's maximum concentration increases 40%, and immediate-release oxycodone's half-life increases to 4.6-24.4 hours (average 14 hours; its usual half-life is ~3.5 hours). Initial oxycodone dosing in patients with severe hepatic failure should be reduced to 30%-50% of the recommended starting dose.

Codeine & Meperidine Both these drugs should be avoided entirely in patients with liver failure. Codeine is a prodrug that is hepatically converted to morphine by CYP2D6. In patients with liver dysfunction, pain control can be compromised if codeine is not metabolized. Meperidine is metabolized by CYP3A4 to normeperidine and also by hydrolysis. In hepatic disease, meperidine clearance is reduced and its half-life is prolonged. Seizures, a major side effect of meperidine and normeperidine, can occur at reduced doses in patients with hepatic failure (see *Fast Fact* #71).

Hydromorphone & Hydrocodone **Hydromorphone** is glucuronidated to metabolites which have no analgesic properties but can be neurotoxic (see *Fast Facts* #57, 58, 142). **Hydrocodone** is a prodrug metabolized by CYP2D6 to hydromorphone and other metabolites, and is only available in combination with non-opioids such as acetaminophen. Hydrocodone dose titrations are limited by the non-opioid component, and overconsumption of acetaminophen-containing products is hepatotoxic. In patients with severe liver disease, initial starting doses of

each drug should be reduced to 50% of normal and as the disease progresses, prolonged dosing intervals may also be necessary.

Fentanyl Fentanyl is primarily metabolized by CYP3A4 and quickly redistributes to muscle and fat upon administration. In single-bolus studies, intravenous fentanyl's pharmacokinetics were unchanged by liver failure, however its half-life is prolonged in liver failure with repeated dosing or high dose therapy. Transdermal fentanyl has not been adequately studied in liver failure. Hepatic failure can alter skin permeability and drug absorption; the clinical relevance of this, if any, has not been determined. Some experts suggest fentanyl is a preferred opioid in liver failure (1, 4), although this judgment appears to be entirely empiric.

Methadone Methadone is metabolized by CYP3A4, 2D6 and 1A2. Methadone's clearance is reduced in severe liver disease. Notably, however, hepatitis C infection stimulates CYP3A4 activity and may actually increase methadone clearance, particularly early on (before overt liver failure occurs).

Clinical Management Pearls As in any clinical setting, the 'right dose' of an opioid analgesic medication is that which provides adequate pain relief in conjunction with an acceptable side effect profile. This statement is especially true in end stage liver disease (ESLD). Opioid doses should not be decreased solely out of concern for hepatic disease (e.g., if a patient with ESLD appears to tolerate and require q3 hour dosing of oxycodone, that dosage should continue). In general, lower doses of most opioids should be initiated in patients with ESLD, and clinicians should be cautious prescribing opioids at 'regular' dosing intervals until patients have demonstrated an ability to tolerate them. Patients with deteriorating liver function should be closely monitored for signs of drug accumulation and need for dose reductions, assuming the level of analgesia remains acceptable. Finally, potential drug interactions involving the CYP450 enzyme system must always be considered as there is potential for non-opioid medications to either induce or inhibit the metabolism of any opioid that is a CYP450 enzyme substrate.

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PALLIATIVE CARE NETWORK OF WISCONSIN

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 polyethelyne 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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PALLIATIVE CARE NETWORK OF WISCONSIN

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

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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 methylnatrexone 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).
Linactolide has a different mechanism than lubiprostone, but is also a small intestinal secretogogue. 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, methylnatrexone 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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