Management of cancer pain

A practical approach

Gordon Coates

ABSTRACT: One in five deaths in Australia is due to cancer. Pain is an important symptom in many of these patients, but it is often either unrelieved or poorly controlled. Misconceptions about the nature of cancer pain and its control are detailed, and the practical management of these patients is discussed in the light of personal experience. Proper use of older therapeutic methods is still important, as recent advances allow better results only in a minority of cases. Special attention is given to the use of regular oral doses of morphine. Many of the interacting factors affecting pain perception are considered, so that the sense of impotence in those faced with the management of a progressive incurable disease may be reduced through an understanding of the causes of pain and its correct management.

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IN AUSTRALIA, as in other Western countries, about one in every five persons dies from cancer.[1] Of these, many suffer pain which is often prolonged and severe.[2] Yet, it has been shown by overseas workers that adequate treatment can prevent or relieve cancer pain in the great majority of cases, and that such treatment need be neither unduly complex nor prohibitively expensive.[3,4] My own experience has confirmed these reports and, in this paper, I consider possible reasons for poor pain control and give a brief account of those therapeutic methods which I have found to be most useful.

Misconceptions about cancer pain

The impression that pain is both inevitable and intractable is common among patients and those caring for them, including doctors and nurses. This arises from a variety of causes, such as inadequate professional education, ingrained and widespread fears and taboos, and lack of specific experience in cancer pain management. The result is often a sense of impotence leading to therapeutic nihilism, and many of my patients have previously been told: "Of course you've got pain - you've got cancer". On the other hand, some professionals deny the problem, and this is reinforced by the fact that their patients soon realize the futility of complaining about pain.

A major problem arises from the mistaken beliefs that the long-term use of strong opioids in cancer pain management is precluded by the development of tolerance and the risk of addiction, and that the standard doses of opioids used in the treatment of acute pain are applicable to that of chronic cancer pain. As will be discussed later, the facts are otherwise.[5]

In the terminal phase of their illness, patients with cancer are sometimes transferred to small, non-acute hospitals and nursing homes the staffing levels of which are inadequate for good palliative care.[6] Here they may be "out of sight, out of mind" (but not out of pain!) – the referring clinician having abdicated his own responsibility for their well-being.

Another common error is to rely upon a single method of pain control rather than a combination of techniques. Also, non-specific factors which affect pain perception must not be neglected, as attention to their resolution or alteration may complement the treatment regimen and result in successful pain control.

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Clinical approach

Prophylaxis is obviously the best treatment when it is feasible. In some cases, it is possible to prevent manifestations or complications of cancer which might give rise to pain. One example is excision of an incurable rectal cancer to prevent the later onset of spasm and discharge. Less dramatic, but also important, are the care of pressure points, and the prevention of constipation.

All patients with cancer must be assessed for the presence or absence of pain, which is not always obvious. A patient with an extroverted personality may make frequent complaints about pain and requests for relief. Introverts, especially in the terminal phase of their illness, often make neither; non-verbal communication then becomes critical to the establishment of rapport, and a good rule of thumb is "if you don't sit down, you won't find out".

In an endeavour to understand the pain, diagnose its cause and provide the appropriate treatment, a pain history, such as that incorporated by Melzack in the McGill Pain Questionnaire,[7] should be taken. The checklist should include the site of pain (and its radiation, if any), its type and severity, sleep disturbance, mode of onset, date and place of first attack, frequency and duration of attacks, and anything which precipitates, is associated with, or relieves, the pain.

The examination will then be guided by the history, and any investigations will be chosen on the basis of both. Two important compromises apply here. First, the steps towards diagnosis must be appropriate to the patient's condition: a history may be limited or absent, weakness or pain on movement may restrict examination, and investigations which are tiresome, painful, or require an ambulance ride may cause more distress than is justified. Second, there is rarely any need for all palliation to be withheld pending an accurate diagnosis – in fact, there are occasions when the patient should be receiving a slow intravenous injection of morphine while the doctor gathers information about symptoms and signs. Agony is an emergency.

When a specific diagnosis cannot be made, it is still important to determine the general type of pain: for instance, bone pain from secondary tumours (often described as a severe, nagging, dull ache, and tender on percussion), nerve irritation (sometimes called "toothachey" or "like bad pins and needles", often with sharp shooting episodes precipitated by movement), colic from hollow muscular viscera (with its characteristic periodic nature), and raised intracranial pressure (with headache and, sometimes, vomiting and papilloedema) all respond to different treatments. A useful pointer here is that pain originating from connective tissues can usually be fairly easily described and localized in a way that makes anatomical sense, whereas pain from visceral parenchyma is often vaguely described, poorly localized, and is associated with autonomic effects such as nausea, sweating, and tachycardia.

Palliation

Not all pain in patients with incurable cancer is due to cancer, so non-malignant causes of pain should not be overlooked. More often, however, palliation is the best that can be achieved.

Palliation involves the therapy of tumour deposits and their local effects, interruption of the pain pathway, immobilization of the painful parts, and elevation of the pain threshold.[8] The last of these is often neglected or poorly carried out, and will therefore be described in more detail than the other three.

Therapy of tumour deposits and their local effects

The aim here is to reduce the bulk of tumour deposits to prevent their local effects, and to remove or bypass any obstruction they may be causing in a hollow organ. Tumour bulk can be reduced by surgery, radiotherapy, cytotoxic chemotherapy, hormone therapy, cryotherapy or immunotherapy. The choice of method used should be made in consultation with the appropriate specialist.

Pain from the local effects of bony secondary tumours usually responds to radiotherapy.[9] Fungating lesions are much more comfortable if they are kept clean, and various topical applications may also be useful. When a tumour compresses or infiltrates a nerve, radiotherapy may again be effective,[8] as can the administration of corticosteroid agents, but continuous analgesia or interruption of the pain pathway is usually also necessary.

The severe headache of cerebral oedema associated with primary or secondary brain tumours, often responds to treatment with dexamethasone (4 mg four times a day); occasionally, the dose must be increased, even up to 12 mg each time. After control of pain is achieved, the dose may be reduced cautiously towards 2 mg twice a day if the life expectancy is more than a few months.[10] Even the latter dose is the equivalent of 40 mg of prednisolone a day, so cushingoid effects are not long delayed. The use of diuretic agents and head elevation also reduce intracranial pressure. One should bear in mind that morphine may raise intracranial pressure, but its use may be necessary for pain relief if the other measures, plus the administration of non-narcotic analgesic agents, prove ineffective.

Bowel obstructions may need relieving by open operation; other obstructions are often relieved by the endoscopic or percutaneous passage of various tubes. Multiple or recurrent bowel obstruction, however, is often better treated medically in a terminally ill patient.[11] This is a common problem in patients with carcinoma of the ovary and carcinoma of the bowel. It is usually best managed with nothing by mouth (or ice to suck, sparingly); the administration of opioid analgesic and antispasmodic agents to prevent colic; and (if symptoms of dehydration are present) the intravenous, subcutaneous or rectal administration of fluids. Oral medication is generally contraindicated in these circumstances, but an orally administered combination of diphenoxylate and atropine (Lomotil) has proved to be very effective;[11] the rectal administration of oxycodone (Proladone suppositories) is also suitable.

Interruption of the pain pathway

Nerve interruption can be carried out at any point between the site of origin of the pain and the cerebral cortex.[12] This option should always be considered, as it is occasionally the best treatment, even if it is carried out near the end of the patient's life. The decision on such action is best made in the setting of a multidisciplinary pain clinic, or in consultation with an anaesthetist and a neurosurgeon, when simpler methods fail. Available procedures include peripheral nerve blocks, plexus blocks, posterior root division, intrathecal or epidural blocks, selective anterolateral cordotomy, and commissural myelotomy. Cordotomy, in particular, can give almost miraculous relief of unilateral pain below the level of the neck or of unilateral or bilateral pain below the mid-thoracic level;[12] myelotomy can be similarly effective for pelvic pain or pain in the lower limbs.

Discussion of indications for, and details of, these procedures is beyond the scope of this article. The essential point is that failure of simpler methods is an indication for referral, not despair.

Immobilization

Sometimes, for example, after a pathological fracture, analgesia without immobilization would virtually necessitate general anaesthesia. Thus, a pathological fracture should usually be treated by internal fixation, preferably on the day of fracture, as the patient's fitness for operation may deteriorate rapidly. Even if strong fixation is impossible, because of the extent of bone destruction, it should be possible to render the fracture relatively pain-free with the use of acrylic cement.[13]

When there are multiple pathological fractures, complete bed rest and as near total body immobilization as is consistent with the patient's needs (pressure point care, elimination, etc) is occasionally necessary.

The value of immobilization, sometimes combined with elevation of a limb, is not restricted to fractures. It may, at times, be appropriate for almost any painful lesion.

Elevation of the pain threshold

Medication

The use of analgesic and co-analgesic agents is the most obvious way of raising the pain threshold, and perhaps the most important as well. However, it is a mistake to rely on them entirely. Also, it is absolutely essential to distinguish clearly between acute pain and chronic pain. Acute pain is of short duration, is usually caused by a self-limiting (or fatal) condition, is associated with anxiety, and typically responds to a single injection of a short-acting opioid drug. Chronic pain is endless, is apparently meaningless, is often accompanied by depression, and never responds to "prn"

medication. It is the type of pain usually encountered in the management of patients with cancer.

In general terms, there are four rules for the prescribing of analgesic agents: choose the right drug(s) for the type of pain involved; order the right dosage regimen; take precautions to prevent side-effects; and, most important of all, reassess the requirements frequently.

Choice of drugs

There are three main groups of drugs: non-narcotic analgesic agents, such as aspirin and indomethacin; opioid agents, such as codeine and morphine; and co-analgesic (or adjuvant) agents which enhance the effect of analgesic drugs. It is quite often necessary to prescribe one or (occasionally) more agents from each group for the one patient.

Non-narcotic analgesic agents – such as the non-steroidal anti-inflammatory agents – work by interfering with prostaglandin synthesis,[14] and, with the exception of paracetamol, they are effective at the site of origin of the pain as well as having a central effect. They are specifically indicated for pain of connective tissue (especially bone and visceral capsule) origin. If necessary, an opioid agent should be added rather than substituted.[15]

Opioid agents work by interference with the transmission and perception of pain in the central nervous system.[14] They are specifically indicated for pain of visceral origin (including skeletal muscle), but they may need to be added to other agents in the treatment of severe pain of any origin. A weak opioid agent, such as codeine, or one of medium strength, such as oxycodone, may be sufficient to control pain. (Pentazocine should be avoided; its analgesic effect is weak,[16] but it has serious side-effects,[17] and can precipitate opioid withdrawal symptoms.[18])

The choice of a strong opioid agent remains controversial. Twycross has made an excellent case for morphine,[5] and my own experience leads me to consider this the drug of choice in terminal care. Methadone has the advantages of less variable absorption and a longer duration of action than morphine, usually allowing a twice or three times a day regimen. However, its effective half-life may lengthen unpredictably after dosage stabilization, possibly due to transition from distributive to metabolic clearance from the blood, resulting in delayed cumulative toxicity if regular doses are continued.[19] For this reason, I have reservations about its use in terminal care, in which the diagnosis of delayed toxicity is very easily missed. Buprenorphine has been the subject of some encouraging reports, and it may yet prove to be a useful addition. Pethidine is rarely useful in the management of chronic pain because its action is weak when given by mouth and short-lived when administered by injection,[20] and its maximum dosage is severely restricted by its central nervous system side-effects.[14] Dextromoramide should never be used in the treatment of chronic pain which it could probably control smoothly only if taken every 90 minutes around the clock, that is, 16 times a day;[5] it is, however, useful for "breakthrough pain". Heroin is not available in Australia, but research by Twycross[5] and others suggests that its only major advantage over morphine, when each is used optimally, is its greater solubility in water. Recent research into opioid receptors and endogenous opioids raises the possibility of future breakthroughs in opioid analgesic agents, but has so far contributed only an improved understanding of their mechanisms of action.

Co-analgesic drugs are a loosely defined group, which may help when analgesic agents alone are unsuccessful. They include major and minor tranquillizers, antidepressant, corticosteroid and antispasmodic agents, to which some would add the antiemetics and laxatives used to prevent the side-effects of opioid analgesic agents. Chlorpromazine has been widely used to potentiate the analgesic action of strong opioid agents.[5] It also has antiemetic and anxiolytic effects. However, it is often poorly tolerated by weak or elderly patients, causing confusion and a peculiarly "dead" mental state which is distressing for the patient, relatives and staff. Alternatives include diazepam and haloperidol which have their own, rather different, drawbacks. Tricyclic anti-depressant agents have proved valuable in the treatment of the depression which so often accompanies chronic pain, and of the iatrogenic depression which frequently occurs after a few months' regular treatment with opioid analgesic agents. An antispasmodic agent, such as hyoscine butylbromide, is an obvious co-analgesic drug in the case of colicky pain. Interestingly, indomethacin has been shown to be effective in some types of colic.[21] I have used it successfully in suppository form, in the treatment of rectal spasm.

As mentioned above, it is often necessary to use combinations of drugs, as well as other modalities, to achieve analgesia. A good example is provided by inoperable carcinoma of the pancreas, in which pain may originate from the parenchyma, from spasm of the ducts, from stretching of the capsule, and from inflammation and infiltration of adjacent structures, and it may need coeliac plexus block, radiotherapy, and combined drug therapy to achieve analgesia. Nerve-root infiltration by a tumour is the cause of another type of pain which often seems to require combined therapy.

Dosage regimen

Dosages of the weaker opioid and the non-narcotic analgesic agents are usually limited by side-effects or by the number of tablets required (taking more than three tablets at a time is distressing to many patients). Morphine, however, has no "maximum dose". It can be used in doses much higher than those recommended for the control of acute pain, and neither tolerance nor addiction are real problems when it is used properly in the management of cancer pain.[22,23] The oral dose of morphine required for chronic cancer pain in adults may lie anywhere between 1 mg every six hours (for some cachectic patients) and 1,000 mg every two hours (for occasional patients with severe pain, poor absorption and considerable tolerance). In practice, doses are best adjusted as necessary within a range prescribed by the doctor. These adjustments should be made by someone who is on the spot which, in hospitals, usually means the nursing staff members. A clear chart should be used to keep track of the dosage and, in my experience, this variable dose technique does not work, unless morphine is prescribed and recorded on a chart specifically designed for this purpose, which is very different from the usual hospital medication chart (see figure). (This chart, a part of the monograph entitled *The fixed interval, variable dose [FIVD] regimen*, is available from the writer on request.)

When an adjuvant is used to potentiate the analgesic effect of morphine, a small initial dose should be given,

..... HOSPITAL MORPHINE MEDICATION CHART PAGE 1

FULL NAME:	Age	Sex	D.O.B.	V.M.O.
ALLERGIES:	Admission Date	Unit No.	Ward	Bed

Morphine mixture .....mg fourth hourly. Increase or decrease each dose by .....mg until patient is comfortable without excessive drowsiness, up to a maximum of .....mg fourth hourly by mouth (or up to .....mg by injection – see below). Bedtime maximum dose: oral .....mg, inj .....mg. One extra dose may be given during any four hour period for breakthrough pain. If so, contact M.O. if not effective.

If oral medication not tolerated, give equivalent dose (one third oral dose in mg) by IMI or SCI. Refer to "FIVD Regime" 1984 for further guidance. If in doubt, contact M.O.

RECORD ALL DOSES IN MILLIGRAM (NEVER RECORD IN MILLILITRE)	Bedtime dose..... Next dose..... Signature.....	M.O. Signature: Date ordered:

Date	Time	Amount	Route	Sign	REMARKS (Pain, drowsiness, nausea, confusion etc.)	B.O.

FIGURE: Suggested chart for recording regular morphine medication.

regardless of the morphine dosage currently in force. For example, one should start with administering 10 mg of chlorpromazine every eight hours, then increase the individual doses given to 25 mg, or occasionally, to 50 mg; similarly with diazepam – a dose of 2 mg every eight hours may be increased to 5 mg or 10 mg.

When possible, the oral route is preferred as being the most convenient and comfortable; it also causes less fluctuation in blood levels than do intermittent injections. Morphine is available with tacrine in tablet form, which is convenient to store and administer, but morphine mixture allows for more flexibility in dosage and is easier for very ill patients to swallow.

Morphine mixture need only contain morphine hydrochloride and water, with colouring or flavouring as optional additives. This solution is stable for at least a month, although some additives result in a slight sediment or cloudiness which can be removed by a coffee filter. If a preservative is needed, I prefer metabisulphite, although the use of benzoic acid has also been suggested. Of the common alternatives, alcohol makes the mixture taste sickly and may irritate mouth ulcers or cause vomiting, while chloroform water also seems to cause irritation of the mouth, oesophagus or stomach in some patients, and is potentially hepatotoxic. If necessary, up to 200 mg of morphine hydrochloride may be dissolved in each 10 mL of water, and it is preferable to use a concentration which results in a dose volume of 15 mL or less. Obviously, the concentration of any morphine mixture must be clearly marked on the label. The addition of co-analgesic agents to the same mixture should be avoided, as tolerance does not develop at the same rate for each agent, and in any case, different patients require different proportions from the outset.

When little can be taken by mouth, morphine mixture may be given per rectum through a soft catheter, and co-analgesic agents can be given as suppositories. However, the best route for some patients who cannot take medication by mouth is continuous subcutaneous administration by means of a syringe driver, such as that previously marketed by Pye and now by Graseby Dynamics.[24] If an adjuvant is required, hyoscine may be mixed with the morphine in the syringe, and the mixture given by the subcutaneous route. Other combinations may necessitate intramuscular siting of the needle, and more frequent changes of sites.

Various other routes of morphine administration have been used and, of these, the epidural administration of morphine seems the most promising.[25,26]

Whatever route is used, the timing of doses is of crucial importance. For the control of severe chronic pain there is no place whatsoever for "prn" medication[5,27] – it does not control chronic pain, and sometimes makes it worse. Drugs used for alleviation of chronic pain must be given at regular intervals, so that the blood level of each drug always (day and night) remains within the therapeutic range for that patient. For many analgesic agents, including morphine, the right interval is about four hours. At high dose-levels, smoother control may be achieved with doses given every three hours. Vague instructions, like "qid", are disastrous: the interval is just as important as the number of doses. Once pain control has been achieved, it is often possible to omit one dose during sleep, by arranging the schedule so that the last dose of the day is given at bedtime, and by doubling this bedtime dose. However, if morning pain occurs, it is best to revert to a strict every-four-hours schedule; most patients go back to sleep quite easily after taking their medicine.

Side-effects

The main side-effects of opioids are nausea, constipation, drowsiness and confusion. Respiratory depression is rarely a problem in practice with the regimens described.[5] Depression of affect is, however, likely after some weeks or months of treatment, and should be watched for.

Nausea or vomiting within five minutes of the oral intake of morphine often responds, in my experience, to omission of alcohol and chloroform water from the formula. Nausea caused by morphine itself is usually alleviated by the administration of 5 mg of prochlorperazine by mouth with each dose of morphine. Other measures include the administration of antiemetic combinations such as prochlorperazine with promethazine, the addition of co-analgesic agents or other modalities to allow reduction of the dosage of morphine, or the administration of morphine by a different route, as discussed above. Very rarely, patients respond with uncontrollable nausea and vomiting to any

strong opioid. If they remain in pain despite other measures, an alternative method of pain control, such as cordotomy, should be urgently considered.

Constipation is completely preventable by the routine administration of laxatives with regular analgesic agents. All patients should receive a fibre supplement (for example, Fybogel) and the stool-softening agent, sodium sulphosuccinate. Most will also need a peristaltic stimulant such as danthron, and some will need a lubricant such as liquid paraffin. Bowel actions should be charted meticulously, preferably on the same chart as the oral dosage of morphine. Rectal examination should be performed if there is any rectal discomfort, or after four days without a bowel action; packing of the rectum with firm or hard stool is an indication for an enema (a disposable phosphate enema is convenient) followed by manual removal of faeces if necessary. A rectum packed with soft stool is best evacuated with the high instillation of bisacodyl rectal solution through a flexible catheter. The importance of meticulous bowel care, especially for patients in the terminal phase of their illness, simply cannot be exaggerated.

Drowsiness is normal during the first three or four days of a regular opioid regimen, although some clinicians choose to reduce it by the concomitant use of tacrine[28] (as in the Mortha tablet). The possibility of drowsiness needs to be explained both to the patient and to relatives. It may also recur at times of significant increase in dosage. Although some patients complain about it, most prefer this state to uncontrolled pain.

Confusion is sometimes a difficult problem in the elderly patient, and a change of the opioid used does not always solve it. It may resolve after about a week; the usual methods of assisting orientation are helpful.

Both drowsiness and confusion are more likely if a tranquillizer is used as an adjuvant, especially in high or frequent dosage or, in the case of chlorpromazine, for example, in the presence of reduced hepatic function. The intramuscular administration of diazepam also creates problems caused by erratic absorption, unless it is administered in the deltoid muscle.[29] In my experience, these adjuvants are only occasionally necessary when the comprehensive approach to pain control is used.

Reassessment

All analgesic regimens need frequent reassessment. Doses must be strictly "titrated" by means of reports from the patient and attendants; they may need increasing or decreasing. No amount of knowledge or experience can substitute for regular review; this is especially true in the terminal phase of the illness.

Other factors affecting pain perception

The perception of pain is a complex phenomenon which is affected by the interaction of many factors. Many of these have been described, particularly in the literature dealing with the hospice-palliative care movement.[6,30,31] Here, I simply wish to mention the main points.

First, various physiological factors interact with the perception of pain: the control of other symptoms, such as vomiting, dyspnoea, cough or disagreeable odours, raises the pain threshold considerably; so does the provision of adequate rest and sleep. Nutrition and appropriate exercise are also relevant; and a true anxiety state or depressive illness must be treated if present.

Second, hypophysectomy has been shown to relieve pain in malignant disease, regardless of hormone dependence,[32] and this therapeutic option, though not completely understood, should not be forgotten.

Finally, and of tremendous importance, are other factors which influence pain perception and can be loosely grouped under the heading "peace of mind". Uncertainty breeds anxiety which, in turn, lowers the pain threshold. Uncertainty is dispelled by gentle, but honest, explanation, preferably by the patient's doctor. Environment is also important, the patient's home being preferred, where possible. A high standard of general nursing care is essential for dependent patients. The attitudes of the care-givers are equally important, and here teamwork and staff support are essential. Especially in the later stages, patient and family together should constitute the entity receiving care. Family communication problems, and especially a "conspiracy of silence" regarding diagnosis, can thwart the most expertly conceived analgesic regimen. Bottled-up emotions, such as anger, grief, and fear, may also prevent pain control – in such cases, gentle encouragement to explore and express these feelings is essential.[6] The importance of various types of "unfinished business" has been described elsewhere.[33] Chaplaincy services are frequently required, and it must be borne in mind that patients who are not "religious" may also have spiritual needs. Various specific techniques, such as relaxation training, acupuncture, hypnotherapy, diversional therapy and music therapy, have also been shown to raise the pain threshold.[6]

Conclusion

Increasing experience has shown that cancer pain can almost always be controlled if the standard diagnostic and therapeutic techniques described above are applied. However, it must be borne in mind that there is often more than one cause for pain; that more than one therapeutic modality is often required in management, especially in the case of terminally ill patients; that success may often depend on the many non-specific factors; and that continual review of the patient's needs is an absolute necessity.

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Appendix

Equivalent doses of opioids

These have been combined, and in some cases extrapolated, from figures published by Twycross,[5] Houde,[15] Brophy,[34] and others. They are useful only as a starting point when changing analgesic therapy; there is much variation between individual patients, as well as between published studies. Half-lives also vary from one agent to another.

The following doses of strong opioids are roughly equivalent to 10 mg of morphine administered by intramuscular injection (IMI), and thus to each other:

Morphine	10 mg IMI	30 mg oral
Heroin	5 mg IMI	15 mg oral
Methadone	10 mg IMI	20 mg oral
Oxycodone	15 mg IMI	30 mg oral
Dextromoramide	5 mg IMI	10 mg oral
Pethidine	75 mg IMI	

The following oral doses of various opioids have a mild to moderate analgesic action and are roughly equivalent to 1.5 mg of morphine administered by IMI, and thus to each other:

Dextropropoxyphene HCl	65 mg
Pethidine	50 mg
Codeine	30 mg
Pentazocine	25 mg
Oxycodone	5 mg
Morphine	5 mg
Methadone	3 mg
Dextromoramide	1.5 mg

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