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Clinical review

ABC of palliative care: Difficult pain problems

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Introduction

Roughly 80-90% of pain due to cancer can be relieved relatively simply with oral analgesics and adjuvant drugs in accordance with the World Health Organisation's guidelines. The remaining 10-20% can be difficult to treat.

Useful adjuvant analgesics for neuropathic pain

Our practice is to start with amitriptyline and add an anticonvulsant if the symptoms are not relieved or to substitute an anticonvulsant if the tricyclic is poorly tolerated. If pain is still uncontrolled at this stage, referral for a specialist ***palliative care*** *opinion or to a pain clinic is advisable*

Corticosteroids (for example, dexamethasone 8 mg daily) may be used to reduce inflammation and oedema around a tumour if these are causing nerve compression

Tricyclic antidepressants—The analgesic effect of tricyclics is independent of any antidepressant effect. Mixed reuptake inhibitors such as amitriptyline seem to be more effective analgesics than the selective serotonin reuptake inhibitors. The starting dose should be low (such as amitriptyline 10-25 mg at night) and then titrated upwards on a weekly basis until pain control improves or side effects become intolerable. An analgesic response has been found with amitriptyline within the range 25-75 mg, but, as the dose increases, so does the frequency of unwanted effects (the evidence of analgesic activity is much less strong for drugs other than amitriptyline)

Anticonvulsants—Doses should start low and be titrated upwards. Sodium

valproate (200 mg twice daily up to 1600 mg a day) is often better tolerated than carbamazepine (200 mg at night up to 400 mg twice daily)

Antiarrhythmic drugs—These are reserved as second or third line drugs, when treatment with antidepressant or anticonvulsant, or both, has failed. Mexiletine (50-200 mg thrice daily) is usually the first choice in this class

Corticosteroids (for example, dexamethasone 8 mg daily) may be used to reduce inflammation and oedema around a tumour if these are causing nerve compression

The terminology used to describe pains that are not easily controlled with opioid analgesics is confusing. It is rarely the case that pain can be described as non-responsive or resistant to opioid analgesics because this implies an all or nothing phenomenon. Usually, pain in cancer responds at least partially to opioids, and a preferable term is "opioid-poorly-responsive pain." A pragmatic clinical definition is that such pain is inadequately relieved by opioid analgesics given in a dose that causes intolerable adverse effects despite optimal measures to control them. The most common example is neuropathic pain.

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Neuropathic pain

Neuropathic pain arises from damaged nervous tissue, whereas nociceptive pain results from actual or potential tissue damage. Neuropathic pain may be produced by a tumour infiltrating or compressing nervous tissue, either centrally or peripherally, and may also be caused by surgery, radiotherapy, chemotherapy, or viral infection. Patients may describe the pain as burning, stabbing, stinging, or aching. It may be felt superficially or deeply and be constant or intermittent. It may be spontaneous or precipitated by various stimuli, some of which are not normally painful (allodynia), such as a light touch or cold.

Treatment

Drugs

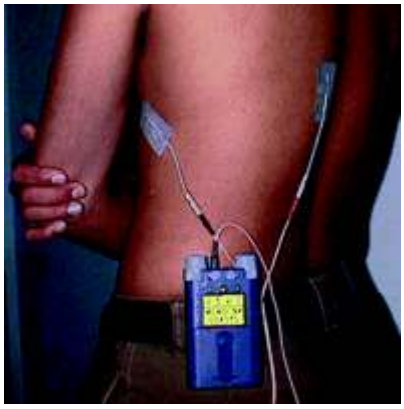
For most patients a trial of opioids is worth while, usually in conjunction with an adjuvant analgesic. Adjuvant analgesics are drugs with a primary indication other than pain but are analgesic in some painful conditions.

Non-drug methods

These are used in conjunction with drug treatment, but not all patients find them helpful. Most rely on counterirritation and range from systematic rubbing of the

affected part, through application of heat, cold, or chemicals, to acupuncture or transcutaneous electrical nerve stimulation.

Transcutaneous electrical nerve stimulation (TENS) uses surface electrodes connected to a small portable battery to stimulate large diameter nerves in the skin and subcutaneous tissues. Success depends on correct positioning of the electrodes and optimal adjustment of the electrical output, and these differ from person to person. It is relatively free of side effects, but it is difficult to predict which patients will benefit and efficacy often declines over a few weeks.



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Transcutaneous electrical nerve stimulation for control of neuropathic pain poorly responsive to opioids

Acupuncture may be a useful alternative for some patients but depends on local availability of a skilled practitioner.

Physiotherapy may relieve, or prevent the occurrence of, the musculoskeletal problems that can accompany neuropathic pain.

Occupational therapy may teach patients how to regain function without provoking painful episodes.

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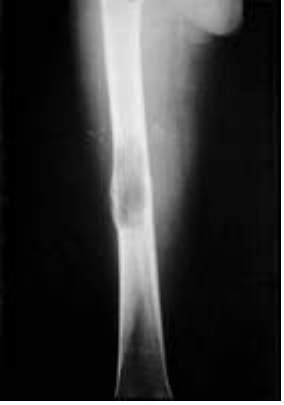
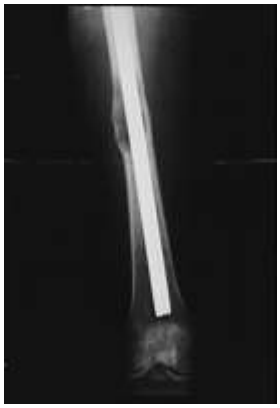
Incident pain



Incident pain is transient pain precipitated by a voluntary action, such as weight bearing or movement in patients with pain due to bony metastases. It often occurs against a background of adequately controlled baseline pain. An increase in the regular dose of opioid to cover incident pain increases side effects, particularly sedation, when patients are at rest and thus free of pain.



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Radiographs showing lytic lesion in femur (top) and internal stabilisation of bone (bottom)

Treatment
Incident pain can severely impair patients' functional ability. Management relies on thorough assessment, treatment of the underlying cause if possible (such as radiotherapy for bone metastases), and optimisation of the analgesic regimen with opioids and appropriate adjuvants by means of "breakthrough doses" in anticipation of pain. For some patients with incident pain, spinal administration of an opioid combined with a local anaesthetic may be worth while, particularly when other treatment options are limited (see below).

Physiotherapy and occupational therapy—Specific rehabilitation in terms of appropriate levels of mobilisation, maintenance of muscle tone and function, ergonomic advice and relevant aids, and necessary changes in lifestyle complement drug treatment and contribute to coping with what may initially seem to be intractable problems.

Surgery—Spinal stabilisation can effectively relieve pain from spinal instability caused by vertebral destruction in a fit patient with a reasonable prognosis (life expectancy of at least three months). Internal stabilisation of a long bone or replacement of a joint may produce considerable benefits even for patients with advanced disease.

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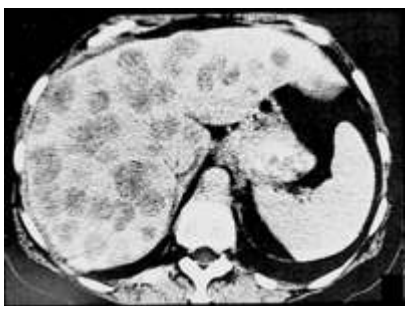
Visceral pain

Visceral pain is often poorly localised and difficult to describe, especially in the early stages, which can make diagnosis of the underlying cause difficult. Localisation often occurs only when disease extends to a somatically innervated structure such as the parietal peritoneum. Abdominal visceral pain is often associated with other unpleasant sensations such as bloating and nausea. Patients may find it difficult to describe the different sensations contributing to their discomfort. There are, however, classic sites of localisation for some organs—such as epigastric pain due to peptic ulcer. Referral of pain to other sites occurs, such as the shoulder tip with diaphragmatic disease or inflammation.

Common causes of visceral pain in cancer patients

- Tumour growth within an enclosed space causing capsular stretch (for example, liver metastases)
- Tumour invasion of parietal (and therefore innervated) surfaces
- Distension and associated muscle spasm provoked by partial or complete blockage of bowel, duct, ureter, or bladder by tumour
- Local inflammation, causing release of pain-producing substances
- Perforation of a viscus
- Occasionally, release of pancreatic enzymes



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Computed tomogram showing enlarged liver due to metastatic spread of cancer

Treatment
As with other types of pain, visceral pain is initially managed with analgesic drugs. However, invasive techniques may be indicated at an early stage. Coeliac plexus block should be considered along with analgesia in patients with pain from carcinoma of the pancreas, not as a last resort. Other upper abdominal malignancies such as carcinoma of the stomach may also benefit from this approach. Visceral pain is nociceptive pain and should respond to conventional analgesics. However, initial good control may be lost as the disease progresses, and a multimodal approach to treatment with drugs and non-drug measures from the outset will produce the best results.

Pelvic tumours may be complicated by bladder and rectal tenesmus, constant severe central perineal pain, and, occasionally, a severe episodic rectal spasm like proctalgia fugax. These pains tend to respond poorly to opioid analgesics, and various other drugs (smooth muscle relaxants, sedative drugs, and anticholinergic drugs) have been advocated. Pharmacological means rarely provide good pain control.

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Anaesthetic techniques

In a minority of patients, carefully managed drug treatment, with or without palliative radiation or chemotherapy, fails to provide acceptable pain relief or does so only at the cost of intolerable side effects. In these patients anaesthetic techniques may be indicated.

Acknowledging that there are situations where adequate pain control may be difficult to achieve is important. A multidisciplinary approach and referral to the appropriate specialist at an early stage can greatly improve the chances of good palliation in these patients

Spinal administration of drugs
It is now common practice to deliver drugs directly to the central nervous system via fine catheters placed within the epidural space or within the cerebrospinal fluid in the subarachnoid space. Placement is not usually difficult and may be performed under local anaesthesia. Catheters may be tunnelled subcutaneously to exit under the skin at an accessible site. They are attached to a bacterial filter for intermittent or continuous drug administration or, alternatively, may be connected to a subcutaneously implanted reservoir or pump delivery system, which can function for weeks or months.

Spinal opioids are indicated in patients with opioid responsive pain who, when the drug is taken by systemic routes, have intolerable adverse effects at the dose needed for adequate analgesia. The addition of a local anaesthetic may be particularly useful in managing movement related, incident pain

Further reading

Hanks GW, Portenoy RK, MacDonald N, Forbes K. Difficult pain problems. In: Doyle D, Hanks GW, MacDonald N, eds. *Oxford textbook of **palliative** medicine*. 2nd ed. Oxford: Oxford University Press, 1997

Gybels JM, Sweet WH. *Neurosurgical treatment of persistent pain*. Basle: Karger, 1989

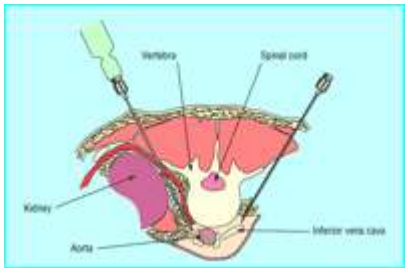
Preconditions for use of neurolytic techniques

- Failure of primary pain management
- Accurate diagnosis of cause of pain
- A condition that responds to neurodestructive techniques
- A risk:benefit ratio acceptable to patient, relatives, and clinicians
- Availability of facilities and skills
- Where appropriate, local anaesthetic blocks should be performed before destructive techniques

Drugs—The most commonly used drugs are opioids. Diamorphine has appropriate physical and chemical characteristics to provide good pain relief, and it causes an acceptably low degree of respiratory depression after spread within the cerebrospinal fluid. Other drugs such as dilute anaesthetic solutions and clonidine may be used alone or in combination with opioids to enhance pain control. The 24 hour epidural dose of opioid may be 20-25% of the 24 hour oral dose, and the 24 hour dose to the subarachnoid space is only about 10%. Drugs administered epidurally have to traverse the dura mater to gain access to the spinal cord, and substantial quantities of drug are absorbed systemically both before and during diffusion.

Complications—Infection and mechanical failure of the drug delivery system are not uncommon. Catheters may migrate out of the subarachnoid or epidural space. Implanted reservoirs or pumps occasionally become disconnected from the catheter.

Destruction of nerve tissue
Invasive neurolytic procedures have declined in use because of improved pharmacological management and the relative incidence of adverse effects. However, destructive techniques may provide excellent relief in selected patients.



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Coeliac plexus nerve block

Coeliac plexus block—The splanchnic innervation of the upper abdominal viscera, notably the pancreas, includes the coeliac plexus. Placement of needles percutaneously, guided by *x* ray or computed tomographic image, permits injection of alcohol or phenol into the nerve plexus. Pain relief may be dramatic and last several months. Early adverse effects are postural hypotension, disturbance of sphincter control, and diarrhoea. Paralysis is an uncommon complication and is most commonly due to damaged arterial blood supply to the spinal cord. Sexual dysfunction is more common.

Subarachnoid neurolysis—Chemicals placed on nerve roots at the level of the dermatomal innervation of somatic pain alter nerve function irreversibly. One example is a neurolytic saddle block in patients with perineal pain due to pelvic malignancy.

Cordotomy lesions are created in the anterolateral tracts of the spinal cord on the opposite side to the pain. Lesions are produced surgically (open cordotomy), or percutaneously by radiofrequency probe passed into the cord guided by *x* ray image. Cordotomy is considered appropriate only for unilateral somatic pain below the fifth cervical dermatome and when life expectancy is less than nine months. Sensory change is an invariable accompaniment, and motor weakness and sphincter disturbances are common. When the operation is provided after proper selection, pain relief may be good for several months.

Notes

The computed tomogram of an enlarged liver is reproduced with permission of Times Mirror International Publishing.

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