**PENTAZOCINE**

**THERAPEUTICS**

**Brands**
- Talwin, Fortral (Talwin PX, without naloxone – Canada)
- Injectable: Pentazocine lactate (Sosegon, Fortwin)
- With acetaminophen: Talacen
- With naloxone: Talwin-NX

**Generic?**
Yes

**Class**
- Opioids (analgesics)
- Pentazocine is a Schedule IV drug under the US Controlled Substances Act

**Commonly Prescribed For**
(FDA approved in bold)
- Parenterally, for the relief of moderate-to-severe pain; may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia
- Orally, for the relief of mild to moderate pain (w/ acetaminophen).

**How the Drug Works**
- Pentazocine is an analgesic with agonist/antagonist action. By competing for the mu receptor in certain circumstances it may act as a mu opioid receptor antagonist and a kappa opioid receptor agonist, which when administered orally is approximately equivalent on a mg-for-mg basis in analgesic effect to codeine. Onset and duration of action and the degree of pain relief are related both to dose and the severity of pretreatment pain
- Pentazocine is well absorbed from the GI tract. Plasma levels closely correspond to the onset, duration, and intensity of analgesia. The time to mean peak concentration is 1.7 hours and the mean plasma elimination half-life is 3.6 hours
- By parenteral route is usually as effective as an analgesic as morphine 10 mg or meperidine 75–100 mg; however, a few studies suggest the pentazocine to morphine ratio may range from 20 mg to 40 mg pentazocine to 10 mg morphine
- Pentazocine may weakly antagonize the analgesic effects of morphine and meperidine; in addition, it produces incomplete reversal of cardiovascular, respiratory, and behavioral depression induced by morphine and meperidine. The antagonistic activity of nalorphine for this compound is about 1/50. It also has sedative activity

**How Long until It Works**
- Onset of significant analgesia with pentazocine usually occurs between 15 and 30 minutes after oral administration, and duration of action is usually 3 hours or longer
- Parenterally, the duration of analgesia may sometimes be less than that of morphine. Analgesia usually occurs within 15–20 minutes after IM or SC injection and within 2–3 minutes after intravenous injection

**If It Works**
- The usual duration of therapy is dependent upon the condition being treated but in any case should be reviewed regularly by the physician
- The SC route of administration should be used only when necessary because of possible severe tissue damage at injection sites
- When frequent injections are needed, the drug should be administered IM. In addition, constant rotation of injection sites is essential

**If It Doesn’t Work**
- Consider switching to another opioid preparation intended for acute (moderate to severe) or chronic (mild to moderate) pain
- Consider alternative treatments for chronic pain

**Best Augmenting Combos for Partial Response or Treatment-Resistance**
- Not applicable

**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 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 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 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 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**

- Infrequently occurring reactions are (a) respiratory: respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received pentazocine during labor; (b) cardiovascular: circulatory depression, shock and hypertension.

**Weight Gain**

- Unusual

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

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**DOSING AND USE**

**Usual Dosage Range**

- The usual oral adult dose is 25–50 mg every 4 hours as needed for pain relief
- The recommended single parenteral dose is 30 mg by IM, SC, or IV route

**Dosage Forms**

- Injection: 30 mg
- With acetaminophen: tablet 25/650 mg
- With naloxone (intended to avoid parenteral use): 50/0.5 mg

**How to Dose**

- Dosage should be adjusted according to the severity of the pain and the response of the patient. Oral dose can be increased up to a maximum of 450 mg/day
- Parenteral administration may be repeated every 3–4 hours. Doses in excess of 30 mg IV or 60 mg IM or SC are not recommended. Total daily dosage should not exceed 360 mg. Constant rotation of IM injection sites is necessary
Dosing Tips
- Because of possible severe tissue damage at injection sites, the SC route of administration should be used only when necessary.
- Pentazocine should be administered with caution to patients with renal or hepatic impairment. Extensive liver disease has been reported to predispose patients to greater AEs from the usual clinical dose.

Overdose
- For pentazocine alone in single doses above 60 mg there have been reports of the occurrence of nalorphine-like psychotomimetic effects such as anxiety, nightmares, strange thoughts, and hallucinations. Marked respiratory depression associated with increased blood pressure and tachycardia have also resulted from excessive doses as have dizziness, nausea, vomiting, lethargy, and paresthesias. The respiratory depression is antagonized by naloxone.

Long-Term Use
- The patients will develop physical dependence and may develop tolerance on long-term use.

Habit Forming
- In patients with addiction vulnerability, risk of aberrant behaviors, and addiction.

How to Stop
- When after more than a few weeks, the patient no longer requires therapy with pentazocine, 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
- The products of the hepatic oxidation of the terminal methyl groups and glucuronide conjugates are excreted by the kidney. Elimination of approximately 60% of the total dose occurs within 24 hours.
- Pentazocine may exist as one of two enantiomers, named (+)-pentazocine and (-)-pentazocine. (-)-pentazocine is a kappa opioid receptor agonist but (+)-pentazocine is not; it has 10-fold greater affinity for the sigma receptor.

Drug Interactions
- Pentazocine is a mild opioid antagonist. Some patients previously given opioids, including methadone for the daily treatment of opioid dependence, have experienced withdrawal symptoms after receiving pentazocine.

Other Warnings/Precautions
- The possibility that pentazocine may cause respiratory depression should be considered in treatment of patients with bronchial asthma.
- Pentazocine should be administered only with caution and in low dosage to patients with respiratory depression, severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.
- The respiratory depressant effects of opioids and their capacity to elevate CSF pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, opioids produce effects which may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution, and only if it is deemed essential.
- Caution should be exercised in the IV use of pentazocine for patients with acute myocardial infarction accompanied by hypertension or left ventricular failure. Data suggest that IV administration of pentazocine increases systemic and pulmonary arterial pressure and systemic vascular resistance in patients with acute myocardial infarction.
- Patients receiving therapeutic doses of pentazocine have experienced hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be closely observed and vital signs checked. If the drug is reinstated, it should be done with caution since these acute CNS manifestations may recur.
- Due to the potential for increased CNS depressant effects, alcohol should be used with caution in patients who are currently receiving pentazocine. It may precipitate opioid abstinence symptoms in patients receiving courses of opiates for pain relief.
- Pentazocine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient should be cautioned accordingly.
Hepatic/Renal Impairment
- Although laboratory tests have not indicated that pentazocine causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater AEs (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Elderly
- Elderly patients may be more sensitive to the analgesic effects of pentazocine than younger patients. Clinical data indicate that differences in various pharmacokinetic parameters of pentazocine may exist between elderly and younger patients.
- Sedating drugs may cause confusion and oversedation in the elderly; elderly patients generally should be started on low doses of pentazocine and observed closely.
- This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Children and Adolescents
- The safety and efficacy of pentazocine as preoperative or preanesthetic medication have been established in pediatric patients 1–16 years of age.
- Use of pentazocine in these age groups is supported by evidence from adequate and controlled studies in adults with additional data from published controlled trials in pediatric patients.
- The safety and efficacy of pentazocine as a premedication for sedation have not been established in pediatric patients less than 1 year old. Information on the safety profile of pentazocine as a postoperative analgesic in children less than 16 years is limited.

Pregnancy
- Category C
- It is also not known whether pentazocine can cause fetal harm when administered to pregnant women or can affect reproduction capacity.
- Pentazocine should be given to pregnant women only if clearly needed. However, animal reproduction studies with pentazocine have not demonstrated teratogenic or embryotoxic effects.

Breast-Feeding
- It is not known whether this drug is excreted in human milk.
- Because many drugs are excreted in human milk, caution should be exercised when pentazocine is administered to a breast-feeding woman.

THE ART OF PAIN PHARMACOLOGY

Potential Advantages
- Talwin-NX may deter opioid addicts from injecting it IV since naloxone will antagonize the effects of the pentazocine.

Potential Disadvantages
- Relatively weak analgesia; not for chronic pain.

Primary Target Symptoms
- Orally, mild-to-moderate chronic pain; or parenterally, for moderate-to-severe acute pain.

Pearls
- In general, “agonist/antagonist” type opioids should never be used to treat long-term chronic pain.
- Analgesic use for rare patients with unmanageable adverse reactions to other first-line opioids.
- Some patients previously given opioids have experienced withdrawal symptoms after receiving pentazocine.
- Pentazocine may increase systemic and pulmonary arterial pressure and systemic vascular resistance in patients with acute myocardial infarction.

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

- Initiate trial of opioid therapy ± adjuvant medications
- 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, psudotolerance, cognitive impairment, encephalopathy, anxiety or personality disorder, depression, addiction, criminal activity)

- 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)

- 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 a 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


