BUPRENORPHINE

THERAPEUTICS

Brands
- Buprenex, Butrans, Subutex, Suboxone (w/ naloxone)
- International
  - Temgesic, Norspan, Addnok, Tidigesic, Bupresic, Morgesic, Norphin, Probuphine – implantable formulation using a polymer matrix sustained-release technology for opioid dependence

Generic?
Yes

Class
- Opioids (analgesics)
- Buprenorphine is a Schedule III drug under the US Controlled Substances Act

Commonly Prescribed For
(FDA approved in bold)
- Parenterally, for the relief of moderate to severe pain; transdermally, indication is the same but in chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time
- Sublingually, is indicated for the treatment of opioid dependence

How the Drug Works
- Buprenorphine is a partial agonist at mu opioid receptors. Buprenorphine is also an antagonist at kappa opioid receptors, an agonist at delta opioid receptors, and a partial agonist at nociceptin opioid peptide (NOP) receptors (ORL-1 [nociceptin] receptors). Its clinical actions result from binding to the opioid receptors
- Although buprenorphine HCl is classified as a partial agonist, under certain conditions it may behave like a mu opioid receptor antagonist
- One unusual property of buprenorphine HCl observed in in vitro studies is its very slow rate of dissociation from its receptor. This could account for its longer duration of action than morphine and the unpredictability of its reversal by opioid antagonists
- Buprenorphine may provide analgesia via other mechanisms including acting as a local anesthetic (blocking sodium channels)

How Long until It Works
- Pharmacological effects occur as soon as 15 minutes after intramuscular injection and may persist for 6 hours or longer. Peak pharmacologic effects usually are observed at 1 hour. When used intravenously, the times to onset and peak effect are shortened
- Time to peak (in plasma) is roughly 30–60 minutes after sublingual administration
- Transdermal delivery studies showed that intact human skin is permeable to buprenorphine. In clinical pharmacology studies, the median time for the patch to deliver quantifiable buprenorphine concentrations (≥25 pg/mL) is approximately 17 hours. Steady state is generally achieved by day 3.

If It Works
- The usual dosage can be administered by deep intramuscular or slow (over at least 2 minutes) intravenous injection at up to 6-hour intervals, as needed. Repeat once (up to 0.3 mg) if required, 30 to 60 minutes after initial dosage, giving consideration to previous dose pharmacokinetics, and thereafter only as needed
- In high-risk patients (e.g., elderly, debilitated, presence of respiratory disease, etc.) and/or in patients where other CNS depressants are present, such as in the immediate postoperative period, the dose should be reduced by approximately one-half. Extra caution should be exercised with the intravenous route of administration, particularly with the initial dose
- Occasionally, it may be necessary to administer single doses of up to 0.6 mg to adults depending on the severity of the pain and the response of the patient. This dose should only be given IM and only to adult patients who are not in a high-risk category. At this time, there are insufficient data to recommend single doses greater than 0.6 mg for long-term use
- The transdermal formulation is intended for patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time

If It Doesn’t Work
- Consider switching to another opioid preparation intended for postoperative acute pain
- Consider alternative opioid treatments for chronic pain or combining it with effective therapies to treat neuropathic pain

Best Augmenting Combos
- Short-acting opioids intended for breakthrough pain
- Antiepileptic (calcium channel alpha-2-delta ligands) or antidepressants for neuropathic pain component

Tests
- No specific laboratory tests are indicated
How Drug Causes Adverse Effects

- **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 myalgias, 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. Although OIH has been observed experimentally in animals and humans, 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 United States. 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 gastrointestinal (GI) effects, which also includes abdominal cramping, bloating, gastroesophageal reflux, 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 gastroesophageal reflux disease (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 IR 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**

- As with other potent opioids, clinically significant respiratory depression may occur within the recommended dose range in patients receiving therapeutic doses of buprenorphine.
  Buprenorphine should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression). Particular caution is advised if buprenorphine is administered to patients taking or recently receiving drugs with CNS/respiratory depressant effects. In patients with the physical and/or pharmacological risk factors above, the dose should be reduced by approximately one-half.

- Naloxone may not be effective in reversing the respiratory depression produced by buprenorphine. Therefore, as with other potent opioids, the primary management of overdose should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required.

- Buprenorphine HCl, like other potent analgesics, may itself elevate CSF pressure and should be used with caution in head injury, intracranial lesions, and other circumstances where cerebrospinal pressure may be increased. Buprenorphine HCl can produce miosis and changes in the level of consciousness which may interfere with patient evaluation.

- Transdermal formulation of buprenorphine at doses of over 20 μg/hour was observed to prolong the QTc interval. Consider these observations in clinical decisions when prescribing this transdermal formulation to patients with hypokalemia or clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Avoid the use of this transdermal formulation in patients with a history of long QT syndrome or an immediate family member with this condition, or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide).

- Transdermal formulation may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone.

- Although not observed with transdermal patch in chronic pain, cases of cytolytic hepatitis and hepatitis with jaundice have been observed in...
individuals receiving sublingual buprenorphine for the treatment of opioid dependence. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of preexisting liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injection drug abuse may have played a causative or contributory role. For patients at increased risk of hepatotoxicity (e.g. patients with a history of excessive alcohol intake, intravenous drug abuse, or liver disease), baseline and periodic monitoring of liver function during treatment with buprenorphine transdermal patch is recommended. Buprenorphine, as with other opioids, may aggravate seizure disorders, may lower seizure threshold, and therefore may induce seizures in some clinical settings. Use Butrans with caution in patients with a history of seizure disorders.

**Weight Gain**
- Unusual

**Sedation**
- Common

- Many experience and/or can be significant in amount
- Dose-related: can be as problematic as morphine at high doses and accompanied by an increase of cardiac work and dysphoria
- Can wear off with time but lasts longer than with other opioids

**What to Do about AEs**
- Wait while treat AE 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.

**DOSING AND USE**

**Usual Dosage Range**
- **Parenteral:** the usual dosage for adults 1 mL buprenorphine HCl (0.3 mg buprenorphine) given by deep IM or slow (over at least 2 minutes) IV injection at up to 6-hour intervals
- **Transdermal:**
  - For opioid-naïve patients, initiate treatment with a 5-μg/hour patch
  - Conversion from other opioids:
    - There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids. For conversion from other opioids, taper the patient’s current around-the-clock opioids for up to 7 days to no more than 30 mg of morphine or equivalent per day before beginning treatment. Patients may use short-acting analgesics as needed until analgesic efficacy with Butrans is attained
    - For patients whose daily dose was less than 30 mg of oral morphine or equivalent, initiate treatment with a 5-μg/hour patch. For patients whose daily dose was between 30 and 80 mg morphine equivalents, initiate treatment with a 10-μg/hour patch
    - Buprenorphine transdermal patch 20 μg/hour may not provide adequate analgesia for patients requiring greater than 80 mg/day oral morphine equivalents
- **Oral (treatment of opioid dependence):**
  - Buprenorphine is administered sublingually as a single daily dose in the range of 12 to 16 mg/day. When taken sublingually, the clinical effects of buprenorphine w/wo naloxone are similar and interchangeable
  - Buprenorphine tablets that contain no naloxone are preferred for use during induction. Following induction, tablets in combination with naloxone are preferred when clinical use includes unsupervised administration
  - The use of tablets not containing naloxone for unsupervised administration should be limited to those patients who cannot tolerate naloxone, for example those patients who have been shown to be hypersensitive
Induction:
- To avoid precipitating withdrawal, induction with sublingual buprenorphine should be undertaken when objective and clear signs of withdrawal are evident.
- Patients should receive 8 mg of sublingual buprenorphine on day 1 and 16 mg on day 2. From day 3 onward, patients should receive buprenorphine plus naloxone tablets at the same buprenorphine dose as day 2.
- Patients taking heroin or other short-acting opioids:
  - At treatment initiation, the dose of sublingual buprenorphine should be administered at least 4 hours after the patient last used opioids or preferably when early signs of opioid withdrawal appear.
- Patients on methadone or other long-acting opioids:
  - Available evidence suggests that withdrawal symptoms are possible during induction to buprenorphine treatment. Withdrawal appears more likely in patients maintained on higher doses of methadone (>30 mg) and when the first buprenorphine dose is administered shortly after the last methadone dose.

Maintenance:
- Buprenorphine plus naloxone is the preferred medication for maintenance treatment due to the presence of naloxone in the formulation.
- Adjusting the dose until the maintenance dose is achieved: the recommended target dose of buprenorphine plus naloxone is 16 mg/day. Also doses as low as 12 mg may be effective in some patients.
- The dosage of buprenorphine plus naloxone should be progressively adjusted in increments/decrements of 2 mg or 4 mg to a level that holds the patient in treatment and suppresses opioid withdrawal effects. This is likely to be in the range of 4 mg to 24 mg per day depending on the individual.
- Prescribers utilizing Suboxone or Subutex for maintenance treatment of opioid dependence need to have a special license to prescribe chronic therapy.
- Reducing dosage and stopping treatment:
  - The decision to discontinue therapy with sublingual buprenorphine after a period of maintenance or brief stabilization should be made as part of a comprehensive treatment plan.
  - Both gradual and abrupt discontinuation have been used, but no controlled trials have been undertaken to determine the best method of dose taper at the end of treatment.

Dosage Forms
- Injection: 0.3 mg/mL
- Transdermal patch: 5 μg/hr, 10 μg/hr, 20 μg/hr
- Sublingual film/tablet (w/wo naloxone) 2 mg, 8 mg, for treatment of opioid dependence

How to Dose
- Parenterally: repeat once (up to 0.3 mg) if required, 30 to 60 minutes after initial dosage, and thereafter only as needed. In high-risk patients (e.g., elderly, debilitated, presence of respiratory disease, etc.) and/or in patients where other CNS depressants are present, such as in the immediate postoperative period, the dose should be reduced by approximately one-half. Extra caution should be exercised with the IV route of administration, particularly with the initial dose. Occasionally, it may be necessary to administer single doses of up to 0.6 mg to adults depending on the severity of the pain and the response of the patient. This dose should only be given IM and only to adult patients who are not in a high-risk category. At this time, there are insufficient data to recommend single doses greater than 0.6 mg for long-term use.
- Transdermal patch:
  - Titrate dose to the needs of the patient
  - 5 μg/hr to 20 μg/hr patch at 72 hours
  - The intent of the titration period is to establish a patient-specific weekly administration that will maintain adequate analgesia with tolerable side effects for as long as pain management is necessary.
  - Patches should be stored at room temperature below 15–30 °C (59°–86 °F).

Dosing Tips
- Physicians should individualize treatment in every case, using nonopioid analgesics, opioids on an as-needed basis and/or combination products, and chronic opioid therapy in a progressive plan of pain management.
- Apply the patch to the upper outer arm, upper chest, upper back or the side of the chest. These 4 sites (each present on both sides of the body) provide 8 possible application sites. Rotate the patch among the 8 described skin sites.
- Apply the transdermal film to a hairless or nearly hairless skin site. If none is available, the hair at
the site should be clipped, not shaven. If problems with adhesion occur, the edges may be taped with first-aid tape. Each patch is intended to be worn for 7 days. Sometimes, some patients may need an earlier replacement of the patch to achieve an adequate pain relief. It is recommended to wait 21 days before reusing the same site.

**Overdose**
- Acute overdosage with buprenorphine can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. In the case of the patch, after its removal, the mean buprenorphine concentrations decrease approximately 50% in 12 hours (range 10–24 hours) with an apparent terminal half-life of approximately 26 hours. Due to this long apparent terminal half-life, patients may require monitoring and treatment for at least 24 hours.

**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**
- When the patient no longer requires therapy with Butrans, taper the dose gradually to prevent signs and symptoms of withdrawal in the physically dependent patient; consider introduction of an appropriate immediate-release opioid medication. Undertake discontinuation of therapy as part of a comprehensive treatment plan.

**Pharmacokinetics**
- Buprenorphine primarily undergoes \( N \)-dealkylation by CYP3A4 to norbuprenorphine and glucuronidation by UGT-isoenzymes (mainly UGT1A1 and 2B7) to buprenorphine 3-\( O \)-glucuronide. Norbuprenorphine, the major metabolite, is also glucuronidated (mainly UGT1A3) prior to excretion.
- Half-life elimination: IV: 2.2–3 hours; apparent terminal half-life: sublingual tablet: \( \sim70\% \); urine (\( \sim30\% \)

**Drug Interactions**
- Coadministration of ketoconazole, a strong CYP3A4 inhibitor, with buprenorphine transdermal patch, did not have any effect on \( C_{\text{max}} \) and AUC of buprenorphine. However, certain protease inhibitors (PIs) with CYP3A4 inhibitory activity such as atazanavir resulted in elevated levels of buprenorphine and norbuprenorphine following sublingual administration of buprenorphine and naloxone. As such, the drug–drug interaction potential for buprenorphine with CYP3A4 inhibitors is likely to be dependent on the route of administration as well as the specificity of enzyme inhibition.
- The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied; therefore it is recommended that patients receiving buprenorphine be closely monitored for reduced efficacy if inducers of CYP3A4 (e.g. phenobarbital, carbamazepine, phenytoin, rifampin) are coadministered.

**Other Warnings/Precautions**
- There have been a number of reports regarding coma and death associated with the misuse and abuse of the combination of buprenorphine and benzodiazepines.
- Buprenorphine, like other opioids, may interact with skeletal muscle relaxants to enhance neuromuscular blocking action and increase respiratory depression.
- Buprenorphine is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.
- Use buprenorphine with caution in the following conditions, due to increased risk of adverse reactions: alcoholism; delirium tremens; adrenocortical insufficiency; CNS depression; debilitation; kyphoscoliosis associated with respiratory compromise; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary, or renal function; and toxic psychosis.
- Buprenorphine may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery; caution patients accordingly.
SPECIAL POPULATIONS

Hepatic Disease
- Pharmacokinetic parameters of buprenorphine did not increase in patients with mild and moderate hepatic impairment. For the transdermal formulation, start patients with the 5-μg/hour dose. The patch is only intended for 7-day application; consider use of an alternate analgesic that may permit more flexibility with the dosing in patients with severe hepatic impairment.

Renal Disease
- The pharmacokinetics of buprenorphine are not altered during the course of renal failure.

Elderly
- Although specific dose adjustments on the basis of advanced age are not required for pharmacokinetic reasons, use caution in the elderly population to ensure safe use.

Children and Adolescents
- Parenterally: buprenorphine HCl has been used in children 2 and 12 years of age at doses between 2 and 6 μg/kg of body weight given every 4 to 6 hours. There is insufficient experience to recommend a dose in infants below the age of 2 years, single doses greater than 6 μg/kg of body weight, or the use of a repeat or second dose at 30 to 60 minutes (such as is used in adults).
- The transdermal formulation is not recommended for use in pediatric patients.

Pregnancy
- Category C
- There are no adequate and well-controlled studies with buprenorphine in pregnant women. It should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and the fetus.
- In animal studies, buprenorphine caused an increase in the number of stillborn offspring, reduced litter size, and reduced offspring growth in rats at maternal exposure levels that were approximately 10 times that of human subjects.

Breast-Feeding
- Buprenorphine has been detected in low concentrations in human milk.
- Breast-feeding is not advised in mothers treated with buprenorphine.

THE ART OF PAIN PHARMACOLOGY

Potential Advantages
- Buprenorphine has high lipid solubility, low molecular weight, and high potency, making it suitable for a transdermal preparation.

Potential Disadvantages
- For the buprenorphine patch, the time from initial application to a stable plasma concentration is 72 hours due to the slow buildup of a subcutaneous reservoir. Peak plasma concentrations are obtained between 17 and 48 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 10–24 hours.

Primary Target Symptoms
- Chronic pain
- Opioid dependence

Pearls
- Transdermal absorption may be a particular advantage in patients with GI disturbances or malabsorption.
- It may be a useful opioid analgesic to treat chronic pain in older persons due to only slight modification of pharmacokinetics in this population.
- Intended for transdermal use on intact skin only. There is a potential for temperature-dependent increase, with the buprenorphine release resulting in possible overdose or death.
- Avoid exposing the buprenorphine 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 buprenorphine who develop fever or increased core body temperature due to strenuous exertion should be monitored for opioid side effects, and the buprenorphine transdermal system dose should be adjusted if necessary.
- Buprenorphine appears to be a safer, more acceptable maintenance or detoxification option for many opiate-dependent addicts.
- It is conceivable that buprenorphine may be particularly useful for certain patients with neuropathic pain.
- High affinity for mu opioid receptor and slowly dissociates from it.
- Highly lipophilic.
- The maximum transdermal dose is 20 μg/hour since higher doses may lead to QTc prolongation.

(continued) BUPRENORPHINE
Patients who are opioid-naïve or taking an opioid oral morphine equivalent of <30 mg/day should start with 5 μg/hour

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 3 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, benefit 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 side effects 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/OR%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 UDT 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 side effects 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 an 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 to 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 adverse effects 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 adverse effects. 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 side effects. Reports of lack of analgesic effects
Predicting a patient’s response to medication has long been a goal of clinicians; it is possible that pharmacogenomics may, in due course, become in common use for screening for variations in the expression of drug-metabolizing enzymes (e.g. cytochrome CYP3A4), and thus provide a potent tool for improving pain management.

**Opioid Rotation**

- Opioid rotation refers to the switch from one opioid to another, and it can be recommended when adverse effects 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.
Suggested Reading


