HYDROMORPHONE

Brands
- Dilaudid
- Exalgo
- Palladone (Palladone sales and marketing in U.S. were suspended in 2005 secondary to rapid release [dose-dumping] phenomenon when combined with alcohol) (other names for controlled release hydromorphone in other countries: Hydromorph Contin, Sophidone LP, Jurnista)
- Hydrostat IR

Generic?
Yes

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

Commonly Prescribed For
(FDA approved in bold)
- Management of pain in patients where an opioid analgesic is appropriate, by oral and parenteral route
- Parenteral High Potency (HP) formulation and enteral extended release formulation (Exalgo) are indicated for the relief of moderate-to-severe pain in narcotic-tolerant patients who require larger than usual doses of narcotics to provide adequate pain relief
- 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 a month
- Severe, painful dry coughing
- Dyspnea

How the Drug Works
- Hydromorphone, a semi-synthetic mu opioid agonist, is a hydrogenated ketone of morphine and shares the pharmacologic properties typical of opioid analgesics. Opiate receptors are coupled with G-protein receptors and function as both positive and negative regulators of synaptic transmission via G-proteins that activate effector proteins. Binding of the opiate stimulates the exchange of GTP for GDP on the G-protein complex. As the effector system is adenylate cyclase and cAMP located at the inner surface of the plasma membrane, opioids decrease intracellular cAMP by inhibiting adenylate cyclase. Subsequently, the release of neurotransmitters such as substance P, GABA, dopamine, acetylcholine, and noradrenaline is inhibited. Opioids also inhibit the release of vasopressin, somatostatin, insulin and glucagon. Opioids close N-type voltage-operated calcium channels ([kappa]-receptor agonist) and open calcium-dependent inwardly rectifying potassium channels ([mu] and [delta] receptor agonist). This results in hyperpolarization and reduced neuronal excitability

How Long until It Works
- After oral administration of hydromorphone, peak plasma concentrations are generally attained within 1/2 to 1 hour
- In chronic pain, doses should be administered around the clock. A supplemental dose of 5–15% of the total daily usage may be administered every 2 hours on an “as-needed” basis
- In patients taking opioid analgesics, the starting dose of hydromorphone hydrochloride should be based on prior opioid usage. Once the total daily dosage has been estimated, it should be divided into the desired number of doses; although only 1/2 to 2/3 of the estimated dose calculated from equivalence tables should be given for the first few doses, then increased as needed according to the patient’s response
- Following extended release (ER) administration, plasma concentrations gradually increase over 6 to 8 hours, and thereafter concentrations are sustained for approximately 18 to 24 hours post-dose

If It Works
- For persistent chronic pain, hydromorphone in extended release formulation can be used for long term maintenance. In this case, it is also necessary to assess the continued need for around-the-clock opioid therapy periodically

If It Doesn’t Work
- Consider switching to another long-acting or extended release opioid preparation
- Consider alternative treatments for chronic pain

Best Augmenting Combos for Partial Response or Treatment-Resistance
- Short-acting opioids for breakthrough pain might be used
- Add adjuvant analgesics, including calcium channel alpha-2-delta ligands and antidepressants
Tests
- No specific laboratory tests are indicated

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 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. OIH has been observed experimentally in animals and humans, but its significance in clinical settings 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 this country. 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 unrelied 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 AE 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 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**
  - In overdose or when taken with CNS depressants, respiratory depression
  - However, though respiratory depression fosters the greatest concern, tolerance to this AE develops rapidly. Respiratory depression is very uncommon if the opioid is titrated according to accepted dosing guidelines

- **Weight Gain**
  - Unusual

- **Sedation**
  - Common

  - Many experience and/or can be significant in amount
  - Dose-related: can be problematic at high doses
  - Can wear off with time but may not wear off at high doses

  **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 adverse effects in a given patient, opioid rotation is an option for the treatment of persistent AEs

### DOSING AND USE

**Usual Dosage Range**
- Opioid-naïve patients:
  - OR: 2–4 mg every 4–6 hours. A gradual increase in dose may be required if analgesia is inadequate, as tolerance develops, or if pain persists.
severity increases. The first sign of tolerance is usually a reduced duration of effect
- SC/IM: 0.4–1.2 mg every 2–3 hours, as necessary
- IV: 0.2–1 mg every 2–3 hours

Conversion from prior opioid:
- OR: Patients receiving oral immediate-release hydromorphone: starting dose equivalent (ER) to the patient’s total daily oral hydromorphone dose, taken once daily. Patients receiving another oral opioid: start ER therapy by administering 50% of the calculated total daily dose every 24 hours. The initial dose of hydromorphone ER can be titrated until adequate pain relief with tolerable AEs have been achieved
- Parenteral: Convert the current total daily amount(s) of opioid(s) received to an equivalent total daily dose of hydromorphone and reduce by one-half due to the possibility of incomplete cross-tolerance. Divide the new total amount by the number of doses permitted based on dosing interval (e.g. 8 doses for every 3-hour dosing). Titrate the dose according to the patient’s response. Do not use hydromorphone-HP for patients who are not tolerant to the respiratory depressant or sedating effects of opioids

**Dosage Forms**
- Oral liquid (HCl): 1 mg/mL
- Immediate release tablet: 2, 4, and 8 mg
- Extended release tablet: 8, 12, and 16 mg
- Injection: 1, 2, and 4 mg/mL; HP: 10 mg/mL

**How to Dose**
- Initiate the dosing regimen for each patient individually, taking into account the patient’s prior analgesic treatment
- Use hydromorphone-HP only for patients who require the higher concentration and lower total volume of the ampoule
- Titrate patients to adequate analgesia with dose increases not more often than every 3–4 days and not higher than 25–50% of the current daily dose, in order to attain steady-state plasma concentrations of hydromorphone at each dose
- If more than 2 doses of rescue medication are needed within a 24-hour period for 2 consecutive days, the dose may need to be titrated upward
- The ER formulation is to be administered no more frequently than every 24 hours

**Dosing Tips**
- Oral dosages higher than the usual dosages may be required in some patients
- The dosage of opioid analgesics like hydromorphone hydrochloride should be individualized for any given patient, since adverse events can occur at doses that may not provide complete freedom from pain
- If pain management is not satisfactory and in the absence of significant opioid-induced adverse events, the hydromorphone dose may be increased gradually. If excessive opioid AEs are observed early in the dosing interval, the hydromorphone dose should be reduced. If this results in breakthrough pain at the end of the dosing interval, the dosing interval may need to be shortened. Dose titration should be guided more by the need for analgesia than the absolute dose of opioid employed
- ER hydromorphone must be taken once every day, at around the same time each day. The formulation should be swallowed whole — never crushed or chewed
- If a patient needs more than 2–3 extra doses of short acting hydromorphone in a day, the dose of ER hydromorphone may need to be reviewed

**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

**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 hydromorphone, taper doses gradually, by 25–50% every 2 or 3 days down to the lowest dose before discontinuation of therapy, to prevent signs and symptoms of withdrawal in the physically dependent patient

**Pharmacokinetics**
- Hydromorphone is extensively metabolized via glucuronidation in the liver, with greater than 95% of the dose metabolized to hydromorphone-3-glucuronide along with minor amounts of 6-hydroxy reduction metabolites

**Drug Interactions**
- The concomitant use of other CNS depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and
alcohol may produce additive depressant effects. Respiratory depression, hypotension, and profound sedation or coma may occur. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Narcotic analgesics, including hydromorphone, may enhance the action of neuromuscular blocking agents and produce an increased degree of respiratory depression.

**Other Warnings/Precautions**

- Safety and effectiveness in children have not been established.
- Respiratory depression is the chief hazard of hydromorphone. Respiratory depression is more likely to occur in the elderly, in the debilitated, and in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.
- Hydromorphone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause CNS depression.
- Infants born to mothers physically dependent on hydromorphone will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms.
- The respiratory depressant effects of hydromorphone with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or preexisting increase in intracranial pressure.
- Opioid analgesics, including hydromorphone, may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics.
- Hydromorphone should be given with caution and the initial dose should be reduced in the elderly or debilitated and those with severe impairment of hepatic, pulmonary or renal functions; myxedema or hypothyroidism; adrenocrotical insufficiency (e.g. Addison’s disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; gall bladder disease; acute alcoholism; delirium tremens; kyphoscoliosis; or following GI surgery. The administration of opioid analgesics including hydromorphone may obscure the diagnoses or clinical course in patients with acute abdominal conditions and may aggravate preexisting convulsions in patients with convulsive disorders.
- Hydromorphone may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g. driving, operating machinery).
- Opioid analgesics, including hydromorphone hydrochloride tablets, should also be used with caution in patients about to undergo surgery of the biliary tract since they may cause spasm of the sphincter of Oddi.
- ER formulation does not prevent patients from developing opioid dependence.

**SPECIAL POPULATIONS**

**Hepatic or Renal Impairment**

- After oral administration of hydromorphone, exposure to hydromorphone (C<sub>max</sub> and AUC 0–48) is increased in patients with impaired renal/hepatic function by 2- to 4-fold in moderate (Clcr = 40–60 mL/min; Child–Pugh Group B) and 3-fold in severe (Clcr <30 mL/min) renal impairment (pharmacokinetics of hydromorphone in severe hepatic impairment patients has not been studied) compared with normal subjects (Clcr >80 mL/min). In addition, in patients with severe renal impairment hydromorphone appeared to be more slowly eliminated with longer terminal elimination half-life (40 hours) compared to patients with normal renal function (15 hours). Patients with moderate renal/hepatic impairment should be started on a lower dose. Starting doses for patients with severe renal/hepatic impairment should be even lower. Patients with renal/hepatic impairment should be closely monitored during dose titration. Use of oral liquid is recommended to adjust the dose.

**Elderly**

- Age has no effect on the pharmacokinetics of hydromorphone.

**Children and Adolescents**

- Safety and effectiveness in children have not been established.

**Pregnancy**

- Category C
- No adequate and well-controlled studies in pregnant women.
- Hydromorphone crosses the placenta. May cause respiratory compromise in newborns when administered during labor and delivery.
Breast-Feeding
- Hydromorphone is found in low levels in breast milk
- Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped
- Hydromorphone is not recommended for use in nursing women

THE ART OF PAIN PHARMACOLOGY

Potential Advantages
- Potent analgesia
- Less itching and nausea than morphine

Potential Disadvantages
- Metabolites, although thought to be less problematic than those of morphine, may be an issue if using high doses in patients with renal failure (hydromorphone-3-glucuronide)

Primary Target Symptoms
- Acute or chronic pain

Pearls
- 4 to 5 times more potent than morphine
- It causes less nausea and pruritus than morphine
- Although evidence is still limited, it seems safer in renal failure than morphine

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 pain 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 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 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. 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 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.

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**HYDROMORPHONE**

(continued)

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**Intrathecal Analgesic Therapies**

Suggested Reading


