

# Techniques of opioid administration

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## Abstract

Opiates remain the mainstay of the management of severe pain in acute, chronic and palliative settings across all population ages. Pharmacological advancement allows alternative routes of drug delivery best suited to individual patients and their conditions, with improved efficacy and safety. The different approaches to administration vary in their convenience, both to staff and patients, which can translate to differences in prescription compliance. Furthermore, the choice of technique can reduce the amount of drug administered, thereby improving the side effect profile. All opiates, regardless of the technique employed, require meticulous and careful titration based upon sound understanding. Training of staff and education of patients regarding the logistics of the chosen route is important to ensure optimal opiate delivery and detection of undesirable adverse events. Abuse and diversion of opiates warrants judicious administration and prescription considerations.

**Keywords** Administration; analgesia; delivery; opiate; opioid; pain; palliative; route; site; technique

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Methods to provide analgesia remain relatively limited, revolving principally around primary or secondary (antineuropathic) analgesics, local anaesthetic techniques, and neuromodulation in addition to psychological based approaches to improve resilience to pain. Opiates are a group of primary analgesics which are in established practice and have long been an important method for providing analgesia across all settings, and form the main pharmacological treatment for acute peri-operative pain control. The reliance on their use has led to advances in drug delivery and pharmacology, which has improved the overall management of pain, patient satisfaction and safety.

Variations in the routes of opiate administration seek to overcome three basic problems. The first is simply the ease and tolerability of administration. The second is targeting specific sites of opiate receptors for localized or generalized effects, while the last is the reduction in non-analgesic opiate effects, though rarely these effects can be used to an advantage (e.g. antitussive, or reducing gut motility in short bowel syndrome). The varying options to administer opiates all have advantages and

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## Learning objectives

After reading this article, you should be able to:

- describe the different routes of opiate administration
- describe the advantages and disadvantages of different routes
- recognize how opiate pharmacology can dictate the route of administration
- relate dose equivalents between different opiate routes of administration
- evaluate the options of opioid delivery in order to provide tailored administration according to individual patient requirements

disadvantages with respect to these three domains, and no single method is 100% effective in all three.

Methods of administration utilize both the pharmacokinetic property of the specific drug in question and the delivery system, whether a pharmaceutical preparation or medical equipment, such that one route of delivery may be effective for one drug and be inappropriate for another.

The physician is therefore required to select the appropriate drug and route of administration to suit the individual patient under their care. Each opiate has a defined therapeutic index and once the proposed drug and method of administration has been established, the aim is then to titrate to clinical effectiveness, while minimizing adverse effects. Titration dose and timing depends upon the opiate, dose, and route used.

## Classification of techniques

Methods of administration can be divided into simple or advanced. Simple methods are, by their nature, relatively safe owing to the fact that plasma and effector-site concentrations take time to be achieved, and so too do any adverse effects, allowing time for help or assistance. Examples include the oral, rectal, intramuscular and subcutaneous methods. Advanced methods rely on a greater understanding of the drug or equipment, and have the potential to result in the rapid onset of adverse effects, to which the administrator needs to be aware of and to be able to manage.

## Comparison and equivalency

Regardless of the drug or route used, the standard by which the clinical effectiveness is benchmarked is that of immediate release oral morphine, i.e. 10 mg morphine per oral. Understanding the relative potencies of different opiates through different routes is essential in converting between opiates. This occurs frequently when specific routes become inaccessible, or side-effects develop to a particular drug. Rotational opiate conversions are also necessary when tolerance develops. Listed conversions, however, are not exact as they do not take into account incomplete cross-tolerance and are derived mainly from single dose studies in opiate-naïve patients. Actual conversions depend upon many factors individual to the patient which should be born in mind when calculating the new opiate and route. A safety factor of 25% dose reduction, and up to 50% for higher doses, on that

calculated is therefore advisable when converting to alternative drugs/routes before upward titration again to achieve therapeutic effectiveness, while monitoring the patient for signs of toxicity or withdrawal.<sup>1</sup> (Table 1)

Caution is especially important if converting between two non-oral opiates as it is common practice to convert back to an oral morphine equivalent (OME) before converting on to the desired opiate and route, regardless of the initial opiate used. This established practice can potentially increase the statistical error within the conversion process. One example where the route of opiate delivery is commonly changed is in 'step-down' analgesia, when a patient-controlled intravenous administration is changed to oral administration. In the case of morphine, understanding that the bioavailability of morphine is 30% allows the calculation that 10 mg intravenous morphine would be equivalent to requiring 30 mg of oral morphine.

### Oral opiates

Advantages of the oral route are that it is simple, easy and well tolerated in most patients. Furthermore, no additional equipment is required, relying instead on the differing pharmacological and pharmaceutical properties of the opioid to achieve differing effects.

Unfortunately, the oral route is not always available or desirable. For example, physical restriction of oral access with limited mouth opening after head-and-neck surgery, vomiting, and bowel obstruction all are relative contraindications for this route. A reduced consciousness level renders this route equally impractical unless an orogastric or nasogastric tube is utilized. Finally, gastroparesis and ileus can prevent drug transit. Opiates can act directly on mu opioid receptors in the gut wall further exacerbating this state.

Another disadvantage of this route is that of first pass metabolism. This renders fentanyl unsuitable due its extensive

hepatic metabolism. Finally, a fraction of opioid will also stimulate receptors in the chemoreceptor trigger zone resulting in nausea, which can further compromise the gastrointestinal function in some individuals and their ability to receive subsequent dosing.

Different pharmaceutical preparations exist in an attempt to modify the delivery of certain opiates. Preparations such as liquid, capsule, and encapsulation exist. These are broadly divided into either immediate-release (IR) or slow-release (SR) preparations (also called extended-release, prolonged-release or controlled-release).

IR preparations typically have an onset of action 20–30 minutes, with analgesia obtained in 45–60 minutes, and a duration of action extending to around 3–4 hours. They are usually simple preparations of the active drug and some can be supplied in liquid form, such as oral morphine and oxycodone liquid/syrup. Differences in pharmacokinetics are mainly related to the different pharmacologic properties of each drug.

SR preparations, by contrast, utilize pharmaceutical techniques to alter the release of the active molecules, delaying their delivery. This allows a higher initial dose to be given and a sustained plasma level with a duration of action of 12–24 hours, avoiding the peaks and troughs typically associated with multiple IR dosing. The disadvantage, however, is that the onset is slow, typically taking 3–4 hours for peak effect. The use of SR preparations is not usually practical as a sole preparation in acute or cancer pain management (i.e. outside of non-cancer chronic pain), and tends to follow, or complement, the use of IR preparations. This is best achieved by calculating the total daily IR dose required and halving it for a twice daily SR regime, with 10% of the total daily dose continued *pro re nata* as IR for incident or breakthrough analgesia. Over reliance on IR preparations in the chronic pain setting should alert the prescriber to look for abnormal pain behaviour.

**Morphine** comes in IR and SR forms and has a bioavailability of 30%. Most of the metabolites of morphine-3-glucuronide provide no analgesia, while morphine-6-glucuronide is more potent than morphine. Both are renally excreted.

**Codeine** is a prodrug and requires hepatic first pass metabolism with the enzyme CYP2D6 for conversion to morphine, with about 10% of the dose being converted to morphine. About 8–10% of Caucasians lack this enzyme, however, and therefore would achieve no benefit, whereas fast acetylators have a reduced duration of affect.

**Oxycodone** is another orally available opioid for the treatment of moderate-to-severe pain. Oxycodone's bioavailability is significantly higher than morphine's (up to 87%), and it has an analgesic onset of action of about 15 minutes, peaking at about 1 hour, with a slightly longer half-life. The SR preparation is indicated where treatment is expected to be prolonged, and has a biphasic release pattern, unlike other SR opiate preparations, resulting in an initial rapid release followed by a more sustained release. A tamper-resistant preparation which produces a lower oxycodone concentration when crushed is available but still requires judicious prescribing to prevent abuse and diversion. A combined pharmaceutical preparation with naloxone aims to

### Approximate equi-analgesic potencies of opioids for oral administration

	Potency ratio with oral morphine	Equivalent dose to 10 mg oral morphine
Codeine phosphate	0.1	100 mg
Dihydrocodeine	0.1	100 mg
Hydromorphone	7.5	1.3 mg
Methadone	*	*
Morphine	1	10 mg
Oxycodone	2	5 mg
Tapentadol	0.4	25 mg
Tramadol	0.15	67 mg

The relative potency of methadone depends on the starting dose and the duration of administration. Conversions to and from methadone should always be undertaken with specialist advice.

Source: British Pain Society: Dose Equivalent and Changing Opioids. <https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware/structured-approach-to-prescribing/dose-equivalents-and-changing-opioids>.

Table 1

reduce opiate-induced constipation, preferentially binding opiate receptors in the gut; there is no clinically relevant reduction in the systemic analgesic effect of the oxycodone, because 97% of the naloxone is removed by first pass metabolism.

**Tramadol** is a centrally acting, non-selective opioid agonist with norepinephrine and serotonin reuptake inhibition. Due to the additional pathway for analgesia, it is useful for both neuropathic and nociceptive pain. It relies on CYP2D6 and CYP3A4 isoenzymes for metabolism into a more potent metabolite (M1). Furthermore, tramadol has a high bioavailability regardless of concomitant food intake, has antitussive properties, reduced gastrointestinal effects and results in less respiratory depression. One significant disadvantage however is the risk of serotonin syndrome with the concurrent use of drugs affecting the serotonergic neurotransmitter system (e.g. SSRI, SNRI, TCA, triptans). This is a potentially life-threatening condition which may manifest as mental-status changes, autonomic instability, neuromuscular aberrations and/or gastrointestinal symptoms.

**Tapentadol** is another  $\mu$  opioid agonist with norepinephrine reuptake inhibition for the treatment of severe chronic pain. It is also effective for management of neuropathic pain due to its dual mechanism of action, but with a lower incidence of serotonin syndrome compared with tramadol. There is significant inter-individual variability requiring dose titration to balance between therapeutic and adverse effects. Due to significant first pass metabolism, it has a bioavailability of 32%, requiring 3–6 hours before maximum serum concentrations are achieved. Drug and metabolite elimination is exclusively via the kidneys.

**Methadone** is a synthetic  $\mu$ -opioid receptor antagonist. It also has NMDA receptor antagonist properties, with serotonin and noradrenaline re-uptake inhibition, rendering it useful for treating neuropathic pain and preventing opioid tolerance, withdrawal, and opiate-induced hyperalgesia. Risks include drug interactions and QTc prolongation. It cannot be cleared by dialysis. Unfortunately, gastric motility, gut perfusion and pH all affect oral absorption. Furthermore, patients demonstrate genetic polymorphisms in the cytochrome P450 3A4 enzyme system, which is possibly also auto-induced during hepatic first-pass metabolism with long-term use. The result is highly variable inter-patient bioavailability of 35–100%.<sup>2</sup> In addition, once absorbed, the fraction of active free drug available is dependent on variable protein binding, renal function, and fat redistribution, resulting in further variations in pharmacokinetics and a long half-life, with the risk of prolonged opiate toxicity after sustained treatment. In the treatment of pain, methadone has typically been used for the management of chronic cancer and non-cancer pain, where dose changes can be done slowly under specialist supervision. More recently, however, there has been renewed interest in its use in the acute setting, especially in orthopaedic and neurosurgery. Even a single dose of methadone given before surgical incision can reduce postoperative pain scores and reduce opioid requirements, with no increase in opioid-related side-effects, probably due to its long duration of action and combined pharmacological effect.<sup>3</sup>

### Rectal route

Rectal opioid administration is rarely used in UK practice; however, preparations exist for morphine, oxycodone and hydromorphone in the form of a micro-enema. Drug absorption from suppositories varies if the rectum is full or empty. Furthermore, placement of the suppository in the lower half of the rectum results in drug absorption into the inferior and middle rectal veins. These drain into the inferior vena cava and therefore avoid first pass metabolism, resulting in higher systemic concentrations. Onset can be rapid, and is a useful route for administration of rapid rescue opioid in cancer patients. Rectal administration, therefore, can prove an advantage where other routes are unavailable or not desirable, but rectal lesions and previous colorectal surgery would be notable contraindications to its use. Patient consent and preference also limits its use.

### Intravenous route

*Intravenous administration* allows a faster onset of pain relief and more predictable pharmacokinetics when compared to other routes due to the 100% bioavailability achieved. Besides the convenience of either intermittent administration or continuous infusion of opioids, it allows rapid early establishment of effective analgesia which is suited to perioperative use. It also allows reliable opioid delivery when the patient is nil-by-mouth or has decreased gut absorption. Disadvantages include the need for cannula insertion and its maintenance, requiring trained staff.

*Target-controlled infusion* of opioids allows a user-defined opiate concentration in the body compartment or tissue of interest, using a drug-specific pharmacokinetic model algorithm. The Minto model has been used for the ultra-short acting opioid remifentanyl to provide analgesia based on patient parameters such as age, weight and height. This requires specialized infusion pumps and adequately trained staff.

*Patient controlled analgesia systems* allow patient autonomy and avoids the inherent delay in staff delivering analgesia by other means. It also allows a more consistent plasma concentration, reducing the peaks and troughs of intermittent administration, resulting in better quality of analgesia. The device consists of a computer controlled portable pump and drug reservoir, and allows a preset bolus dose to be delivered by the patient, with a physician-controlled lock-out time. The computerized lock-outs prevent overdose, and other security features prevent tampering of controlled drugs. A background infusion rate can also be set, but this somewhat reduces the inherent safety of the system requiring a conscious non-sedated patient to be able to use the demand button; it is often used for non-opiate naive patients to off-set their normal opiate requirements. Like other routes of administration, co-analgesics such as ketamine may be added for specific indications.

*Nurse controlled analgesia (NCA) systems* allow the use of a PCA system, where patients lack the cognitive ability to use it themselves. These are especially useful in the paediatric population. A longer lock-out time, typically 20–30 minutes outside of the intensive care environment, is employed in these situations reducing the frequency of bolus administration, but increasing the need for patient observation for adverse effects compared with PCA. Combination PCA and NCA can also be employed with

daytime patient control and night-time nurse control, thereby facilitating patient sleep overnight.<sup>4</sup>

Besides morphine, fentanyl and oxycodone used for post-operative analgesia, IV PCA remifentanyl has also been used for labour analgesia as an alternative to a labour epidural, due to its quick onset and offset.

### **Intramuscular and subcutaneous route**

The rationale for the use of intramuscular (IM) and subcutaneous (SC) administration is to inject a deposit of opioid into the tissue which can then be absorbed into the systemic circulation. It obviates the need for direct intravenous access, and is therefore useful where there is a deficit of suitably trained staff or intravenous access is difficult. Absorption, however, depends on adequate tissue perfusion. Low perfusion states such as hypovolaemia (dehydration, haemorrhage), shock or hypothermia will result in poor uptake into the systemic circulation, leading to inadequate analgesia. The unabsorbed drug deposit can then remain as a reservoir, risking sudden bolus absorption if the perfusion were to quickly improve. Furthermore, the pain on injection may not be tolerated by some patients risking inadequate dosing and poor analgesia.

The subcutaneous route has the advantage over the intramuscular route in being able to be administered via an indwelling cannula. Subcutaneous cannula insertion is easy to train, can be left in situ for some time, can be rotated in its positional siting, and does not carry the risk of nerve injury that IM placement does. Typical sites include the proximal lateral aspect of the arm or thigh, or abdomen. These are well tolerated by patients and are especially used for the management of cancer pain, where alternative routes for opioid medications are less tolerated, pending more advance analgesic techniques.

The utility of SC syringe drivers in these situations is their ease of use. Pumps are typically small, simple and very portable. Many other symptoms are often managed with the pain and adjunctive agents are commonly added with the primary analgesic, such as antiemetics, which can increase local irritation, requiring changing the site of administration more frequently. Otherwise sites can remain useable to days or even weeks at a time. One disadvantage of the system is the time to reach therapeutic plasma concentrations on starting the infusion, and the inability to provide bolus administration, requiring separate loading and breakthrough analgesia.

### **Intra- and peri-articular**

Many different opiates and techniques of intra/peri-articular injections have been demonstrated, often in combination with local anaesthetics to improve postoperative outcomes after joint procedures (e.g. shoulder, hip, knee, ankle), either as a single-shot injection or infusion. Peripheral opioid receptors are thought to play a role in mediating the effects of intra-articular opiates, and reversal of the analgesic effect is demonstrated by intra-articular naloxone.

Intra-articular morphine can produce analgesia for up to 24 hours post-injection. There is a possible dose-dependent effect with various explanations having been described. Furthermore,

significant inter-individual and population variation exists in the analgesic effects of intra-articular morphine. Variations may be attributable to differences in surgical technique, inflammatory reaction, the effect of tourniquets, and systemic uptake.<sup>5</sup>

### **Intraspinal opiates**

Opiates can be delivered directly intraspinally, reducing the effects of redistribution, and allowing a lower total dose of administration to achieve the same local effect-site concentration at the dorsal horn. This stems from its direct delivery to opioid receptors within the central nervous system, which translates into a rapid onset of action (the fastest of all routes of opiate administration), superior analgesia, prolonged therapeutic effects, and a reduction in systemic side effects. The dose reduction required to achieve similar analgesic effects depends on the lipophilicity of the drug, with highly lipid soluble drugs requiring less reduction. They can be administered either epidurally or intrathecally, and it is important to use proprietary preservative free preparations to avoid potentially devastating neurotoxicity. The dose required for intrathecal administration is less than epidural administration. For example, intrathecal morphine 0.2–0.3 mg would achieve a similar effect to 2–3 mg of epidural morphine.

Epidural analgesia has traditionally been considered a 'gold standard' analgesia for major surgery and labour analgesia, and opiates can be used as a sole agent or, more commonly, as an adjunct with local anaesthetics. These are typically administered as infusions, but can be given as a single-shot administration or patient controlled epidural analgesia (PCEA). Such PCEA systems are typically employed in labour, polytrauma and postoperative analgesia, as well as rib fracture management. While opiates administered in this way improves the overall analgesic effect, pruritus can be a limiting side effect.

Opiates can also be delivered directly into the cerebrospinal fluid (CSF) in the intrathecal space either solely or as an adjunct to local anaesthetics in spinal anaesthesia, or for analgesia for malignant and non-malignant pain through an external pump or an implantable drug-delivery system. Problems with intrathecal opiates can be divided into mechanical, drug and patient-related complications. Mechanical problems are mainly related to long term intrathecal catheter use and are the same as for epidural administration (kink, migration, obstruction, dislodgement, disconnection) and pump failure (battery depletion, implant migration or erosion, technical issues, device interactions). Catheter and pump insertions also carry risks of bleeding, infection and injury to surrounding structures, in addition to the anaesthetic risks for the device insertion. Drug-related issues involve formulation compatibility for CSF infusion for the intrathecal route, drug interactions with concurrently infused medication, dilution errors, infection control during administration or pump reservoir refilling, respiratory depression, and granuloma in long-term infusions.

Neuraxial morphine and fentanyl have improved labour and post caesarean section analgesia, however, respiratory depression has been a recognized side effect. Pre-Botzinger complex neurons with neurokinin-1 receptors in the medulla are

selectively inhibited by opioids and mediate the opioid-induced respiratory depression, rather than the previously thought ventral medullary opioid receptors interaction with CSF opioids. The risk is increased with morphine which is more water soluble, resulting in rostral spread within the CSF. Fentanyl, on the other hand, is more lipid soluble and tends to be taken up more readily in the spinal cord at the site of injection. Local vascular uptake with cranial transport of drug can also occur.

Caution must be exercised when prescribing neuraxial opioids as the complex pharmacokinetics of intrathecal, epidural and plasma opioids have variations within the relative compartments depending on their exact level of placement. Concurrent systemic (oral, transdermal or intravenous) opioids with existing neuraxial opioids may predispose patients to early or delayed respiratory depression.

### Transmucosal

Transmucosal routes allow rapid absorption of common lipid soluble opiates via a rich capillary plexus, bypassing first-pass metabolism. This allows the rapid non-parenteral administration of opiates that would otherwise be rendered ineffective by the oral route due to extensive hepatic metabolism, e.g. buprenorphine. Transmucosal immediate release fentanyl is another example, which is useful for breakthrough pain, and exists in various formulations; sublingual tablet, sublingual spray, intranasal spray, pectin-based nasal spray, buccal lozenges/lollipops and buccal soluble film. Its utility is especially seen in head and neck cancers with or without radiation-induced mucositis.

The intranasal route is an ideal non-invasive route to providing analgesia in paediatric patients, avoiding the time spent in establishing intravenous (IV) access which often delays prompt analgesia in emergency settings, especially in uncooperative paediatric patients who may not tolerate IV access. Furthermore, intranasal naloxone has also been used for the treatment of opiate overdose.

A novel sublingual sufentanil tablet PCA system (SSTS) using 15 µg with a 20-minute lockout interval has recently been compared to IV PCA morphine 1 mg with a 6-minute lockout interval for the management of acute postoperative pain.<sup>6</sup> Apart from overcoming the disadvantages of a traditional intravenous

PCA system, such as IV access and attached tethering lines, it has been demonstrated to produce quicker onset of analgesia with fewer adverse effects, along with enhanced patient and nursing-staff satisfaction. Sufentanil is rarely used in the UK, but it is highly lipophilic allowing its rapid sublingual absorption. Furthermore, it has a rapid equilibration half-life between plasma and CNS (6 minutes compared to 2.8 hours for morphine) aiding its quick onset of analgesia. It also lacks active metabolites and possesses a high therapeutic index (26,000 compared to 70 for morphine in pre-clinical trials) aiding safety. The system works by using a hand-held device which is secured to the bedside and loaded with a 40 tablet cartridge which is said to last approximately 2 days. It is preprogrammed with a 20-minute lockout interval and uses a radiofrequency identification (RFID) thumb tag aiding security and safety in only allowing the patient to operate the device. The lack of programmability reduces the potential of such errors, but is one disadvantage in the minority of opiate tolerant patients who may require baseline infusions and alteration of the bolus dose. Each tablet comes in the form of a small bioadhesive disc (3 mm diameter; 0.75 mm thick) which is dispensed from the tip of the device upon demand.

### Pulmonary opioids

Various opioids have been nebulized in palliative care, most commonly morphine, diamorphine and fentanyl. Off-label use of intravenous formulations is preferred over the oral formulations, particularly preservative-free, due to the reduced risk of bronchospasm. Fentanyl probably has the lowest incidence of bronchospasm of all opiates given by this route. Furthermore, nebulized naloxone is a safe and effective alternative to parenteral administration in suspected opioid overdose in spontaneously breathing patients.

### Transdermal

Transdermal patches utilize lipophilic opiates' ability to be passively absorbed through the skin for continuous analgesia in severe chronic and cancer pain. The steady-state plasma concentration is usually attained 12–24 hours after application, to provide a controlled drug delivery rate independent of gastrointestinal function. Care must be taken with anything which

## Transdermal opioid equivalents

	5 µg/hr (weekly patch)	10 µg/hr (weekly patch)	20 µg/hr (weekly patch)	35 µg/hr (twice a week patch)	52 µg/hr	70 µg/hr
<b>A. Buprenorphine transdermal patch</b>						
Codeine phosphate (mg/day)	120 mg	240 mg				
Tramadol (mg/day)	100 mg	200 mg	400 mg			
Morphine sulphate (mg/day)	12 mg	24 mg	48 mg	84 mg	126 mg	168 mg
<b>B. Fentanyl transdermal patch</b>						
Patch strength (µg/hr)	12	25	50	75	100	300
Oral morphine (mg/day)	45	90	180	270	360	1120

Source: British Pain Society: Dose Equivalent and Changing Opioids. <https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware/structured-approach-to-prescribing/dose-equivalents-and-changing-opioids>.

Table 2

changes the uptake of the drug through the skin, for example altered peripheral perfusion, heat exposure (heating pads, baths, electric blankets, sunbathing or fever, strenuous exertion), and local skin condition. Transdermal opiate delivery reduces the need for repeated dosing and fluctuations in pain scores, but alternative analgesia often needs to be prescribed to account for breakthrough or incident pain, and some patients can develop local skin irritation that limits further use.

Conversion tables (Table 2) exist to guide dosing, with conversion from other opiates and routes of administration, but they should not be used in reverse, as this could result in an overestimation of the oral equivalent. Alternative conversion tables exist for this purpose. In the case of fentanyl, it is recommended to upward titrate no sooner than 3 days after initiation, and every 6 days thereafter.

Buprenorphine patches provide transdermal delivery via a matrix. It is a partial agonist at mu and delta opioid receptors and ORL-1 (nociception) receptors, and an antagonist at kappa receptors. Transdermal buprenorphine demonstrates a ceiling effect for respiratory depression, although this is lost when combined with another CNS depressant. Patients are also less likely to demonstrate tolerance or withdrawal. Furthermore, it has favourable pharmacokinetics meaning that standard dosing, even for elderly patients with decreased renal function is possible. Application site irritation, however, is a problem that often limits persistent use.

Fentanyl iontophoretic transdermal system (ITS) is a portable patient-controlled analgesia system which uses an electric current to increase the rate of transfer of ionized fentanyl through electro-repulsion as compared to simple diffusion from transdermal patches. Serum fentanyl concentration decline is similar to IV fentanyl injection. The disposable ITS delivers 40 µg fentanyl over 10 minutes, with a maximum of six doses/hour and functions up to 24 hours or 80 doses, when it will automatically

shut down. The skin site of application can then be changed. The PCA system provides convenient portability and patient mobility compared to existing PCA pumps. The low morphine lipophilicity hinders its use with this system. ◆

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## FURTHER READING

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