TRANSDERMAL:

Fentanyl: this drug can be administered via a patch on the skin. It is simple, non-invasive and allows continuous release into the bloodstream. In passive (conventional) transdermal administration, the patch is available in 4 sizes and provides sustained release of fentanyl at rates of 25,50,75 and 100 micrograms/hour for periods of 48-72 hours.

The patch is attached to the skin using a contact adhesive, adjacent to which is a microporous membrane that controls the rate at which fentanyl is transferred from the drug reservoir to the skin.

The reservoir is a shallow compartment with a gel matrix and may contain up to 10mg of fentanyl, in order to provide a high concentration gradient to facilitate diffusion across the skin.

It has a backing to prevent escape of fentanyl. The skin layers act as a secondary reservoir and thereby dampen any fluctuation in fentanyl level. This also means that after the patch has been removed, there is a prolonged residual effect. Other disadvantages include slow onset time and inability to adjust the dose during the period of application.

Side-effects tend to be the same as for oral opiates, and there may be slight redness around the site of the patch.

There is also a new type called the iontophoretic(active) transdermal system which enhances drug delivery using a skin electrode, a skin current returning electrode and an electric power source. However, this has yet to be used clinically.

TRANSMUCOSAL:

Again, fentanyl : **oral transmucosal fentanyl citrate** (OTFC) : this has been recently marketed as Actiq?. This is a lozenge on a stick which allows rapid absorption of fentanyl and onset of analgesia within 5-10 minutes.

It has a duration of action of 2-3 hours. It is useful to treat incident pain, as it allows delivery of sufficiently high doses to cover the transient increase in level of analgesia needed without necessitating a sustained level that may be too high once the incident pain has passed (which would increase the risks of side-effects and tolerance).

A single 800microgram dose is roughly equivalent to a single intravenous bolus of 10mg morphine in terms of speed of onset, duration and quality of analgesia.

INTRASPINAL NARCOTIC ANALGESIA (INA):

Intraspinal drug delivery systems, sometimes referred to as "the pump" are implanted therapy for drug infusion, commonly using opiates.

Epidural and intrathecal infusion of opioids concentrates the drug at the receptors in the dorsal horn of the spinal cord, a vital part of the pain pathway. Drug levels at other receptors(in the brain and gut for example) are low and therefore there are potentially fewer adverse effects.

Intrathecal injections are more efficient than epidural ; 90% of an epidural dose which does not reach the spinal fluid goes into the systemic circulation so that if large doses are given, there will be the usual side-effects.

An estimate of the equianalgesic doses necessary for conversion from epidural to intrathecal route is 10:1 (10mg epidural dose is approximately equal to 1mg intrathecal)

Several different delivery systems are available, including the Infusaid? Model 400 which provides constant flow at a predetermined rate, generally between 1 and 6 mL per day. A side port allows additional bolus injections. The device is driven by Freon? gas.

The Synchromed™ delivery system comprises a pump in a round metal housing that stores and releases presribed amounts of drug. There is a miniature peristaltic pump, drug reservoir, battery, antenna and microprocessor.

The pump is implanted surgically, usually in or near the abdomen and can be refilled through the skin using a needle and syringe. A catheter of silicone tubing is tunneled under the skin from the pump to the delivery site.

This system can deliver very specific doses ranging from 0.096 mL/day to 0.9mL/hour. There is an optional side port to allow bolus injections.

Selection criteria for pump implantation include:

1. Chronic intractable pain that has failed to respond to less invasive methods of pain control.

2. Systemic (oral, rectal, intravenous) analgesics cause intolerable side effects

3. Good to excellent pain relief from test dosing

4. Patient is not allergic to morphine

To ensure that the technique will be successful a preimplantation screening is necessary. This may involve bolus injections or a continuous epidural infusion over 2-3 days.

Implantation can be performed under local anaesthesia or regional blockade and patients may be discharged 2-3 days later. Initial intrathecal doses are calculated from the epidural doses necessary to provide good pain relief, at a ratio of a tenth the epidural dose and can continue to be titrated after discharge.

The pump is activated at the time of implantation. The pump reservoir holds approximately 30-90 days' worth of medication, refill being done at intervals depending on pump delivery rate (usually every 25-50 days) Refill can be easily done by a nurse in an outpatient setting and takes up to half an hour.

Analgesic agents:

Morphine is the standard drug used in intraspinal analgesia.

The important points to consider are:

1. lipid solubility

2. binding affinity to receptors

3. equianalgesic dosage

Highly lipid soluble opioids provide better segmental analgesia, whereas the less lipid soluble drugs can be distributed further and thus provide analgesia at more distant sites (e.g. lumbar administration of morphine can be used to treat head and neck pain). Low lipid solubility in morphine also means a slower onset of action and longer duration of central nervous system effects.

Receptor binding affects the degree of efficacy: a drug with high receptor affinity, such as sufentanil, produces a greater effect at a lower receptor occupancy than a drug with low receptor affinity such as morphine.

A high lipid solubility, high affinity drug such as sufentanil will have a rapid onset of action (as does fentanyl) and a relatively long duration of action.

Opioid	Epidural dose	Duration
Morphine	5-10mg	6-24 hrs.
Hydromorphone	1-1.5 mg	6-16 hrs.
Methadone	4-8 mg	6-10 hrs.
Fentanyl	25-100 mcg	2-4 hrs.
Sufentanil	10-30 mcg	4-6 hrs.

Other drugs which may be used include beta-endorphin and DADL (D-Ala2-D-leu5-enkephalin)

which are endogenous opiates and agents such as clonidine (an alpha-2 agonist) or local anaesthetic agents such as bupivicaine. The latter is quite often used in conjunction with intraspinal opioids.

Midazolam may be used for refractory neuropathic pain and baclofen may be added to opioid medication to combat spasticity.