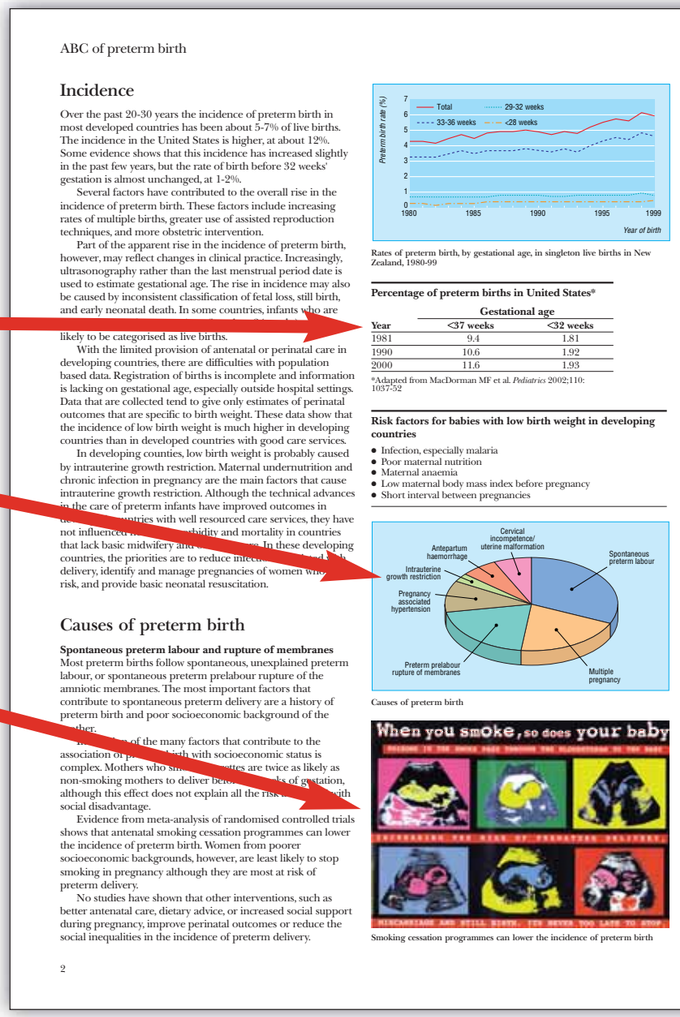
ABC SERIES

Features of the ABC Series

- The ABC titles are serialised and peer reviewed in the **BMJ** before being published in this great series of books
- The pages are always laid out in two columns with the highly illustrated ‘slide show’ of relevant visual aids alongside the text, pulling out key points from the text
- Each book is easy to read and contains a consistent style and the following key features which help to show the important aspects of the text



ABC of preterm birth

Incidence

Over the past 20-30 years the incidence of preterm birth in most developed countries has been about 5-7% of live births. The incidence in the United States is higher, at about 12%. Some evidence shows that this incidence has increased slightly in the past few years, but the rate of births before 32 weeks' gestation is almost unchanged, at 1-2%.

Several factors have contributed to the overall rise in the incidence of preterm birth. These factors include increasing rates of multiple births, greater use of assisted reproduction techniques, and more obstetric intervention.

Part of the apparent rise in the incidence of preterm birth, however, may reflect changes in clinical practice. Increasingly, ultrasonography rather than the last menstrual period date is used to estimate gestational age. The rise in incidence may also be caused by inconsistent classification of fetal loss, still birth, and early neonatal death. In some countries, infants who are likely to be categorised as live births.

With the limited provision of antenatal or perinatal care in developing countries, there are difficulties with population based data. Registration of births is incomplete and information is lacking on gestational age, especially outside hospital settings. Data that are collected tend to give only estimates of perinatal outcomes that are specific to birth weight. These data show that the incidence of low birth weight is much higher in developing countries than in developed countries with good care services.

In developing counties, low birth weight is probably caused by intrauterine growth restriction. Maternal undernutrition and chronic infection in pregnancy are the main factors that cause intrauterine growth restriction. Although the technical advances in the care of preterm infants have improved outcomes in [illegible] countries with well resourced care services, they have not influenced [illegible] bility and mortality in countries that lack basic midwifery and [illegible]. In these developing countries, the priorities are to reduce infec[illegible] delivery, identify and manage pregnancies of women who risk, and provide basic neonatal resuscitation.

Rates of preterm birth, by gestational age, in singleton live births in New Zealand, 1980-99

Percentage of preterm births in United States*

	Gestational age	
Year	<37 weeks	<32 weeks
1981	9.4	1.81
1990	10.6	1.92
2000	11.6	1.93

*Adapted from MacDorman MF et al. *Pediatrics* 2002;110: 1037-52

Risk factors for babies with low birth weight in developing countries

- Infection, especially malaria
- Poor maternal nutrition
- Maternal anaemia
- Low maternal body mass index before pregnancy
- Short interval between pregnancies

Causes of preterm birth

Smoking cessation programmes can lower the incidence of preterm birth

Causes of preterm birth

Spontaneous preterm labour and rupture of membranes
Most preterm births follow spontaneous, unexplained preterm labour, or spontaneous preterm prelabour rupture of the amniotic membranes. The most important factors that contribute to spontaneous preterm delivery are a history of preterm birth and poor socioeconomic background of the [illegible]ber.

[illegible] of the many factors that contribute to the association of p[illegible]th with socioeconomic status is complex. Mothers who sm[illegible]ttes are twice as likely as non-smoking mothers to deliver be[illegible]ks of gestation, although this effect does not explain all the risk [illegible]with social disadvantage.

Evidence from meta-analysis of randomised controlled trials shows that antenatal smoking cessation programmes can lower the incidence of preterm birth. Women from poorer socioeconomic backgrounds, however, are least likely to stop smoking in pregnancy although they are most at risk of preterm delivery.

No studies have shown that other interventions, such as better antenatal care, dietary advice, or increased social support during pregnancy, improve perinatal outcomes or reduce the social inequalities in the incidence of preterm delivery.

The rate of preterm birth varies between ethnic groups. In the United Kingdom, and even more markedly in the United States, the incidence of preterm birth in black women is higher than that in white women of similar age. The reason for this variation is unclear because differences remain after taking into account socioeconomic risk factors.

Preterm births by ethnic group in United States 2000*

- Black—17.3%
- Hispanic—11.2%
- Non-Hispanic white—10.4%

*Adapted from MacDorman MF et al. *Pediatrics* 2002;110:1037-52

Multiple pregnancy and assisted reproduction
Multifetal pregnancy increases the risk of preterm delivery. About one quarter of preterm births occur in multiple pregnancies. Half of all twins and most triplets are born preterm. Multiple pregnancy is more likely than singleton pregnancy to be associated with spontaneous preterm labour and with preterm obstetric interventions, such as induction of labour or delivery by caesarean section.

The incidence of multiple pregnancies in developed countries has increased over the past 20-30 years. This rise is mainly because of the increased use of assisted reproduction techniques, such as drugs that induce ovulation and in vitro fertilisation. For example, the birth rate of twins in the United States has increased by 55% since 1980. The rate of higher order multiple births increased fourfold between 1980 and 1998, although this rate has decreased slightly over the past five years. In some countries two embryos only are allowed to be placed in the uterus after in vitro fertilisation to limit the incidence of higher order pregnancy.

Singleton pregnancies that follow assisted reproduction are at a considerable increased risk of preterm delivery, probably because of factors such as cervical trauma, the higher incidence of uterine problems, and possibly because of the increased risk of infection.

Twin pregnancy increases the risk of preterm birth

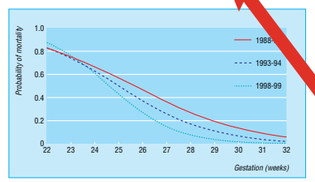
Maternal and fetal complications
About 15% to 25% of preterm infants are delivered because of maternal or fetal complications of pregnancy. The principal causes are hypertensive disorders of pregnancy and severe intrauterine growth restriction, which is often associated with hypertensive disorders. The decision to deliver these infants is informed by balancing the risks of preterm birth for the infant against the consequence of continued pregnancy for the mother and fetus. Over the past two decades improved antenatal and perinatal care has increased the rate of iatrogenic preterm delivery. During that time the incidence of still birth in the third trimester has fallen.

Outcomes after preterm birth

Broadly, outcomes improve with increasing gestational age, although for any given length of gestation survival varies with birth weight. Other factors, including ethnicity and gender also influence survival and the risk of neurological impairment.

The outcomes for preterm infants born at or after 32 weeks of gestation are similar to those for term infants. Most serious problems associated with preterm birth occur in the 1% to 2% of infants who are born before 32 completed weeks' gestation, and particularly the 0.4% of infants born before 28 weeks' gestation. Modern perinatal care and specific interventions, such as prophylactic antenatal steroids and exogenous surfactants, have contributed to some improved outcomes for very preterm infants. The overall prognosis remains poor, however, particularly for infants who are born before 26 weeks' gestation.

The outcome for preterm infants of multiple pregnancies can be better than that of singleton pregnancies of the same gestation. In term infants the situation is reversed. The

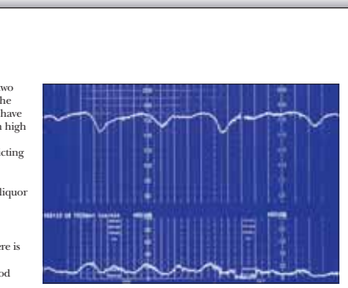


Mortality in UK neonatal intensive care cohorts of infants born before 32 weeks' gestation. Adapted from Parry G, et al. *Lancet* 2003;361:1789-91

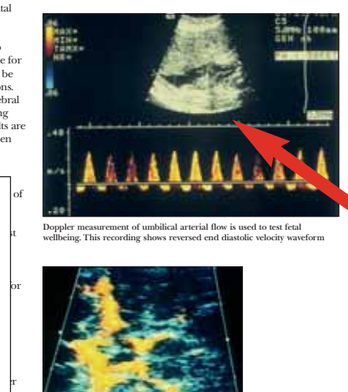
Outcomes for infants live born before 26 weeks' gestation in British Isles*

Gestation (weeks)	Survival to discharge (%)	Survival without handicap at 30 months (%)
22	1	0.7
23	11	5
24	26	12
25	44	23

*Adapted from Wood NS et al. *New Engl J Med* 2000;343:378-84



Monitoring the fetal heart rate can help determine the physiological wellbeing of the fetus. This cardiotocogram shows fetal tachycardia with reduced variability and decelerations



Doppler measurement of umbilical arterial flow is used to test fetal wellbeing. This recording shows reversed end diastolic velocity waveform

Doppler measurement of middle cerebral arterial flow. Abnormal waveforms can show cardiovascular adaptations to placental insufficiency

Induction of labour is most likely to be successful in a woman with a favourable cervix (as assessed by the Bishop score) who has had no caesarean sections and has a history of vaginal delivery

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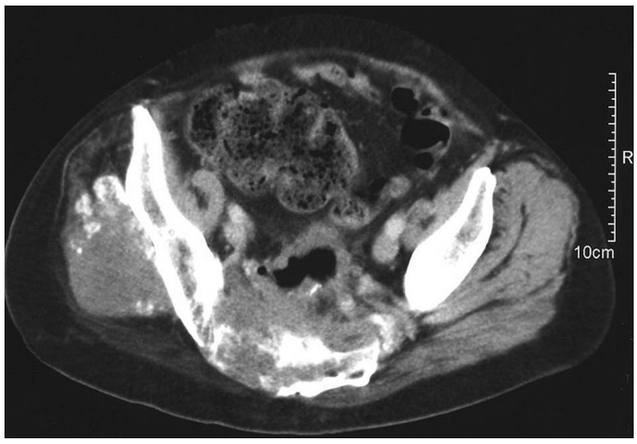
3 Difficult pain

Lesley Colvin, Karen Forbes, Marie Fallon

Pain occurs in up to 70% of patients with advanced cancer, and in about 65% of patients dying from non-malignant disease. For most of these patients (about 80%) pain can be controlled by using a simple, stepwise approach and a limited number of oral analgesics as set out in the WHO's analgesic ladder (chapter 2). About 10% of patients will require more complex, sometimes invasive, management to control their pain, leaving another 10% with cancer pain that is difficult to control.

This group of patients with "difficult pain" present complex management problems. Their pain often falls into one of three categories: it responds poorly to opioids, it is episodic and breaks through despite background opioid analgesia, or opioids are irrelevant in its management.



Computed tomography scan showing advanced pelvic disease from colorectal tumour resulting in severe pain

Opioid irrelevant pain

Pain is not just a physical experience. Patients with pain that does not respond to escalating doses of opioids should be reassessed and other contributors to their pain explored. "Total pain" is best treated by exploring the underlying issues, rather than using opioids. The term "total pain" is used to describe the final sensation of pain perceived by a patient, acknowledging that this perception can be exaggerated by factors other than a physically noxious stimulus—for example, psychosocial distress.

Patients may be overwhelmed by their situation and the central nervous system can express this as physical pain, though social, psychological, or spiritual factors may be major components

Pain that responds poorly to opioids

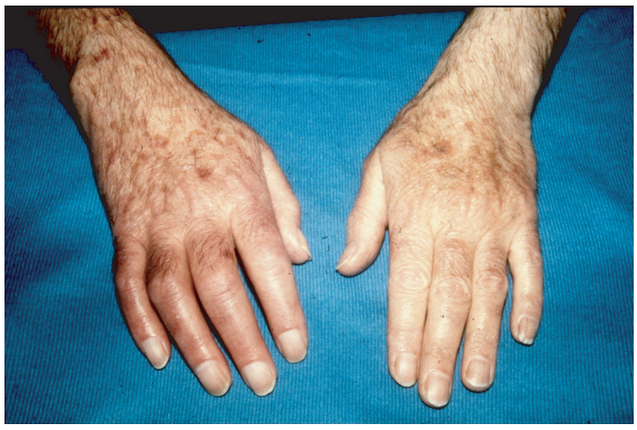
The European Association for Palliative Care (EAPC) guidelines on the use of morphine and alternative opioids in cancer pain confirm oral morphine as the opioid of choice for moderate to severe pain. Dose titration with normal release morphine every four hours, with the same dose for breakthrough pain as required, is suggested. The patient's 24 hour morphine requirement can then be reassessed daily and their regular dose adjusted accordingly. Measures to treat such patients include exploring psychosocial issues, managing the side effects, reducing the dose of opioid, switching to an alternative opioid, or changing the route of administration. The use of adjuvant drugs or co-analgesics may be appropriate, depending on the cause of the pain. Many such patients will have neuropathic pain.

About 10% of patients will have pain that responds poorly to opioids and is uncontrolled even with a dose of morphine sufficient to give them intolerable side effects

Neuropathic pain

Nociceptive pain results from real or potential tissue damage. Neuropathic pain is caused by damage to the peripheral or central nervous system. A simple definition is "pain in an area of abnormal sensation." Pain may be described as aching, burning, shooting, or stabbing and may be associated with abnormal sensation; normal touch is perceived as painful (allodynia). It may be caused by tumour invasion or compression but also by surgery, radiotherapy, and chemotherapy. Many patients have neuropathic pain that responds to opioids, and so initial management should include a trial of opioids. Patients who remain in pain will require additional measures.

The early addition of adjuvant analgesics, such as a tricyclic antidepressant or an anticonvulsant, should be considered. The number needed to treat is 3 for both categories. There is no evidence for a specific adjuvant for specific descriptors of neuropathic pain.



Classical changes associated with a brachial plexopathy due to a right Pancoast tumour: oedema, trophic changes, muscle wasting

In addition, there is no evidence for combining adjuvants. In clinical practice, an adjuvant is chosen for an individual patient after all symptoms and potential side effects are considered. Doses should be titrated to balance analgesia with adverse effects. If titration has reached a limit and pain has only partially responded then a second adjuvant may be added in some cases. This usually means a reduction in the dose of the first. A common example of combining adjuvants is gabapentin, which at maximum tolerated dose can sometimes be reduced to allow the addition of amitriptyline.

Adjuvant analgesics*

Drug	Dose	Indications	Side effects
NSAIDs—for example, diclofenac or COX 2 NSAID (evidence of GI side effects)	50 mg oral every 8 hours (slow release 75 mg every 12 hours); 100 mg per rectum once a day	Bone metastases, soft tissue infiltration, liver pain, inflammatory pain	Gastric irritation and bleeding, fluid retention, headache; caution in renal impairment
Steroids—for example, dexamethasone	8–16 mg a day; use in morning; titrate down to lowest dose that controls pain	Raised intracranial pressure, nerve compression, soft tissue infiltration, liver pain	Gastric irritation if used together with NSAID, fluid retention, confusion, Cushingoid appearance, candidiasis, hyperglycaemia
Gabapentin	100–300 mg nightly (starting dose) (titrate to 600 mg every 8 hours; higher dose may be needed)	Nerve pain of any cause	Mild sedation, tremor, confusion
Amitriptyline (evidence for all tricyclics)	25 mg nightly (starting dose) 10 mg nightly (in elderly patients)	Nerve pain of any cause	Sedation, dizziness, confusion, dry mouth, constipation, urinary retention; avoid in patients with cardiac disease
Carbamazepine (evidence for all anticonvulsants)	100–200 mg nightly (starting dose)	Nerve pain of any cause	Vertigo, sedation, constipation, rash

*Drugs with a primary indication other than pain, but analgesic when used as above.

Non-pharmacological techniques

There are several non-pharmacological techniques for the management of neuropathic pain.

Psychological techniques

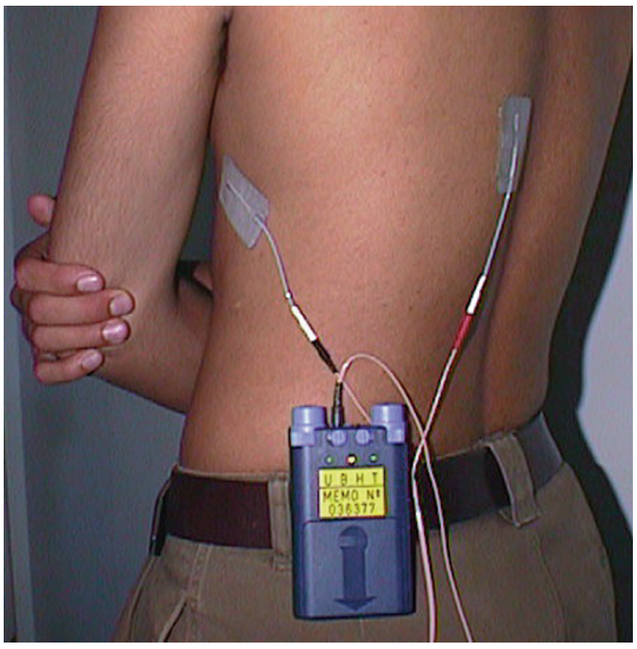
Psychological techniques, such as cognitive behavioural therapies, include simple relaxation, hypnosis, and biofeedback. These methods focus on overt behaviour and underlying cognitions and train the patient in coping strategies and behavioural techniques. Though this is clearly of more use in chronic non-malignant pain rather than in patients with cancer pain, simple relaxation techniques should not be forgotten.

Stimulation therapies

Acupuncture has been used successfully in eastern medicine for centuries. There does seem to be a scientific basis for acupuncture, with release of endogenous analgesics within the spinal cord. Acupuncture is particularly useful for myofascial pain, which is a common secondary phenomenon in many cancer pain syndromes.

Transcutaneous electrical nerve stimulation (TENS) may have a similar mechanism of action to acupuncture. There is evidence to support its use in both acute and chronic pain.

Herbal medicine and homoeopathy are widely used for pain, but often with little evidence for efficacy. Regulations on safety for these treatments are limited compared with those for conventional drugs, and doctors should be wary of unrecognised side effects that may result.



TENS for control of neuropathic pain that responds poorly to opioids

Episodic pain

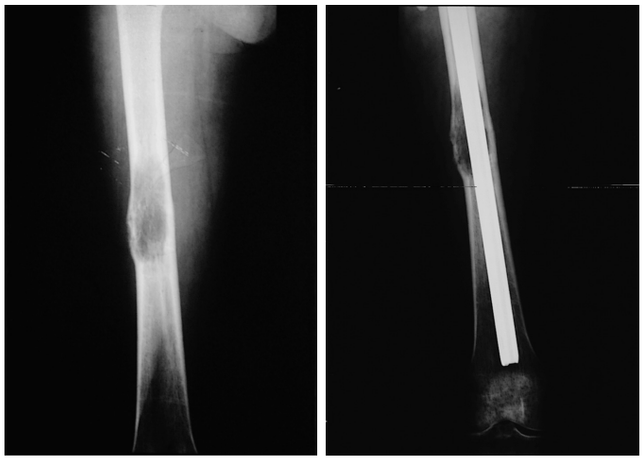
In 2002 an EAPC working group suggested the term episodic pain to describe "any acute transient pain that is severe and has an intensity that flares over baseline." Episodic pain thus encompasses breakthrough pain and incident pain.

Breakthrough pain includes pain returning before the next dose of opioid is due or acute exacerbations of pain occurring on the background of pain usually controlled by an opioid regimen. Incident pain is usually defined as that occurring due to a voluntary action, such as movement or passing urine or stool. Pain due to bony metastases exacerbated by movement or weight bearing can be particularly problematic.

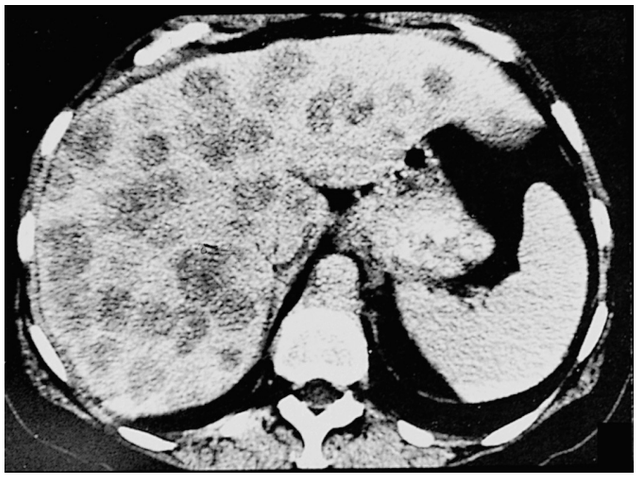
Incident pain

Patients with bony metastases in the spine, pelvis, or femora may have pain that escalates on movement, walking, standing, or even sitting. Opioid analgesics along with non-steroidal anti-inflammatory drugs are the mainstay of treatment, with the aim of making the patient comfortable at rest. Increasing the opioid dose further is often unhelpful as a dose sufficient to make movement possible is too sedating when the resting patient's opioid requirement is decreased. Rescue or breakthrough doses of normal release opioid are usually used in anticipation of movement, along with non-drug measures such as radiotherapy, possible surgery, and appropriate aids and appliances.

Bisphosphonates are interesting drugs established in the prevention of skeletal events due to metastases in most solid tumours. In some patients, analgesia can be achieved acutely, and trial evidence is emerging for good analgesia in pain due to bone metastases.



Radiographs showing lystic lesions in femur (left) and internal stabilisation of bone (right)



Computed tomogram of enlarged liver due to metastatic spread of cancer (reproduced with permission from Times Mirror International Publishing)

Interventional techniques

Before interventional techniques are considered, it is important to exclude untreated depression, general anxiety, and distress (though untreated pain may also lead to any or all of these).

Chapter 2 discusses the role of trying a different opioid. The fundamental limiting factor in most patients with uncontrolled difficult pain is the inability to give higher doses because of side effects. It is worthwhile remembering all the strategies to "open the therapeutic window," including using a different drug.

Methadone deserves a special mention in this context. It has unusual properties, which we do not fully understand. It has a different receptor binding profile from the pure μ agonists and can be remarkably potent at small doses.

It is not unusual to achieve markedly superior analgesia and a better side-effect profile with a switch to methadone. In addition, difficult elements of a pain—such as neuropathic or incident pain, or both—may become easier to control.

Starting or switching to methadone can be complicated in some patients, and specialist advice should usually be sought.

Methadone equianalgesic conversion—seek specialist advice

NB: the ratio depends on the dose of previous opioid

- If morphine 30–90 mg (oral) use ratio of 4:1 (for instance, morphine 30 mg is approximately equivalent to 7 mg of methadone)
- If morphine 90–300 mg (oral) use ratio of 8:1 (for instance, morphine 300 mg (oral) is approximately equivalent to 35 mg methadone (oral))
- If morphine >300 mg (oral) use ratio of 12:1 (for instance, morphine 400 mg (oral) is approximately equivalent to 35 mg methadone (oral))
- If previous morphine dose is *much* higher than 300 mg, the dose ratio will be higher than 12:1

Invasive analgesic techniques

Despite appropriate use of analgesia and non-drug therapies, chemotherapy, and radiotherapy by multidisciplinary teams, a considerable number of patients will still have uncontrolled pain or unacceptable side effects, or both.

Such patients should be considered for some form of invasive analgesic technique as part of their overall management. This may range from a simple nerve block to more invasive techniques such as regional or neurodestructive blocks.

The choice of technique is influenced by:

- *Patient's expectations*—Adequate assessment of pain is the first step in management. Involvement of patients and relatives is important and aids decisions about treatment
- *Prognosis and required duration of analgesia*—Although often difficult to predict, prognosis will affect how appropriate any

particular intervention may be. Further planned oncological treatment may require short term use of interventions for pain control
- *Pathology*—The site and extent of disease will affect the response to analgesics and direct which interventions have a high chance of improving pain control. Plexus or nerve root involvement is common, as is incident pain
- *Personnel*—Early involvement of pain specialists in a multidisciplinary setting is important for planning analgesic strategies. This can help to minimise the length of stay in hospital and reduce problems with severe uncontrolled pain. Local availability of expertise and adequate training of staff and relatives must be considered when technique is selected.

A basic rule is that the technique with the least likelihood of severe side effects should be chosen by using simple techniques before progression to more complex strategies.

In general, neurodestructive techniques should be reserved for when other measures have failed or when life span is obviously limited.

Spinal routes of drug delivery

With improvements in catheter and pump technology, use of spinal lines is becoming more common in pain control. If the technique is carried out by appropriately trained personnel, complication rates are low, allowing flexible, long term analgesia that can be used in an outpatient setting. Catheters can be inserted either into the epidural space or into the subarachnoid (intrathecal) space, where the cerebrospinal fluid is found. The line may be tunnelled subcutaneously to reduce risks of infection and movement of the catheter. The choice of technique depends on several factors.

Drugs

As the patients who need this technique tend to have complex pain problems, multimodal analgesia has the best results. A combination of low dose local anaesthetic, opioid, and clonidine is effective for most patients. Midazolam can be useful as an additional agent, particularly if there are problems with opioid tolerance. If ketamine is used then it should be preservative-free to reduce problems with neurotoxicity. The initial conversion of opioid dose from oral or systemic opioid is variable and depends on the opioid used and comorbidity of the individual patient. Long acting opioids should be stopped before the line is inserted and the patient converted to short acting agents. An approximate dose calculation from subcutaneous diamorphine is:

- Epidural: 1/10 of systemic dose
- Intrathecal: 1/10 of epidural dose

Thus, if a patient was on 100 mg of subcutaneous diamorphine a day, the equivalent epidural dose would be 10 mg and the equivalent intrathecal dose would be 1 mg per 24 hours.

The initial solution used for epidural infusion is normally:

- 9 ml 0.5% bupivacaine
- 75–150 μg clonidine
- Diamorphine according to individual patient.

This gives a total volume of 10 ml infused over 24 hours.

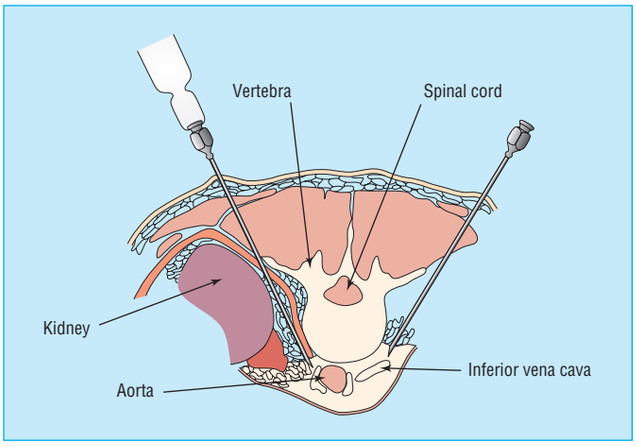
Should there be a major problem with pump malfunction, and the whole syringe were accidentally given at once, this should not give a major life threatening overdose. Education and training of staff is important to minimise potential complications.

The future

Agents not currently widely available in the UK that may be helpful in managing patients with cancer pain include:

Examples of invasive analgesic techniques

Peripheral	Central
Peripheral nerve block	*Non-destructive*
• Intercostal	• Epidural
• Femoral	• Intrathecal
• Sciatic	
Major nerve block	*Neurosurgical/destructive*
• Brachial plexus	• Rhizotomy
• Psoas	• Cordotomy
• Paravertebral sensory nerve root ablation	• Intrathecal phenol
• Coeliac plexus	



Coeliac plexus nerve block

Factors affecting choice of regional technique

Epidural	Intrathecal
Procedural	
• Simple procedure—local anaesthetic with or without sedation	• Sedation or general anaesthesia usually required
• Fixation can be difficult	• Deep fixation at time of insertion
• Catheters not designed for long term use	• Silastic catheter designed for long term use
• Drug spread may be limited, especially if there is tumour in the epidural space, or scarring related to radiotherapy	• Drug spreads within CSF, unless obstruction to flow; lipid solubility determines degree of spread
• Safety—catheter migration to intrathecal space delivering potential overdose	• Safety—catheter can only migrate OUT of intrathecal space
Prognosis	
Short term use:	Longer term use:
• Limited prognosis	• Several different options—for example, external or fully implantable
• Other definitive treatment planned—for example, radiotherapy	
• Trial for intrathecal line	

- *Lidocaine patches*—These are currently available in the US but not in the UK. They have a good side effect profile and studies have shown efficacy in neuropathic pain. We have also used them in our centre for bone pain, particularly vertebral metastases, with some success.
- *Pregabalin*—This agent is a 3-alkylated analogue of GABA (γ-amino butyric acid), with a similar pharmacological profile to gabapentin, acting via the α2/δ subunit on voltage gated calcium channels in the central nervous system. However, it has greater potency than gabapentin. Randomised controlled trials to date have shown efficacy against some forms of neuropathic pain and an improved sleep pattern. Side effects seem similar to those seen with gabapentin. Titration of dose is easier than with gabapentin.
- *N-methyl-d-aspartate (NMDA) subtype selective agents*—Currently available agents are non-selective. There is evidence from animal models that particular subtypes of the NMDA receptor may have potential for analgesia with reduced side effects and opioid sparing effects. These include agents acting at the glycine-B modulatory site or the NR2B subunit.
- *Calcitonin gene-related peptide (CGRP) antagonists*—CGRP is found in sensory neurones. Non-peptide analogues with a favourable pharmacokinetic profile may have potential as analgesics.

Potential complications of spinal line

Complication	Sign/symptom	Action
CSF leak	Severe headache (postural)	Lie flat, encourage fluid intake (iv if necessary); blood patch
Infection	Local signs, pyrexia	Avoid—aseptic technique for any dressing changes, line changes etc; antibiotics
Cord compression—may be secondary to tumour, haematoma, abscess	Signs of cord compression—sensory level, weakness, may be pain	Rare, may need surgical treatment
Catheter block or fracture	Acute increase in pain, may be leakage of infusion fluid	Replace catheter
Catheter disconnection	Leakage of infusion fluid from disconnection site	Wrap in sterile saline soaked swab immediately Replace syringe, line, and distal filter

Complications related to drugs

Complication	Sign/symptom	Action
Opioid withdrawal	Agitation, insomnia, etc	Increase opioid dose either via catheter or short acting oral dose
Opioid toxicity	Hallucinations, sedation, twitching, respiratory depression	Decrease dose, stop opioids by other routes, use naloxone if clinically important respiratory depression
Acute opioid tolerance	Requiring rapid dose escalation despite stable situation with tumour	Add midazolam to infusion mixture, switch to different opioid
Pruritus—uncommon with long term use	Itching—often nasal	Naloxone (low dose), change or stop opioid
Urinary retention—more common in men	Unable to pass urine	Catheterise
Excess motor block	Leg weakness	Decrease local anaesthetic dose

Further reading

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