## FENTANYL

### THERAPEUTICS

#### Brands
- **TRANSDERMAL DELIVERY SYSTEM – SLOW-RELEASE:**
  - Duragesic (patch)
  - Sandoz brand (patch)
  - Mylan brand (patch)
  - Mallinckrodt brand (patch)
  - Others (patch)
- **TRANSMUCOSAL (ORAL, INTRANASAL) DELIVERY SYSTEM – IMMEDIATE-RELEASE:**
  - Abstral (sublingual tablets)
  - Actiq (lozenge on a stick) (50% bioavailability)
  - Fentora (buccal tablet)
  - Onsolis (buccal soluble film)
  - Lazanda (intranasal spray) (PecFent – in Europe)
  - Subsys™ (Sublingual Fentanyl Spray)
- **PARENTERAL INTRAVENOUS (IV) OR INTRAMUSCULAR (IM)**
  - Sublimaze
  - Innovar (Fentanyl and Droperidol) – was used for “neuroleptic anesthesia”
- **IONTOPHORETIC TRANSDERMAL SYSTEM**
  - Ionsys (patch for inpatient use only)

#### Generic?
Yes

#### Class
- Opioids (analgesics)
- Fentanyl is a Schedule II drug under the US Controlled Substances Act

#### Commonly Prescribed For
1. **TRANSDERMAL FENTANYL SYSTEM** is commonly prescribed for (FDA approved in bold):
   - **Persistent moderate-to-severe chronic pain**, which is defined as pain of intensity >4 on the numerical rating scale 0–10 (where 0 means no pain and 10 the worst pain imaginable), in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require continuous opioid administration for an extended period of time. The patients who are considered opioid tolerant are those have been taking at least 60 mg of oral morphine or at least 30 mg of oral oxycodone daily, or equivalent daily dose of another opioid for at least 1 month
2. **TRANSMUCOSAL FENTANYL SYSTEM** is commonly prescribed for (FDA approved in bold):
   - **Breakthrough cancer pain** in patients who are already undergoing opioid therapy for persistent cancer pain, are considered opioid tolerant, and take at least 25 µg of transdermal fentanyl per hour, 60 mg of oral morphine, or at least 30 mg of oral oxycodone daily
3. **PARENTERAL INTRAVENOUS (IV) or INTRAMUSCULAR (IM) FENTANYL** is commonly prescribed for (FDA approved in bold):
   - **Patients with moderate to severe acute pain in need of analgesia of short duration** during procedures, regional or general anesthesia (premedication, induction, and maintenance); in the immediate postoperative period; as anesthetic agent with oxygen in selected high-risk patients
   - In hospitalized patients with moderate to severe pain via IV PCA to achieve better pain control or titration to effect
4. **IONTOPHORETIC FENTANYL TRANSDERMAL SYSTEM** is commonly prescribed for (FDA approved in bold):
   - **Short-term management of acute postoperative pain in adult patients requiring opioid analgesia during hospitalization.** Patients should be titrated to an acceptable level of analgesia before initiating treatment with Ionsys, which is not recommended for home use. It is not recommended for patients under the age of 18 years

#### How the Drug Works
- Fentanyl is a synthetic opioid that was first introduced to the market in the 1960s as an intravenous anesthetic under the brand name of Sublimaze
- Fentanyl and other opioids are exogenous substances that act as agonists on the opioid receptors located in the CNS (spinal and supraspinal levels) as well in the peripheral nervous system (PNS). Endogenous opioid ligands include beta-endorphins, met-enkephalins, and dynorphins. A number of receptors are known to be responsible for the opioid effects, including analgesia. These include mu, delta, and kappa receptors. For example, at the presynaptic spinal level, opioids reduce...
Ca\(^{2+}\) influx in the primary nociceptive afferents, resulting in decreased neurotransmitter release. At the postsynaptic level, opioids enhance K\(^{+}\) efflux, resulting in hyperpolarization of the dorsal horn pain-signaling sensory neurons. The net result of the opioid action is a decrease in nociceptive transmission.

It is now recognized that opioids can exert analgesic effects at peripheral sites. Of note, the opioid peripheral effect on primary nociceptive afferents might play a role in painful inflammatory states. In the midbrain, opioids will activate the so-called “off” cells and inhibit “on” cells, leading to activation of a descending inhibitory control on spinal neurons.

- Fentanyl is a mu opioid receptor agonist with high lipid solubility. It quickly crosses the blood–brain barrier and produces a rapid, but short onset of analgesia.
- In terms of analgesia, fentanyl is about 80–100 times more potent than morphine.

**How Long until It Works**

- The transdermal system (“patch”) will allow fentanyl to penetrate from the skin to the bloodstream. Progressive increases in fentanyl serum concentration occur. The serum concentration will level off after approximately 12 hours from the patch application and remain variably consistent for 42–72 hours. A steady-state serum concentration is also determined by skin permeability and clearance of fentanyl. After the patch is removed, serum fentanyl concentrations decline gradually, falling about by 50% after 17 hours.
- The transmucosal system fentanyl products deliver analgesia within a few minutes, and some may elicit clinically meaningful pain relief in 10 minutes.

**If It Works**

- For persistent chronic pain, fentanyl transdermal system can be used for long-term maintenance.
- The transmucosal system for breakthrough cancer pain can be used as needed as long as the clinical condition allows.

**If It Doesn’t Work**

- Consider switching to another opioid preparation.
- Consider alternative treatments for chronic pain or breakthrough cancer pain.

**Best Augmenting Combos for Partial Response or Treatment-Resistance**

- Short-acting opioids for breakthrough pain might be used.
- Add adjuvant analgesics, including gabapentinoids and antidepressants.

**Tests**

- No specific laboratory tests are indicated.

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**ADVERSE EFFECTS (AES) AND PATIENT BEHAVIORS DURING THE COURSE OF OPIOID THERAPY**

**How Drug Causes AEs**

Via CNS opioid receptors and opioid receptors in the periphery.

- **Physical dependence**
  
  Physical dependence is defined by the occurrence of an abstinence syndrome (withdrawal) following an abrupt reduction of the opioid dose or the administration of an opioid antagonist. An abstinence syndrome might include myalgia, abdominal cramps, diarrhea, nausea/vomiting, mydriasis, yawning, insomnia, restlessness, diaphoresis, rhinorrhea, piloerection, and chills. Although there is extensive individual variability, it is prudent to assume that physical dependence will develop after an opioid has been administered repeatedly for several days. Physical dependence is not an indicator of addiction. Opioids can be safely discontinued in physically dependent patients. The syndrome is self-limiting, usually lasting 3–10 days, and is not life-threatening (unless occurring in highly debilitated patients or premature infants).

- **Tolerance**
  
  Tolerance (“true” analgesic tolerance or pharmacodynamic tolerance) describes the need to progressively increase the opioid dose in order to maintain the same degree of analgesia.

- **Opioid-induced hyperalgesia (OIH)**
  
  Hyperalgesia is a form of pain hypersensitivity. Hyperalgesia is a symptom of the opioid withdrawal syndrome seen when opioid administration is abruptly terminated or reversed by the administration of an opioid antagonist. It is still debatable if OIH develops independently from opioid withdrawal or if it becomes more significant during withdrawal because its symptom is no longer opposed by the opioid analgesic effect. OIH has been observed experimentally in animals and humans, but its significance in clinical setting is still unclear. Based on preclinical studies, opioids are thought to have a dual effect: an initial analgesic effect followed by the parallel activation of a hyperalgesic system to counteract the...
analgesic effect of the opioid. The mechanisms that may contribute to OIH remain uncertain.

- **Pseudotolerance**
Pseudotolerance is the patient’s perception that the drug has lost its effect. It requires a differential diagnosis of conditions that mimic “true” analgesic tolerance. These conditions include progression or flare-up of the underlying disease, occurrence of a new pathology, increased physical activity in the setting of mechanical pain, lack of treatment adherence, pharmacokinetic tolerance, manufacturing differences of the same opioid agent, and OIH.

- **Addiction**
A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, craving, compulsive use, and continued use despite harm.

- **Aberrant behaviors**
Opioids are the second most commonly abused drugs in the U.S. Aberrant behaviors include a wide variety of actions, some of criminal purpose:
  - selling prescription drugs
  - prescription forgery
  - stealing another patient’s drugs
  - injecting oral formulations
  - obtaining prescription drugs from nonmedical sources
  - concurrent use of licit or illicit drugs
  - multiple unauthorized and uncontrollable dose escalations

- **Pseudoaddiction**
Pseudoaddiction refers to the occurrence of problematic behaviors related to extreme anxiety associated with unrelieved pain. This includes unsanctioned dose escalation, aggressive complaining about needing more drugs, and impulsive use of opioids. It can be differentiated from addiction by the disappearance of these behaviors when access to analgesic medications is increased and pain control is improved.

- **Opioid-induced constipation (OIC)**
Opioid-induced constipation is a common adverse effect associated with opioid therapy. OIC is commonly described as constipation; however, it refers to a constellation of adverse GI effects, which also includes abdominal cramping, bloating, gastroesophageal reflux disease (GERD), and gastroparesis. The mechanism for these effects is mediated primarily by stimulation of opioid receptors in the GI tract. In patients with pain, uncontrolled symptoms of OIC can add to their discomfort and may serve as a barrier to effective pain management by limiting therapy or prompting discontinuation. Prophylactic treatment should be provided for constipation. Constipation can be managed with peripherally acting opioid antagonist compounds (e.g. alvimopan, methylnaltrexone) when available or by a stepwise approach that includes an increase in fluids and osmotic agents (e.g. sorbitol, lactulose), or with a combination stool softener and a mild peristaltic stimulant laxative such as senna or bisacodyl, as needed. Oral naloxone, which has minimal systemic absorption, has also been used empirically to treat constipation without reversing analgesia in most cases.

- **Nausea and vomiting**
A meta-analysis of opioids in moderate to severe noncancer pain found nausea to affect 21% of patients. Opioids can cause dizziness, nausea, and vomiting by stimulating the medullary chemoreceptor trigger zone, increasing the inner ear vestibular system (i.e., motion sickness), or inducing gastroparesis (or even GERD). With vomiting, parenteral administration of antiemetics may be required. If nausea is caused by gastric stasis, treatment is similar to that of GERD. Tolerance to nausea usually develops.

- **Biliary tract increased pressures and/or spasm**

- **Drowsiness**
Common, related to dose, especially observed at initiation of treatment or when dose is increased. Tolerance may develop over time. Daytime drowsiness can be minimized by using a low starting dose and titrating progressively. If somnolence does occur, it usually subsides within a few days as tolerance develops. The use of a stimulant (e.g. modafinil, methylphenidate) can be considered if persistent somnolence has a detrimental effect on the patient’s functioning.

- **Delirium**
Delirium is frequent in elderly patients, particularly those with cognitive impairment. It can be prevented or treated by using low doses of immediate-release opioids and discontinuing other CNS-acting drugs.

- **Hypogonadism**
Hypogonadism (low testosterone serum levels) can occur in male patients. The testosterone level should be verified in patients who complain of sexual dysfunction or other symptoms of hypogonadism (e.g. fatigue, anxiety, depression). Testosterone supplementation may be effective in treating hypogonadism, but close monitoring of
the testosterone serum level as well as screening for benign prostate hypertrophy and prostate cancer should be carried out

**Life-Threatening or Dangerous AEs**
- In overdose or when taken with CNS depressants, respiratory depression
- However, though respiratory depression fosters the greatest concern, tolerance to this adverse effect develops rapidly. Respiratory depression is very uncommon if the opioid is titrated according to accepted dosing guidelines

**Weight Gain**
- Unusual

![Weight Gain chart](chart)

**Sedation**
- Common

![Sedation chart](chart)

- Many experience and/or can be significant in amount
- Dose-related: can be problematic at high doses
- Can wear off with time

**What to Do about AEs**
- Wait while treat symptomatically
- Lower the dose
- Switch to another opioid agent
- The assessment and management of AEs is an essential part of opioid therapy. By adequately treating AEs, it is often possible to titrate the opioid to a higher dose and thereby increase the responsiveness of the pain
- Because different opioids can produce different AEs in a given patient, opioid rotation is an option for the treatment of persistent AEs

**Transdermal fentanyl system dosage forms**
- 12 µg/hour, 25 µg/hour, 50 µg/hour, 75 µg/hour, 100 µg/hour
- Fentanyl patch forms include the reservoir design (e.g. Duragesic) and the matrix design (e.g. Mylan brand). The reservoir patch is filled with a fentanyl gel. The matrix patch has a semisolid fentanyl within or surrounded by the adhesive substance

**How to Dose**
1. **Transdermal patch**
   - Titrate dose to the needs of the patient
   - 12 µg/hour to 100 µg/hour patch every 72 hours
   - Some patients require dosing every 48 hours
   - May wear more than one patch to achieve the correct analgesic effect
   - Patches should be stored at room temperature below 30 °C (86 °F)

**Overdose**
- Confusion, extreme sedation, respiratory depression, and death
- Fatalities have been reported due to overdose both in monotherapy and in conjunction with sedatives, in particular benzodiazepines, or alcohol use
- Patients must avoid exposing the patches to excessive heat as this promotes the release of fentanyl from the patch and increases the absorption of fentanyl through the skin which can result in fatal overdose

**Long-Term Use**
- The patients will develop physical dependence and may develop tolerance on long-term use
- In patients with addiction vulnerability, risk of aberrant behaviors and addiction

**How to Stop**
- Assuming that the pain has improved, the fentanyl transdermal dose can be decreased by 25% every 3–6 days to prevent or minimize withdrawal symptoms
- Alternatively, fentanyl can be converted to an oral long-acting agent, and then, similarly, the dose of this agent can be tapered down by 25% every 3–5 days

**2. Transmucosal delivery system**
- Abstral: 200 µg, 400 µg, 600 µg, 800 µg
- Actiq: 200 µg, 400 µg, 600 µg, 800 µg, 1200 µg, 1600 µg

**DOSING AND USE**

**Usual Dosage Range**
- Varies, depending on the total daily dose of opioid equivalent and intensity of pain
How to Dose
- Titrate dose to the needs of the patient
- Dosage forms are not equivalent on a microgram per microgram basis among the transmucosal fentanyl products and therefore when switching from one to another product, independent dose titration is required

Overdose
- Confusion, extreme sedation, respiratory depression, and death
- Fatalities due to overdose in conjunction with sedatives, in particular benzodiazepines, or alcohol use

Long-Term Use
- The patients may develop tolerance on long-term use
- In patients with addiction vulnerability, risk of aberrant behaviors and addiction

How to Stop
- If needed, the transmucosal fentanyl dose for breakthrough pain (BTP) can be decreased by 25% every 2–3 days to prevent or minimize withdrawal symptoms

4. Fentanyl iontophoretic transdermal system
- Ionsys is a patient-controlled iontophoretic transdermal system that can deliver on-demand fentanyl for a maximum of 80 doses or up to 24 hours, whichever comes first. Patient-activated dose is initiated by pressing the dosing button twice firmly within 3 seconds. Each time the dose button is activated, Ionsys can deliver a 40-μg fentanyl bolus (equivalent to 44.4 μg of fentanyl hydrochloride) over a 10-minute period. An audible tone (beep) indicates the start of delivery of each dose; the red light remains on throughout the 10-minute dosing period

Pharmacokinetics
- CYP3A4 is the major catalyst involved in fentanyl oxidation to norfentanyl

Drug Interactions
- Active substances that inhibit CYP3A4 activity such as antibiotics (e.g. erythromycin, troleandomycin, clarithromycin), antifungal agents (e.g. ketoconazole, itraconazole, fluconazole), certain protease inhibitors (e.g. ritonavir), and other drugs such as verapamil, diltiazem, nefazodone, amiodarone, fluvoxamine, fluoxetine can increase the bioavailability of fentanyl by decreasing its systemic clearance, and potentially cause fentanyl related prolonged adverse effects. Grapefruit juice is also known to inhibit CYP3A4. Fentanyl should therefore be given to patients with caution if administered concomitantly with CYP3A4 inhibitors
- Concomitant use of other CNS depressants, alcohol, benzodiazepines, skeletal muscle relaxants, sedative antidepressants, sedative H₁ antihistamines, barbiturates, hypnotics, antipsychotics, clonidine, and related substances may produce increased CNS depressant effects
- Fentanyl is not recommended for use in patients who have received MAOIs within 14 days
- The concomitant use of partial opioid agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) is not recommended. They have high affinity to opioid receptors with relatively lower intrinsic activity and therefore partially antagonize the analgesic effect of fentanyl, so tend to induce withdrawal symptoms in physically dependent opioid patients
Other Warnings/ Precautions

- The safety of fentanyl transdermal system has not been established in children less than 2 years of age
- Fentanyl transdermal system should be administered to children only if they are opioid tolerant
- Substances that inhibit CYP3A4 activity can increase fentanyl plasma levels and cause potentially severe adverse effects, including clinically relevant respiratory depression
- CYP3A4 inducers such as carbamazepine may increase clearance of fentanyl and lower its plasma levels, so to induce withdrawal symptoms in physically dependent opioid patients
- Do not use in patients when there is a proven allergy to fentanyl

Breakthrough pain (BTP) in patients with cancer pain

- BTP is a common feature in patients with cancer and it is associated with significant physical and psychosocial burden on patients as well as their care-givers. BTP is a severe pain that achieves peak intensity within a few minutes. It is a transitory attack of pain superimposed on an otherwise stable background pain in an oncological patient. BTP can be incident when it is due to movement (commonly associated with bone metastases or fractures), idiopathic when it occurs spontaneously, with no obvious precipitating event, or incident nonpredictive, which is precipitated by non-volitional factors (e.g. bladder spasm or coughing)
- In order to optimally manage BTP, the background pain should be well controlled by around-the-clock (ATC) analgesics
- Patients should have BTP purposely assessed. For example, consideration should be given to: treatment of the underlying cause of BTP, avoidance/treatment of the precipitating factors of BTP, dose modification of the background opioid regimen, as needed, individual titration of the fast-onset opioid dose, use of nonopioid analgesics, use of nonpharmacologic methods, use of interventional techniques
- The management of cancer-related BTP should be individualized. Traditionally, it was suggested that a supplemental opioid dose roughly equivalent to 5–10% of the total opioid background daily dose can be administered as needed every 3–6 hours for BTP. Studies investigating various supplemental opioid formulations have, however, suggested the absence of a relationship between the effective dose of immediate release preparations and the fixed ATC opioid daily dose. The current recommendation is therefore that each patient is titrated to an effective opioid dose that produces adequate analgesia and minimal AEs
- Transmucosal fentanyl has a rapid onset of effect and a short duration of action matching the temporal characteristics of a BTP episode. It provides a noninvasive method of administration and has demonstrated a faster onset of relief and greater degree of BTP relief than oral morphine

SPECIAL POPULATIONS

Hepatic or Renal Impairment

- Insufficient information exists to make recommendations regarding the use of fentanyl transdermal systems in patients with impaired renal or hepatic functions. Fentanyl is metabolized primarily via the CYP3A4 isoenzyme system and mostly eliminated in urine
- If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl

Elderly

- Clearance of fentanyl may be greatly decreased in a population above the age of 60
- Respiratory depression is the main hazard in elderly or debilitated patients
- Respiration can be depressed following a large initial dose in nontolerant patients or when opioids are given in conjunction with other agents
- Fentanyl transdermal system should be used very cautiously in the elderly or debilitated patients. They may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance
- Due to frequent comorbidities and polypharmacy, as well as increased frailty, older patients are more prone to AEs from opioids. Concerns regarding AEs are held by healthcare professionals, patients, and patients’ families, and can prevent older patients from receiving adequate pain control. Unfortunately, untreated pain also has a detrimental effect on older people, including reduced physical functioning,
depression, sleep impairment, and decreased quality of life. The inadequate management of postoperative pain has also been shown to be a risk factor for delirium. Most opioid analgesics can be used safely and effectively in older patients, providing the regimen is adapted to each patient’s specificities and comorbidities (e.g. the presence of renal or hepatic failure, dementia). As in all patients, regardless of age, the opioid should be started at the lowest available dose and titrated slowly, depending on analgesic response and adverse effects. Slow-release, long-acting formulations can be used safely, but they should only be given to patients for whom an effective and safe daily dose of a short-acting opioid has been established. The efficacy of the opioid should be re-evaluated on a regular basis and it should be discontinued if not effective. The presence of AEs should be assessed systematically, and they should be treated where possible. For frequent AEs, it might be appropriate to institute a preventive regimen (e.g. a prophylactic bowel regimen in patients at risk of constipation). Nonopioid analgesics (e.g. acetaminophen), adjuvant analgesics, and nonpharmacologic treatments (e.g. physical therapy, exercise) should be used concurrently with opioid therapy. These will reduce the opioid dose that is required to achieve analgesia, and hence reduce the associated AEs.

**Children and Adolescents**
- Transdermal fentanyl should not be used in children under 2 years of age
- In non-opioid-tolerant pediatric patients, the fentanyl plasma concentration was approximately twice as high as that of adult patients

**Pregnancy**
- Category C
- No congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported

**Breast-Feeding**
- Fentanyl is excreted in human milk
- Fentanyl transdermal system is not recommended for use in women who are breast-feeding

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**THE ART OF PAIN PHARMACOLOGY**

**Potential Advantages**
- Fentanyl has high lipophilicity, low molecular weight, and high potency and all these characteristics make multiple routes of administration feasible, including the intranasal route
- Transdermal absorption in patients with GI disturbances or malabsorption
- Fentanyl reportedly causes less histamine release than other mu opioid receptor agonists (e.g. morphine, oxycodone)
- Several potent analogues of fentanyl have been developed: alfentanil (Alfenta), a short-acting fentanyl-like analgesic used in anesthesia; sufentanil (Sufenta), an analog with high mu-receptor potency (about 10 times more potent than fentanyl) as well binding affinity; sufentanil can be used in highly tolerant opioid patients during anesthesia and in acute posttraumatic severe pain occurring in patients who have been on high-dose buprenorphine therapy; remifentanil (Ultiva), the shortest-acting opioid available used in anesthesia; carfentanil (Wildnil) more than 100 times potent than fentanyl and used in veterinary medicine for large animals such as elephants

**Potential Disadvantages**
- Intended for transdermal use on intact skin only
- There is a potential for temperature dependent increase, with the fentanyl release resulting in possible overdose or death
- Avoid exposing the fentanyl site and surrounding area to a direct external heat source such as heating pads or electrical blankets, heat or tanning lamps, saunas, hot tubs, and heated waterbeds
- The patients wearing transdermal fentanyl who develop fever, increased core body temperature due to strenuous exertion, should be monitored for opioid side effects, and the fentanyl transdermal system dose should be adjusted if necessary
- For the fentanyl patch, the time from initial application to a stable plasma concentration is 12–24 hours due to the slow build-up of a subcutaneous reservoir. Peak plasma concentrations are obtained between 24 and 72 hours after the initial application; following removal of the patch, a residual depot is present so that, on average, plasma concentrations fall by 50% in 17 hours
- Fentanyl appears to produce muscle rigidity with higher frequency than other opioids
There is a risk of skin burn during an MRI scan from transdermal patches with metallic backing. Patients should be advised to remove any patch and replace it with a new patch after the MRI study has been performed.

**Primary Target Symptoms**
- Moderate to severe acute and chronic pain

**Pearls**
- No known significantly active metabolites; can be used cautiously in hepatic and/or renal insufficiency
- Less “constipating” than morphine
- No significant histamine release (can be used in patients with asthma/reactive airways disease)
- Hemodynamically stable; may produce moderate bradycardic response
- Lipophilic
- When administered epidurally stays in the epidural region that it is injected into (segmental spread)

**Universal Precautions and Risk Management Plan**
- Opioids are highly effective drugs for treating moderate to severe pain. However, both patients’ and physicians’ fears of drug abuse and addiction (and potential associated legal sanctions) are an important barrier to the effective use of opioids for this indication. Unfortunately, this can result in the undertreatment of pain.
- The physician is responsible for assessing whether the patient is at a relatively low or high risk of addiction and/or abuse. Risk factors for addiction can be divided into three categories:
  - Genetic factors (e.g. family history of addiction). One of the most consistent predictors of addiction is a personal or family history of substance abuse
  - Psychosocial factors (e.g. depression, anxiety, personality disorder, childhood abuse, unemployment, poverty)
  - Drug-related factors (e.g. neuroadaptation associated with craving)
- The application of a standardized approach to managing chronic pain patients with opioids has been referred to as UNIVERSAL PRECAUTIONS. An integral component of such precautions is the implementation of a risk management plan, including strategies to monitor, detect, manage, and report addiction or abuse. The following points are of relevance:

1. Interview and examine the patient
2. Try to establish the pain diagnosis; outline the differential diagnosis
3. Recommend the appropriate diagnostic work-up
4. Discuss opioid therapy, benefits and risks, and potential exit strategies. The criteria for stopping opioid therapy should be discussed with the patient prior to starting therapy, and a written exit strategy should be in place, in case the patient:
   - fails to show decreased pain or increased function with opioid therapy
   - experiences unacceptable AEs or toxicity
   - violates the opioid treatment agreement (see below)
   - displays aberrant drug-related behaviors
5. Perform a psychosocial assessment of the patient including screening for low or high risk of addictive disorders; proactive screening strategies should be employed, based on the perceived level of risk. Validated screening tools and questionnaires for patients with pain include: (1) opioid risk tool (ORT) www.painknowledge.org/physiciantools/ORT/ORT%20Patient%20Form.pdf, (2) screener and opioid assessment for patients with pain (SOAPP) www.painedu.org/soapp-development.asp. If appropriate, obtain urine drug testing (UDT) at baseline
6. Document informed consent and treatment agreement
7. Initiate trial of opioid therapy ± adjuvant medications
8. Assess ANALGESIA, ACTIVITY, ADVERSE EFFECTS, and ABERRANT BEHAVIORS (4As) at follow-ups. For assessments of pain and function may use the Brief Pain Inventory (BPI). Pill count and urine drug testing are the most common strategies to assess compliance. UDT can be performed to check for the presence of prescribed medications as evidence of their use, and for the presence of illicit drugs. A negative test for prescribed medications does not necessarily indicate diversion, but could be due to laboratory test inaccuracy or to inadequate dosing or problematic use. This result would, however, merit further discussion with the patient. The aim of UDT is not simply to ensure adherence, but to enhance the doctor–patient relationship by providing documentation of adherence to the treatment plan. If problematic or
aberrant behavior is identified, the physician should reassess the patient to provide a potential diagnosis (e.g. pseudoaddiction, pseudotolerance, cognitive impairment, encephalopathy, anxiety or personality disorder, depression, addiction, criminal activity)

9. Continue or discontinue opioid therapy, or discharge patient from practice. On the basis of the severity of the problematic behavior, patient history, and the findings of the reassessment, the physician must make a decision regarding treatment continuation and referral (e.g. to an addiction specialist). Treatment should only be continued if pain relief and maintained function are evident, control over the therapy can be reacquired, and there is improved monitoring. Any changes in the treatment plan must be comprehensively documented. All physicians should follow federal and state laws regarding the prescribing of controlled substances. Regarding the prescription of opioids to a reliable and clinically stable patient who is affected by a chronic disabling painful disorder, federal regulations are articulated under the Controlled Substances Act (CSA) and monitored by the Drug Enforcement Administration (DEA)

10. Avoid withdrawal symptoms if you discontinue opioid therapy by using a slow tapering schedule (reducing the opioid dose by 10–20% each day). Anxiety, tachycardia, sweating, and other autonomic symptoms that persist may be lessened by slowing the taper. Clonidine at a dose of 0.1–0.3 mg/day over 2–3 weeks can be recommended for individuals who are known to have a history of a problematic withdrawal

Opioid Treatment Agreement
- Before the start of therapy, the expectations and obligations of both the patient and physician should be clearly established in a written or verbal agreement. The opioid agreement facilitates informed consent, patient education, and adherence to the treatment plan
- As a tool, the opioid agreement may also describe the treatment plan for managing pain, provide information about the AEs and risks of opioids, and establish boundaries and consequences for opioid misuse or diversion. The agreement can help to reinforce the point that opioid medications must be used responsibly, and assure patients that these will be prescribed as long as they adhere to the agreed plan of care. An example of agreement is available for perusal at www.ampainsoc.org/societies/mps/downloads/opioid_medication_agreement.pdf

Patient Education
- Patient education is an essential part of opioid therapy; it should begin before therapy is instituted, and continue throughout the course of treatment. The physician has to address the following components of education while talking to the patient:
  - Opioids are powerful pain-relieving drugs, and are effective in a number of painful disorders. However, they are strictly regulated and must be used as directed, and only by the patient for whom they are prescribed
  - The goals of pain management are to help the patient feel better and live a more active life. It takes more than pain medications: wellness program, comprehensive assessment, exercises, appropriate diet, physical therapy, and relaxation are also very important
  - These medicines cannot be stopped abruptly, and they need to be tapered off gradually and only under and according to the physician’s directions
  - Common AEs include nausea, dry mouth, and drowsiness with cognitive impairment, impaired voiding, and itchy skin. These usually last 1–2 weeks until tolerance develops. They can be managed. Nausea and itch may be prevented by antiemetics, Constipation does not go away, but can usually be managed by eating the right foods, drinking enough liquids, and, as a rule, always taking some laxatives
  - The patient has to work with his/her pain management team
  - A patient information sheet can be downloaded from www.ohsu.edu/ahec/pain/patientinformation.pdf

Goals of Opioid Therapy
- The goal of opioid therapy is to provide analgesia and to maintain or improve function, with minimal AEs. The careful use of opioid analgesics may be considered in the treatment of pain when nonopioid analgesics (e.g. acetaminophen, NSAIDs, calcium channel alpha-2-delta ligands, duloxetine) and nonpharmacologic options have proven inadequate for pain control. When medically appropriate, opioid analgesics can be recommended for chronic, moderate to severe pain, which, for practical purposes, is defined as
pain of intensity >4 on the numerical rating scale 0–10 (where 0 means no pain and 10 the worst pain imaginable)

- Opioids are still considered among the most potent and effective “broad-spectrum” analgesics in the treatment of acute and chronic pain. As such, they have been prescribed to patients suffering from moderate to severe disabling pain of both cancer and noncancer origin. The indications for the use of opioids in moderate to severe chronic pain of noncancer origin are osteoarthritis, musculoskeletal pain, and neuropathic pain, with the common denominator that various pharmacologic and nonpharmacologic procedures have proved unsuccessful.

- It is crucial to recognize that patients will respond differently to various opioids in terms of both potency and effectiveness. Variability among patients can be quite profound. This can extend towards both the analgesic effects and the AEs. Reports of lack of analgesic effects should be checked for regimen and adherence.

Opioid Rotation

- Opioid rotation refers to the switch from one opioid to another, and it can be recommended when AEs or onset of analgesic tolerance limit the degree of analgesia obtained with the current opioid; opioid rotation is commonly recommended and performed between pure opioid agonists. In pain management, opioid rotation of mixed opioid agonist–antagonists to/from pure opioid agonists can be difficult and clinically unfeasible to be carried out. If necessary, it is recommended that the initial opioid (e.g. a pure agonist) be tapered down and almost discontinued before starting with the upward titration of the new opioid.

- According to clinical experience and observations, opioid rotation may result in clinical improvement in >50% of patients with chronic pain who have had a poor response to one opioid.

- Opioid rotation should always be based on an equianalgesic opioid conversion table, which provides values for the relative potencies among different opioid drugs. The first step is to determine the patient’s current total daily opioid utilization. This can be accomplished by adding up the doses of all long-acting and short-acting opioids taken by the patient per day. If the patient is on multiple opioids, convert all of them to morphine equivalents using standard equianalgesic tables.

- Usually, when switching from opioid A to opioid B, it is initially prudent to reduce the calculated equianalgesic dose of opioid B by 50%. If opioid B is methadone, and you are switching from ≥ 200 mg/day dose of morphine or morphine equivalent, the initially calculated dose of methadone should be reduced by 90%, and given in divided doses not more often than every 8 hours. If you are rotating to opioid B and opioid B is transdermal fentanyl, then maintain the equianalgesic dose.

- The initial dose of opioid B should also be further reduced based on clinical circumstances, for example in the elderly or in patients who have significant cardiopulmonary, hepatic, or renal disease.

- The patient must remain under close clinical supervision to prevent overdose. Under supervision, a safe, effective, and rapid opioid rotation and titration (RORT) can also be performed via IV patient-controlled analgesia. This option should be considered for patients with severe disabling pain who are on large daily doses of opioids, including oral methadone or multiple opioids, and for frail or elderly patients.

- Intrathecal Analgesic Therapies

Suggested Reading


