How Cancer Pain is Treated

A comprehensive but non-technical guide for patients and carers, explaining clearly how cancer pain can be relieved

Dr Gordon Coates

Most cancer patients require pain management as part of their overall treatment. Effective pain management is always possible, but it can only be achieved by close collaboration between patient and doctor. Such collaboration is greatly assisted when patients and carers have a clear understanding of the many treatments available, and when and how they are used.

How Cancer Pain is Treated is a comprehensive and easy-to-read guide to achieving that understanding**.** It explains in clear, non-technical language the many ways in which cancer pain can be relieved, providing all the information necessary for effective collaboration with the treating professionals. It is written particularly for patients and their carers, but it is also a very useful resource for nursing and allied health professionals, medical students and indeed for anyone interested in the topic.

The author, Dr Gordon Coates, has been a medical practitioner for more than forty years. Much of his clinical career was spent working in the field of palliative medicine, during which time he developed departments of palliative care in two Sydney teaching hospitals, attended patients in a number of hospices, ran a community palliative care service and was a founding vice-president of the Palliative Care Association of New South Wales. He now maintains a self-help website and writes eBooks and articles on a wide range of health related topics.

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None

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HOW CANCER PAIN IS TREATED

DISCLAIMERS

This booklet, written by a senior medical practitioner with considerable experience in palliative medicine and hospice care, is offered purely for educational purposes. Nothing in it should be taken as therapeutic advice for any particular patient. Mention of any trade (brand) name should not be taken as an endorsement of the brand or its manufacturer.

CAUTIONS

If you read this booklet carefully, and think about the information in it, in relation to a particular pain management problem affecting you or someone you love, you may sometimes be able to think of modifications to the current treatment which might be expected to improve the situation.

However, it is very dangerous to make changes to a patient's medication without first discussing them with the prescribing doctor. The doctor must always know *exactly* what the patient is taking, as virtually all medications can cause unwanted side effects and interact in various ways with other medications.

Importantly, this also applies to "natural", "alternative" or "complementary" therapies, many of which have significant interactions with prescribed medications. Therefore, even if you feel that the current pain management is not optimal, never make any changes without first discussing them with the doctor.

INTRODUCTION

Most patients with advanced cancer experience severe pain if they do not receive good pain management, but their pain can almost invariably be relieved if it is managed correctly.[1, 2] Patients whose cancer has been cured or is in remission may also need treatment for pain in some cases.

The principles of cancer pain management are well established[1], and indeed they have changed very little since I summarised them for a medical readership a quarter of a century ago[2]. However, there have been a number of useful practical developments, which have made treatment more convenient, reduced associated side effects, or, in some cases, provided better solutions to previously difficult problems.

This booklet is intended for a general readership. Therefore, although many medications will be named in it, no medical or nursing knowledge will be assumed. It is my hope that a better understanding of what can be achieved, and how to achieve it, will be helpful to patients and their relatives when discussing treatment with their doctors or other health care professionals.

Cancer pain can be relieved by treating the cancer itself; by inhibiting the mechanisms by which cancers can give rise to pain stimuli; by interrupting the "pain pathway" which carries pain stimuli to the brain; or by inhibiting the perception of pain stimuli which reach the brain, either by the use of medications or by non-drug interventions. I will discuss all of these methods in this booklet, but I will go into more detail about the optimal use of medications, as these are often the mainstay of treatment.

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[1] World Health Organization. 1996. Cancer Pain Relief: with a Guide to Opioid Availability - 2nd ed. Geneva: WHO Publications.

[2] Coates, GT, "Management of cancer pain. A practical approach", Med J Aust 1985 vol. 142, pp. 30-35.

MYTHS ABOUT CANCER PAIN

There are many myths and misconceptions about cancer pain, but the one which is most important to dispel in the present context is the mistaken idea that cancer, and especially advanced cancer, inevitably causes pain which cannot be relieved. Nothing could be further from the truth!

Although the majority of cancer patients need pain management as part of their overall treatment, excellent pain control, without severe side effects, can be achieved in most cases by using simple, cheap and readily available methods.

In the approximately fifteen percent of patients who do not respond to these methods, more complex interventions are necessary, often requiring the services of a Pain Clinic or Palliative Care Service. But even in the most difficult cases, there is no such thing as "pain for which nothing can be done".

Unfortunately, even today, many people do not know this. There are even some doctors and nurses who do not have a good understanding of pain management. They may have great expertise in some other field, but perhaps not in this one. So, if you are ever told that "nothing more can be done for your pain", or if something similar is said about a loved one who is suffering, you should certainly request referral to a Pain Clinic, a Palliative Care Service, or a Pain Management specialist.

Another problem which sometimes interferes with good pain management is simply failure to acknowledge the need for it. For various reasons, cancer patients or their doctors sometimes brush the issue aside as if it did not exist. This is, of course, a particular example of the denial which is very common as an initial response to any unwanted experience or situation.

Unfortunately, denial of its existence never solves any problem, and cancer pain is no exception to this rule. The first step in pain management is therefore to face and accept the fact

that something needs to be done. That may sound obvious, but denial is a common error, so it is well worth watching out for.

Mistaken beliefs about strong "opioid"[3] analgesics are also responsible for inadequate pain control in many cases. Although the misuse of strong opioids as recreational drugs often leads to severe psychological addiction as well as rapidly escalating physiological tolerance, it has been known for many decades that neither tolerance nor addiction is a significant problem when strong opioids are used correctly in the management of cancer pain.[4] Indeed, a strong opioid such as morphine is very often (though by no means always) an essential component of the overall management of cancer pain.

Some patients also fear that the use of strong medications too early in the course of their illness might leave them with nothing to relieve severe pain later on. If anything, the opposite is true, as pain control is easier to maintain than to achieve, and easier to achieve before a pain has been too long established. This is probably at least partly because the ability of the central nervous system to perceive pain improves with practice.

Various other common attitudes, such as the ideas that pain should be accepted stoically, that "mind over matter" should be sufficient to control pain, or that doctors are so busy with "more important" matters that they should not be interrupted by complaints about pain, may also inhibit timely intervention. (It is true that doctors are usually very busy. However, the relief of suffering is one of their most important tasks.)

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[3] Although "opiates" were originally extracts of the crude opium harvested from the common edible poppy, while "opioids" also included synthetic compounds with similar effects, the two terms have effectively become synonyms. I will use the latter term in this booklet.

[4] Twycross, RG. Relief of pain. In: Saunders C, ed. The management of terminal disease. London: Edward Arnold, 1978: pp. 65-92.

Yet another misconception about the management of cancer pain is the idea that a single method of pain control should be tried first, and then *replaced* with something else if the results are not satisfactory. The truth is that multiple methods of pain control are frequently necessary in the treatment of cancer pain.

FACTS ABOUT PAIN

Definition

Firstly, what is the definition of physical pain? I think most people would say it is "anything that hurts". A more specific definition is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[5] As is the case with most brief definitions, a little further explanation may be useful.

Being an "experience", pain is essentially subjective. It therefore cannot be measured directly by an external observer. Having both "sensory" and "emotional" components, both of which can vary enormously, pain is inevitably a complex and highly individual phenomenon. Incidentally, the word "described" in the definition is not intended to restrict the existence of pain to patients who *can* describe it. On the contrary, it is very important to consider the possibility of pain in those who, for whatever reason, are unable to communicate.

General Classification

It is important to distinguish between different types of pain, because different types of pain respond to different treatments. In general terms, the two main types are "acute" and "chronic"

[5] This definition was first proposed, with slightly different wording, by Dr Harold Merskey in 1964 (Merskey, H, 1964, An Investigation of Pain in Psychological Illness, DM Thesis, Oxford). With various qualifications, it has been used by the International Association for the Study of Pain (IASP) since 1979.

pain. Some people also talk of an intermediate classification, called "subacute". These three types of pain, and some extra terms which are used in certain situations, are explained below.

Acute Pain

Acute pain comes on fairly quickly, usually as a result of an accident or a new or recurrent illness, and is usually fairly brief in duration. This is usually either because it motivates the patient to seek urgent treatment, or because the pain goes away by itself. Occasionally, it is because the cause of the pain is so serious that it soon results in the death of the patient.

Chronic Pain

Pain is described as chronic when it has been present for a long time. It may have developed so gradually, and been present for so long, that it simply seems endless. Because it is not a sign of a new problem, requiring a new diagnosis and new treatment, it may seem meaningless as well as endless. Alternatively, if a meaning is ascribed to it, it is quite often a frightening one.

Subacute Pain

Some doctors use the term "subacute pain" when referring to cancer pain, because patients with cancer sometimes have some features of acute pain and some features of chronic pain, both at the same time. Other patients with cancer may have no pain, or occasional episodes of acute pain, or chronic pain with or without the additions described under the next heading.

New, Incident and Breakthrough Pain

Of course, the first episode of a new pain might occur during the course of any chronic pain. Until the cause is diagnosed, it is best to simply refer to it as a new pain. When it is known to have a specific cause, such as a medical procedure or an accident, it is often referred to as "incident pain". On the other

hand, if it represents a temporary failure of the relief of the existing chronic pain, it is called "breakthrough pain".

Physiological Classification

It is also useful to classify pain according to the physiological mechanism by which it is produced. From this perspective, most pain is either "nociceptive" or "neuropathic", as described below. I will also mention some less well understood mechanisms by which pain can probably be produced. In some cases, more than one mechanism may be involved, and in other cases the mechanism may be difficult or impossible to determine.

Nociceptive Pain

How do we become conscious of pain? The simplest, and also the commonest, way is as follows. Processes affecting the body in such a way as to cause actual or potential tissue damage are almost always recognised by specialised sense organs at the ends of peripheral nerve fibres. These sense organs then send electrochemical signals back along their nerve fibres, which join larger and then still larger nerves, pass through nerve plexuses, and ultimately connect with one or more spinal nerve roots. The spinal nerve roots pass between adjacent vertebrae to join the spinal cord, which then carries the signals up to the brain.

Because they have become specialised so that they respond specifically to potentially or actually "noxious" (harmful) processes, the sense organs described in the previous paragraph are called "nociceptors". For the same reason, the pain which is experienced when such a process causes signals to be sent from nociceptors to the brain is called "nociceptive pain". Much of the pain caused by cancer is in fact nociceptive pain.

Neuropathic Pain

The second major mechanism which can cause pain to be experienced occurs as a result of an injury or illness affecting the nervous system itself. Damage to various parts of the

nervous system can sometimes result in electrochemical phenomena which are ultimately interpreted by the brain as pain. Because the nervous system is the origin of the phenomenon, rather than simply being the transmitter of the signals, this second type of pain is called "neuropathic pain".

Cancer is only one of many possible causes of neuropathic pain, other examples being the "post-herpetic neuralgia" which sometimes develops after shingles (herpes zoster), and the "phantom limb pain" which may develop after an amputation. However, cancer is a very important cause, as neuropathic pain due to cancer accounts for many of the most difficult pain management challenges encountered in medical practice.

In many cases, neuropathic pain appears to be a response by some part of the central nervous system (brain and spinal cord) to the *absence* of normal incoming signals. Because incoming signals are referred to as "afferent" (meaning towards the brain) this type of neuropathic pain is called "**de-afferentation pain**".

De-afferentation pain sometimes, though far from always, develops some time after an injury to, or destruction of, a peripheral nerve, a spinal nerve root, or a "tract" of nerve fibres carrying signals up the spinal cord to the brain. The injury or destruction might be due to a local tumour deposit, a complication of cancer therapy, or a toxic substance produced by cancer cells elsewhere in the body and released by them into the bloodstream. In a few cases, it might be caused by something else, which might not be related to the cancer at all.

It is also possible for neuropathic pain to be caused by direct stimulation of a nerve or spinal tract by a local tumour deposit, even though no permanent damage is done. This causes signals to flow up the nerve fibres *as if* they had been sensed by nociceptors at the nerve endings. This second type of neuropathic pain is thus produced by the presence of abnormal

signals, rather than the absence of normal signals, and is therefore not quite the same as de-afferentation pain.

However it is caused, neuropathic pain can often be suspected from the description given by the person suffering from it. It is often described as "burning", "tingling", "shooting" or "like electric shocks", and it has often persisted after other pains have responded to analgesic medication. Also, the region in which the pain is felt usually corresponds anatomically to the area supplied by some part or parts of the nervous system.

Examination by the doctor may also reveal a neurological abnormality, such as the absence of a normal reflex, or an area of diminished or heightened sensation. It may also be possible to demonstrate "allodynia" (pain resulting from a stimulus which is not normally painful). However, the exact details of the chain of events responsible for a particular example of neuropathic pain are often difficult to establish.

Sympathetic Dependent Pain

Sympathetic dependent pain, which is also called sympathetic(ally) maintained pain, is probably a rare and poorly understood type of neuropathic pain which has its origin in the sympathetic division of the autonomic nervous system[6]. However, at the time of writing it is usually classified separately, as its characteristic features are very different from those described above under the heading Neuropathic Pain.

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[6] The autonomic nervous system is a specialised part of the peripheral nervous system which automatically controls all those bodily functions that go on constantly without our conscious awareness. Its two main divisions are the sympathetic nervous system, which joins the central nervous system via certain thoracic and lumbar spinal nerve roots, and the parasympathetic nervous system, which joins the central nervous system via certain cranial nerves and sacral nerve roots.

Sympathetic dependent pain often affects part or all of a limb, usually a lower limb, in a distribution which does not match that of any spinal nerve roots or peripheral nerves. It is often associated with abnormalities of skin colour, hair growth and sweating in the affected region. It responds poorly to analgesic medication, and is usually best treated by a specialised type of nerve block called a "sympathetic (plexus) block".

Vascular Pain

The term "vascular pain" should really be reserved for pain which arises from the walls of a blood vessel, but it is sometimes used loosely to mean ischaemic pain (see next heading). Blood vessels probably have specialised pain receptors in their walls which can produce pain stimuli when something damages the vessel or causes it to dilate or constrict, but vascular pain, like sympathetic dependent pain, is very incompletely understood at the time of writing.

Some patients with cancer experience pain which seems to arise from blood vessels damaged by tumour deposits. The region in which pain is felt usually corresponds anatomically to the area supplied by some part of the vascular system, rather than the nervous system. Medical examination or special investigations may sometimes provide independent evidence of vascular damage. The treatment of vascular pain is complex and difficult, and is usually best left to pain specialists.

Ischaemic Pain

Ischaemic pain is pain which results from an insufficient blood supply, and it may involve a number of mechanisms. When the blood supply of a tissue or organ is insufficient for its needs, the tissue or organ is said to be "ischaemic" and the condition is referred to as "ischaemia". Depending on the severity of the ischaemia, a variable amount of tissue irritation or damage occurs, thereby stimulating local nociceptors and causing the nociceptive type of pain previously described.

However, depending on the tissue involved and the degree and duration of ischaemia, damage may also occur to nerves within the tissue, giving rise to neuropathic pain as well. In addition, if blood vessels in the tissue suffer ischaemic damage, vascular pain may also occur. Ideally, ischaemic pain is treated by medical or surgical treatment to relieve the ischaemia itself. When this is not possible, treatments which target nociceptive, neuropathic and/or vascular pain may be necessary.

Pain Disorder

Sometimes, no known physiological mechanism can be discovered to account for a patient's pain, or else the severity of the pain is greater than can be accounted for by any known mechanism. In this situation, the patient is sometimes said to be suffering from a "pain disorder" if the physiological mechanism is completely unknown, or from an "organic pain disorder" if a known mechanism exists but is considered to be only partially responsible for the pain which the patient reports.

Pain disorders probably have various psychological factors as major or contributing causes in many cases, but there may also be unknown physiological factors awaiting discovery. Pain disorders are rarely the main reason for pain in patients with cancer, but various psychological factors can certainly contribute to the severity of cancer pain in some cases.

HOW CANCER CAUSES PAIN

There are many types of cancer, but they all share the same essential feature: the cells of which a cancer consists have lost the ability to respond to the body's normal control over cell division. Not only that, but they have also gained the ability to survive the body's available defences (which would otherwise recognise them as abnormal, and then destroy them). As a result, the number of cancer cells increases, and the cancerous tissue therefore keeps growing larger and larger.

To make matters worse, any cancer cells which are washed into the blood capillaries or lymph vessels passing through the cancerous tissue may "metastasise" (spread) to other parts of the body, where they then continue to divide and thus create secondary deposits of the same type of cancerous tissue. Either the primary cancer, or one or more of these secondary deposits, may then cause pain by damaging adjacent body tissues.

An enlarging mass of cancer naturally causes pressure on nearby structures, and it can also lead to stretching of other tissues, such as the capsule of a solid organ. Either compression or stretching can stimulate the nociceptors in nearby nerve endings. In addition, compression of blood vessels can lead to damage to the tissues which were previously supplied with oxygen by those blood vessels.

Another possible cause of pain occurs when a normally hollow structure (such as the intestine, or a duct which carries secretions) is obstructed by a growth inside it, or by pressure from outside it. The muscles in the walls of the hollow structure then try very hard to overcome the obstruction, causing the recurring spasms of pain often referred to as colic.

As mentioned previously, a peripheral nerve, or a part of the central nervous system, could be damaged by a cancer deposit, which sometimes results in neuropathic pain. Some of the methods used to treat cancer or to relieve its effects also have complications which can result in pain. In addition, simply being unwell, with the associated lack of normal activity, can cause or exacerbate musculoskeletal pains (common types of pain from muscles, tendons, ligaments and joints).

Finally, if a cancer deposit is growing inside a bone, then in addition to causing pain in the ways mentioned above, it may also weaken the bone so much that a fracture can occur without any significant injury. This is called a "pathological fracture". The fracture itself will then be a cause of pain in its own right

until it is treated to prevent movement of the broken pieces of bone against each other. If a blood vessel or some part of the nervous system is also damaged as a secondary effect of the fracture, this may, of course, lead to further painful results.

As you can see from the above examples, there are many different ways in which cancer can cause pain. In many cases, the mechanism responsible for a pain can be suspected from the description of the pain itself. Knowing the mechanism can be helpful when choosing the best method of treating the pain, so it is very helpful to the doctor to be given a good description.

For example, infiltration of an organ by cancer often causes a dull and poorly localised pain as a result of damage to its component tissues. However, if the cancer deposits increase the overall size of the organ sufficiently to stretch its capsule, that causes a sharper, and more localised type of pain.

Infiltration of bone causes a pain rather like toothache, which is quite well localised and is associated with local tenderness, especially on impact. (It may also include a neuropathic element, which, as mentioned previously, might cause burning, tingling or shooting pains, or might feel like electric shocks.)

HOW CANCER PAIN IS TREATED

It is bad enough to have an illness which requires a great deal of tiresome treatment, and which may ultimately prove fatal, but suffering frequent or constant pain as well makes matters much worse. As mentioned previously, this extra problem can be managed. Cancer pain can usually be relieved by quite simple methods, and in the approximately fifteen percent of cases where these simple treatments are not fully effective, more complex methods of pain management can be used.

This last point is tremendously important. Although cancer pain is initially treated in relatively simple ways, as discussed

below, in about fifteen percent of cases these standard treatments are not effective. However, that does not mean that the pain cannot be relieved. It simply means that more complex methods of treatment are necessary. *Any patient who is told that nothing more can be done for a pain caused by a cancer is therefore being misinformed, and should immediately request referral to a Pain Management or Palliative Care specialist.*

In general terms, good pain management involves prevention (whenever possible), assessment (always), and then either cure or palliation. When the cause of a pain can be cured, this is obviously the ideal solution, but when cure is not possible, palliation takes centre stage. I will give prevention, assessment and palliation their own headings, below, but I will deal with palliation at greater length, as it can be very helpful to patients if they and their loved ones understand how it can be achieved.

Prevention

When it is possible, prevention is always better than cure, and this has important implications for cancer pain. Of course, prevention of cancer itself is also important, but that topic is outside the scope of this booklet. However, even if a person has a cancer which cannot be cured, active therapy for that cancer may often prevent predictable future problems.

For example, surgery to remove a primary bowel cancer can prevent future problems due to intestinal obstruction, even if secondary tumours which are already present in other organs mean that cure is difficult or impossible. Radiotherapy may help to prevent a future pathological fracture, thus preventing the pain so caused, as well as avoiding the need for orthopaedic surgery. Excision of a primary cancer close to the skin may prevent the later development of ulceration and "fungation" (growing out from the skin in a way reminiscent of a fungus).

There are many other examples of treatments designed to prevent a possible future problem, and they should always be considered by the medical and surgical specialists involved in the patient's care. From the point of view of the patient, the main thing is to understand that some recommended treatments may be aimed at prevention of future symptoms, rather than complete cure of the cancer itself.

Assessment

The first step in any endeavour is assessment, and the relief of cancer pain is no exception to this rule. It cannot be assumed that either the presence or the characteristics of pain will be obvious. Some people, especially those whose personality is not very extroverted, do not mention pain at all unless they are asked about it. This is particularly so near the end of life.

When gathering information about pain, or indeed any other important matter, non-verbal communication is very important. I have discussed this in some detail in my earlier ebook entitled "Notes on Communication"[7], so I will not go into it here. However, in the present context, I particularly recommend the chapters on non-verbal communication and active listening.

Health care professionals assessing a patient with pain would normally take a detailed "pain history", followed by physical examination and, in many cases, one or more investigations. At the end of this process, it should be possible for the doctor to determine the cause of the pain (which may, of course, not be due to the cancer at all, though it very often is). Knowing the cause, the most likely pain mechanism(s) can be deduced, and the most suitable method of pain relief can then be chosen.

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[7] Coates, G.T. 2009. Notes on Communication. Wanterfall eBooks, Sydney; available as a free download from http://www.wanterfall.com/downloads.htm.

It is often very helpful if the patient or a relative or friend can present the basic facts about a pain to the medical or nursing staff. The simple mnemonic **"6 S**hots **PAR** from the **T**ee**"** may be helpful in remembering to ask the following questions.

Pain Assessment Questions

Site: where is each pain felt?

Sort: what does it feel like?

Severity: how bad is it?[8]

Starting: when and how did, or does, it start?

Shooting: does it "go" anywhere else?

Sleep: does the pain prevent or interrupt sleep?

Precipitating factors: does anything precipitate or aggravate it?

Associated symptoms: do other symptoms, such as sweating, nausea, diarrhoea or breathlessness, occur at the same time as the pain?

Relieving factors: have you found anything which helps it?

Time factors: when was this pain first experienced? Is its severity constant, or does it vary in intensity? If it is intermittent, how often does it occur, and how long does each episode last? If it is relieved by any treatment, how long does that relief last?

In addition to the basic information outlined above, it is also helpful for the doctor to know about any changes which the pain has brought about in the patient's daily activities, work or

[8] Severity is impossible to measure exactly, but is, nevertheless, very important. Various semi-quantitative pain assessment tools are available, such as comparison with past experiences, placement on a numerical or visual analogue scale, and choosing from a range of images of facial expressions.

relationships, and what meaning the patient ascribes to the pain. Then, all of the information collected about the pain can be considered in the context of the status of the cancer and any other physical or psychological conditions which are present.

The success or otherwise of previous treatments, where applicable, is also important. Attitudes and beliefs in relation to pain and its treatment also need to be discussed with the doctor, as they may have a considerable influence on the acceptance, and in some cases the effectiveness, of the treatments recommended.

Palliation

Palliation simply means relieving something unpleasant without curing its cause. Whenever assessment shows that a patient is experiencing pain, the cause of which cannot be cured, the next step should always be palliation. The remainder of this booklet will be about the palliation of cancer pain.

There are a number of methods by which pain caused by primary or secondary cancer deposits can be relieved. These methods could be classified in various ways, but I will look at them under the following general headings:

- Shrinking the tumour deposits themselves
- Reducing the local effects of tumour deposits
- Immobilising structures which cause pain when moved
- Interrupting the "pain pathway" to the brain
- Elevating the "pain threshold" in various ways
- Prescribing analgesic and co-analgesic medication

Shrinking tumour deposits to relieve pain

It should come as no surprise that one approach to reducing pain caused by progressively enlarging deposits of cancer is to make those deposits smaller. This can be done by surgery, radiotherapy, chemotherapy, hormone therapy or various other

methods. The choice of method used should be made in consultation with the appropriate specialist. More than one method is usually helpful, and different methods are often recommended at different times in the course of the illness.

Reducing the local effects of tumour deposits

Some of the local effects of tumour deposits can be reduced in fairly simple ways. For example, if a tumour breaks through the skin to cause an ulcerated growth, it will be much more comfortable if it is kept clean and covered with a suitable dressing, and if any infection occurring within and around it is treated appropriately. Special dressings which absorb unpleasant odours may be very helpful in some cases.

On other occasions, the best treatment for the local effects of a tumour deposit may involve more complex interventions. For example, if a hollow organ, such as the intestine or a bile duct, becomes obstructed by a tumour deposit, the severe colic which results from the body's attempts to force a way through the obstruction may be completely relieved by bypassing the obstruction. This can sometimes be done simply by passing a tube (called a "stent") through the obstructed region at endoscopy[9], but sometimes a surgical operation is required.

The effects of obstruction of a hollow organ can also be relieved to a considerable extent by the use of medications alone, and sometimes this is preferable. For example, if multiple or recurrent bowel obstructions are not suitable for either stenting or open surgery, then a combination of medications which reduce local inflammation, swelling, production of secretions, and spasm of the "smooth muscle"

[9] Endoscopy is a procedure in which an instrument called an endoscope is passed through a natural orifice such as, for example, the mouth, anus or urethra, in order to gain access to, for example, the gastrointestinal or urinary tract, without the need for open surgery.

fibres in the walls of the organ, in conjunction with antiemetic and analgesic medications, can be extremely effective.

These are just three examples of the relief of pain by reducing the local effects of a tumour deposit, even when it may not be possible to shrink it. There are many other similar examples.

Immobilisation to relieve pain

Many pains are made worse by moving the painful part, and the minimisation of painful movements is a normal part of nursing care. In many cases, elevation of the painful part, to reduce swelling, also helps. Sometimes, both of these things can be achieved simply by resting a limb on some carefully arranged pillows. However, there are also more specific methods of immobilisation, and sometimes they are essential.

For example, in the case of a pathological fracture, which can occur when cancer invades a bone and weakens it, complete immobilisation of the bone fragments is almost always necessary in order to relieve the pain. This is usually best achieved by "internal fixation" of the fracture by an orthopaedic surgeon, which should be done with as little delay as possible, and ideally on the same day as the fracture. Even if strong fixation is impossible, because of the extent of bone destruction, it is usually possible to reduce movement of the bone fragments by using acrylic cement to glue them together.

Interruption of the pain pathway

Another way of relieving pain is to interrupt the transmission of pain stimuli along their pathway towards the part of the brain which is responsible for the experience of pain. Actually, a number of parts of the brain interact to produce the experience of pain, but for the sake of simplicity we can nominate the cerebral cortex, which is the folded outer part of the brain composed of "grey matter" (mainly nerve cell bodies).

In the case of nociceptive pain, this "pain pathway" starts with individual nerve fibres, each of which has a nociceptor at its peripheral end in some part of the body. A pain stimulus, created by the nociceptor as a response to local tissue irritation or damage, passes along each of these nerve fibres, which later join other nerve fibres to become part of a peripheral nerve.

The peripheral nerve ultimately connects via spinal nerve roots to the spinal cord. The pain stimuli then travel upward along certain spinal tracts until the spinal cord joins the brain. They then continue along cerebral tracts, passing through various parts of the brain and finally reaching the cerebral cortex.

The pain pathway just described could theoretically be interrupted at any point between the nociceptors and the cerebral cortex. However, in order to interrupt all of the pain stimuli emanating from a painful part of the body, the interruption must occur after they have all conveniently come together. In practice, this means blocking transmission along a fairly large peripheral nerve, or else further up the pathway.

A temporary interruption of this sort can be achieved by injecting a local anaesthetic near a peripheral nerve, a nerve plexus, a spinal nerve root, or the spinal cord itself. If the local anaesthetic is infused continuously, the duration of analgesia can be extended for days, weeks or even months. However, extended local anaesthesia can cause various complications, such as infection at the infusion site, so although it can be very useful in certain cases, it is certainly not a panacea.

Another way of reversibly inhibiting the transmission of pain stimuli is transcutaneous nerve stimulation (TENS). This technique has the great advantage of having very few side effects, which are mostly very minor if they occur at all. However, its effect is not nearly as strong as that of a local anaesthetic injection. TENS may be very helpful to a minority

of patients, but in most cases it either provides part of the overall pain control or is not found to be helpful at all.

Various neurosurgical procedures which interrupt pain pathways permanently are also available. However, various recently developed non-destructive techniques, such as neuromodulation (electrical stimulation) of the spinal cord, or sometimes of a part of the brain called the cingulum, have superseded many of the irreversible neurosurgical pain control techniques which were previously used.

The details of modern neurosurgical and neurophysiological techniques are outside the scope of this booklet. The important point is that, if simpler interventions have been tried and have failed, there are always many further options to consider. Assessment by a multidisciplinary pain clinic is sometimes very helpful when considering these further options.

Elevation of the pain threshold

Because pain is an entirely subjective experience, the term "pain threshold" is inevitably vague and imprecise. However, it can be useful to doctors as a starting point when considering two very important aspects of pain management. The first of these aspects is that apparently similar injuries or illnesses can result in very different degrees of pain in different people. The second is that a person with an apparently unchanged injury or illness can suffer very different degrees of pain from it under different circumstances.

An individual's pain threshold was traditionally envisaged as the lowest intensity of a potentially painful stimulus which resulted in pain being experienced by that individual. Simple experiments in which the subjects were tested with harmless but painful stimuli of varying intensity showed that some people reported pain at a lower stimulus intensity than others. If a stimulus of low intensity caused pain, the pain threshold

was said to be low. If a stimulus of higher intensity was needed before pain occurred, the pain threshold was said to be higher.

Further experimentation showed that the pain threshold could also be influenced by various changes in the circumstances under which the test was carried out. In other words, a single individual could have a lower pain threshold under some circumstances, and a higher pain threshold under others.

The fact that only the stimulus can be measured, while the pain itself can only be reported and described, makes it unlikely that such experiments will ever yield much more information than the basic observations described above. However, knowing that a person's pain threshold can be influenced by various circumstances, immediately suggests the possibility of relieving pain by altering any factors which affect the pain threshold.

There is broad agreement among health professionals with experience in pain management that many different factors can indeed be modified in ways which appear to elevate a patient's pain threshold. Some of these factors exert their influence by a physical (including physiological) mechanism, while others act on the other four aspects (intellectual, emotional, social and spiritual) of what is often referred to as the "whole person".

I will look briefly at various examples of factors which can affect the pain threshold, grouping them under five subheadings, one for each of the five aspects of the whole patient referred to above. After that, I will suggest some further reading for those who may wish to explore this "holistic" (whole person) approach to elevation of the pain threshold further, or perhaps apply a similar approach to other aspects of the challenge of living with advanced cancer.

Physical Factors

A wide range of physical factors can affect the pain threshold. Firstly, basic aspects of physical comfort, such as temperature,

humidity, furnishings, and levels of noise or other forms of pollution, create the environment in which the patient's own innate resources work. If these environmental factors are optimised, those innate resources can work better.

Secondly, adequate rest and sleep, and exercise and nutrition suitable to the patient's needs, are necessary if these same innate resources are to be maintained in as good a state as possible. Thirdly, various physical interventions, such as massage, acupuncture, and changes in the temperature of painful parts of the body, also appear to help in various ways.

In addition, any other physical symptoms the patient may have, such as nausea, constipation, breathlessness, cough, or the presence of disagreeable odours from an open wound or a stoma, are bound to reduce the overall tolerability of the situation. Relieving these symptoms, regardless of whether they are due to the cancer itself or to some other illness, is therefore very likely to raise the patient's pain threshold.

Intellectual Factors

It is natural to think a great deal about a serious illness such as cancer, and it is well established that thought interacts closely with both emotion and sensation. In particular, uncertainty tends to breed anxiety, so a lack of understanding about the illness and its effects can interact with the emotional factors discussed next. Cognitive therapies are sometimes helpful in changing the ways that thoughts influence the pain threshold.

The meaning ascribed to symptoms is also strongly influenced by thoughts about their origin and likely effects. If the meaning of a symptom is clouded in mystery, it is very easy for it to assume a terrifying aspect. This can usually be ameliorated by simple, clear and honest discussion with the patient's doctor.

Doctors often provide fairly limited information unless specific questions are put to them. Therefore, it is a good idea for the

patient to decide before a consultation what information he or she would like to know *and is ready to hear*, and then to ask the appropriate questions directly, repeating them if necessary. It can be helpful to write down the main points during the consultation, as it is often difficult to remember the details later. If the patient is accompanied by a friend or relative, their recollections of the consultation will also be helpful later.

Emotional Factors

Perfectly normal, but nonetheless distressing, emotions, such as non-specific anxiety, more specific fears, or the sadness and anger which are felt while grieving over an adverse diagnosis or prognosis, can make any aspect of life seem worse, and pain is no exception. I have written elsewhere about various aspects of normal emotions[10], and also about some communication techniques[11] which are helpful when discussing difficult subjects, so I will not go into the details here.

For now, I will just say that I am quite certain that pain is much more easily controlled when a person's questions have been honestly addressed, and the emotions which may result have been "encouraged, expressed, explored and evaluated", as described in the first of the two books just mentioned.

The overall emotional environment created by the attitudes and behaviour of those providing care is also important in facilitating the resolution of painful emotions. Good teamwork and effective staff support in a clinic, hospital ward or hospice may not always be obvious to an external observer, but they contribute greatly to the welfare of patients and their loved ones.

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[10] Coates, GT, 2008.Wanterfall. Wanterfall eBooks, Sydney.

[11] Coates, G.T. 2009. Notes on Communication. Wanterfall eBooks, Sydney.

(Both of the above books may be read online at www.wanterfall.com or downloaded free of charge from www.wanterfall.com/downloads.htm)

Specific mental illnesses, such as the various types of anxiety and depressive disorders, must be distinguished clearly from the normal emotions which accompany adversity. However, mental illnesses have adverse effects on the patient's emotional state, so treating them can also elevate the pain threshold.

In addition, a wide range of strategies which are sometimes used as adjuncts in the treatment of mental illnesses, such as relaxation therapy, cognitive, behavioural and mindfulness therapy, meditation, guided imagery, hypnotherapy, music therapy and diversional therapy, may also be of great help in relieving the normal emotional responses to illness and loss.

Social Factors

The social factors which are most relevant to effects on the pain threshold are usually the patient's relationships and communication with family and other loved ones. There is considerable overlap and interaction between emotional and social factors, so they usually need to be considered together.

Family communication problems, and especially a "conspiracy of silence" regarding the diagnosis, can sometimes thwart the most expertly conceived analgesic regimen, as well as causing much other avoidable distress. Health professionals can help in this situation, but it can be avoided in the first place if the patient and family discuss matters openly and honestly, and do not try to avoid the inevitable strong emotions which arise.

Spiritual Factors

Although a "spiritual" aspect of the whole person is a difficult concept to define, it is nevertheless considered important by many patients, including many who do not consider themselves religious. Those who are religious may receive great comfort from the attendance of a chaplain or other suitable person, and also from their own prayers and the prayers of others. Those who do not consider themselves religious may nevertheless

wish to discuss questions such as the possible meaning and purpose of life, and the nature and significance of death.

Detailed discussion of such matters is outside the scope of this booklet. However, I have noticed that patients who view death as a natural part of life, and life as some sort of continuum, however vaguely conceived, often approach their own death with relative equanimity. Not all patients wish to discuss these issues, but those who do should be encouraged, as it may help them greatly in coming to terms with their situation.

Further Reading

The previous five subheadings, though here only applied to examples of possible strategies for elevation of the pain threshold, could equally well be used as a framework for the "holistic" approach to the overall challenge of living with advanced cancer, or indeed any other challenging life situation.

For readers who would like to explore the remarkable possibilities offered by a holistic approach to the stress, fear and grief which inevitably accompany any serious problem, I recommend the book "Full Catastrophe Living"[12] by Jon Kabat-Zinn. Although now in its fifteenth anniversary edition, this book is as applicable today as when it was first published.

Although many other books which are based on the same principles have since been written, and many more surely will be written, I very much doubt whether any of them will ever surpass the clarity and comprehensiveness of this one. For any person who is faced with a serious illness, bereavement or any

[12] Kabat-Zinn, J. 1990. Full Catastrophe Living. New York: Bantam Dell. ISBN 978-0-385-30312-5. (For information about courses and self-help materials based on the book, see the Center for Mindfulness in Medicine, Health Care, and Society page at the University of Massachusetts Medical School's website (http://www.umassmed.edu/cfm/home/index.aspx).

other devastating life event, and would rather feel better than worse, I recommend this book without reservation.

Relieving pain with medications

Although the five methods of palliation already discussed are very important, I will say much more in this booklet about relieving pain with medications than I have said about the previous five headings. That is why I have given this topic its own major heading, More about Pain Medications, below.

This is partly because the five methods already discussed often involve quite complex interventions by a range of medical and allied specialists, the details of which are best left to those specialists, but more importantly it is because *medication is very often the mainstay of palliation*.

Incidentally, although I have given the use of medications a separate heading, their actions could equally well have been considered under three of the previous headings, namely:

- Reducing the local effects of tumour deposits (because both opioid and non-opioid analgesics often reduce the local effects of tumour deposits on peripheral nociceptors)
- Interruption of the pain pathway (because opioid analgesics inhibit transmission of pain stimuli along the spinal cord)
- Elevation of the pain threshold (because opioid analgesics also act within the brain to reduce the perception of pain)

However, for practical purposes, I think it is most helpful to consider the use of medications as a distinct method of pain control, even though their various mechanisms of action (some of which are very incompletely understood) overlap with some of the methods already described.

Reassessment

Regardless of the method (or usually methods) employed to prevent or relieve pain, frequent reassessment of each

individual patient is crucial to continuing success. No amount of knowledge or experience on the part of the doctor and allied health care professionals can substitute for regular review of each individual patient. This is especially true in the terminal phase of cancer (or any other illness), but it is also very important for all patients at every stage of any illness, and so patients should expect to be reviewed frequently.

MORE ABOUT PAIN MEDICATIONS

The optimal use of medications is almost always pivotal in the effective control of cancer pain, and the basic principles governing their use can and should be understood by all cancer patients and all those who care about their welfare. I have therefore given this aspect of pain management its own major heading, and will devote most of the rest of the booklet to it.

I will mention many medications under the present heading, and say quite a bit about how they can best be used. Do not be deterred by their strange, and sometimes lengthy, names. Everything needs a name, just as everybody needs a name. The names of some medications may seem very weird at first, but they are just names, and you will soon get used to them.

The WHO Analgesic Ladder

A simple introduction to the effective use of medications for the relief of cancer pain is provided by the so-called "analgesic ladder"[13] recommended by the World Health Organisation (WHO). Here are the "steps" on the WHO analgesic ladder:

[13] WHO online, "WHO's Pain Relief Ladder", © 2010. Accessed on 30 September 2010 at http://www.who.int/cancer/palliative/painladder/en/

Step 1

- Non-opioid analgesia (e.g. paracetamol, aspirin etc)
- Plus adjuvant[14] medication(s) if necessary

Step 2

- A mild opioid (such as codeine)
- Plus non-opioid analgesia if necessary
- Plus adjuvant medication(s) if necessary

Step 3

- A strong opioid (such as morphine)
- Plus non-opioid analgesia if necessary
- Plus adjuvant medication(s) if necessary

On the WHO website, the following explanation accompanies the three-step "ladder" shown above:

'If pain occurs, there should be prompt oral administration of drugs in the following order: non-opioids (aspirin and paracetamol); then, as necessary, mild opioids (codeine); then strong opioids such as morphine, until the patient is free of pain. To calm fears and anxiety, additional drugs – "adjuvants" – should be used. To maintain freedom from pain, drugs should be given "by the clock", that is every 3-6 hours, rather than "on demand". This three-step approach of administering the right drug in the right dose at the right time is inexpensive and 80-90% effective. Surgical intervention on appropriate nerves may provide further pain relief if drugs are not wholly effective.'

Despite its brevity, that summary provides a very useful overview. I will flesh it out by describing the medications it refers to, and after that, I will discuss some very important

[14] "Adjuvant" (or "co-analgesic") medications are discussed later.

aspects of the correct use of opioid analgesics. Even though it is the doctor who prescribes the medications, it can be very helpful if the patient and carers understand the principles involved well enough to facilitate discussion, and to request referral if pain is not well controlled.

The various medications which can be used to relieve pain fall into three main groups:

- Simple (non-opioid) analgesics
- Opioid analgesics (sometimes called narcotic analgesics)
- Co-analgesics (also called analgesic adjuvants)

Although the second group contains more powerful analgesics than the first group, and the members of the third group are not primarily analgesics at all, any of the three groups may be the most important in a particular case, depending on the cause of the pain. In quite a few cases, one or more drugs from *each* group must be used simultaneously for best results. I will now discuss each of these three main groups of medications in some detail, before going on to discuss some very important aspects of the use of opioid analgesics in the management of cancer pain.

Simple analgesics

Simple analgesics often play an important role in the management of cancer pain, regardless of the severity or complexity of the pain in question. They are particularly useful for pain of "connective tissue" origin. Two important examples of connective tissue are bone, and the outer (capsular) layer of any organ in the abdomen or chest. When simple analgesics do not relieve cancer pain, it is very often best to *add* an opioid analgesic, rather than stopping the simple analgesic when the opioid analgesic is commenced.

Most simple analgesics are quite well known to many people because they are used to relieve common pains such as

headache, backache, or sore throat. Many of them can be purchased without prescription in most countries. However, they should not be thought of as weak or insignificant, as they play a very valuable role in many cases of cancer pain. Sometimes, they are the only analgesics needed, but in most cases they need to be used in combination with an opioid, or sometimes with an opioid plus one or more adjuvant drugs.

All simple analgesics exert their effect by interfering with the synthesis of substances called prostaglandins, which are chemical "messengers" that are involved in many physiological processes, including pain, fever, blood coagulation and inflammation. To distinguish them from another group of drugs (glucocorticosteroids) which also reduce inflammation, they are called non-steroidal anti-inflammatory drugs (NSAIDs). However, NSAIDs are not all identical in their actions, and the differences are sometimes important, as discussed below.

Paracetamol (acetaminophen)[15] differs considerably from other NSAIDs in that its antiprostaglandin effect is almost entirely limited to the central nervous system. For this reason, although it reduces pain and fever, it has very little effect on blood coagulation or inflammation. For practical purposes, it is therefore an "NSAID" in name only, and in fact it is not very often called one at all, except by pharmacologists.

The great advantage of paracetamol (acetaminophen) is that, because its peripheral effects are so slight, it almost never causes gastric or duodenal ulcers, or a generalised bleeding tendency – things which all other NSAIDs sometimes do.

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[15] The trade (brand) names of paracetamol (acetaminophen) include Acamol, Apiretal, Benuron, Calpol, Dafalgan, Datril, Depon, Dexamol, Doliprane, Dolo, Dolprone, Dymadon, Efferalgan, Febridol, Pacimol, Pamol, Panado, Panadol, Panamax, Paralgin, Perfalgan and Tylenol.

Indeed, although adverse reactions to paracetamol (at correct dosage) can occur, they are extremely uncommon.

Another advantage of paracetamol (acetaminophen) is that it can be given in combination with another NSAID, often resulting in significantly better analgesia without adding any appreciable side effects. This is most likely to be effective when the other NSAID is needed to reduce local inflammation.

It is usually recommended that not more than four grams of paracetamol (acetaminophen) be given to an adult patient in any twenty-four hour period. This is sometimes increased to six grams per twenty-four hours in the management of cancer pain in adults with good liver function (which should then be monitored). On the other hand, when liver function is very poor, which is quite often the case in patients with advanced cancer, paracetamol dosage may need to be reduced to less than two grams per twenty-four hours, or even avoided altogether.

Aspirin (acetylsalicylic acid)[16] has been used for a very long time, both as an analgesic and as an anti-inflammatory drug. It differs from other NSAIDs in the opposite direction to paracetamol, by interfering much more strongly with blood coagulation than most NSAIDs do, while sharing their tendency to cause gastric or duodenal ulceration.

Depending on the individual patient, reducing the tendency of the blood to coagulate can be an advantage or a disadvantage. However, in patients with advanced cancer, it is more often a disadvantage, and for this reason aspirin is not used as much in cancer pain management as other simple analgesics are.

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[16] The trade (brand) names of aspirin (acetylsalicylic acid, sometimes provided as an acetylsalicylate) include Acenterine, Acetophen, Acetylin, Adiro, Albyl, Aquapin, Asatard, Aspegic, Aspisol, Aspro, Astrin, Bamyl, Colfarit, Coryphen, Delgesic, Dispril, Disprin, Ecotrin, Empirin, Magnecyl, Novasen, Premaspin, Rhonal, Rhusal, Solprin and Soluspril.

Other NSAIDs, such as naproxen[17] and many others[18], are the third type of simple analgesic. They also have some inhibitory effect on blood coagulation, but not usually enough to cause significant problems. Their main advantage is that they can directly reduce inflammation in peripheral tissues, as well as having an analgesic effect within the central nervous system.

A major disadvantage of these other NSAIDs is that, like aspirin, they quite often cause gastric or duodenal ulceration. Although this can often be prevented, by adding one or more medications to protect the mucosal lining of the stomach and duodenum, it considerably reduces their overall value, and indeed makes them completely unsuitable for some patients.

These other NSAIDs also have various other side effects, especially when used in combination with common treatments for high blood pressure, so they must be used with care. As some of them are available without prescription in many countries, it is very important to tell your doctor if you are taking one of them. (Of course, this also applies to all other medications, including "natural", "complementary" or "alternative" remedies, as harmful interactions are common.)

Opioid Analgesics

Opioid analgesics are named after the opium poppy, from which the oldest (and in most ways still the best) example, morphine, is extracted. They relieve pain mainly by interfering

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[17] The trade (brand) names of naproxen include Aleve, Anaprox, Bonyl, Equiproxen, Flanax, Floginax, Inza, Laraflex, Laser, Naixan, Naprelan, Napren, Naprium, Naprius, Naprogesic, Naprosine, Naprosyn, Naprosyne, Narocin, Proxen and Xenobid.

[18] Many other NSAIDs, including celecoxib, etodolac, fenoprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, piroxicam, sulindac and tenoxicam, are available, under brand names too numerous to include here.

with its transmission and perception in the central nervous system (spinal cord and brain). They also have a variety of other effects, some of which affect other parts of the body. They are particularly useful for pain arising from organs in the abdomen or chest, or from skeletal muscle tissue, but may also be needed as part of the treatment of severe pain of any origin.

Opioid analgesics are often classified as either weak or strong, according to the degree of analgesia they can provide without causing excessive side effects. This is a fairly loose classification, and in some cases the same opioid might be considered weak or strong depending on the route by which it is administered. When an opioid is needed in an analgesic regimen, it is common practice to start with a weak opioid, and then replace it with a strong opioid if and when necessary. However, this two step approach is entirely optional.

The main reason that starting with a weak opioid is common practice is the reluctance of both patients and their doctors to accept the need for a strong opioid – even if the low dosage employed means that its effect is actually quite weak. The reason that it is entirely optional is simply that a smaller dose of a strong opioid can provide exactly the same effect as a larger dose of a weak opioid. In fact, it usually does this with fewer unwanted side effects or undesirable interactions with other medications, thus giving a better end result.

Weak Opioids

Weak opioids include codeine, dihydrocodeine, pentazocine, dextropropoxyphene, butorphanol, nalbuphine and tramadol. (The last one mentioned, tramadol, is not a typical opioid at all, as it has many other actions in addition to its weak opioid effect. As discussed below, it should never be used for its weak opioid effect alone. However, because of its other effects, it can be a useful drug in some circumstances.)

Codeine and Dihydrocodeine

Codeine[19] is found naturally, along with morphine and many other alkaloids[20], in the crude opium harvested from the opium poppy, and it can also be easily and cheaply synthesised. It has a weak opioid analgesic effect on most people.

Dihydrocodeine, as its name suggests, is very similar in chemical structure to codeine. Its actions are also similar. However, both the metabolism and mechanism of action of codeine and dihydrocodeine are very incompletely understood.

These two weak opioids both undergo metabolism in the liver, and some of their metabolic products also have opioid analgesic actions. Especially in the case of codeine, one of these metabolites is morphine. It is probable that the morphine produced by metabolism provides a considerable proportion of the analgesic effect of codeine.

Variations in the ability of different people to perform this metabolic transformation may account for the fact that codeine has an unexpectedly strong effect (including side effects) on some people, but produces only its usual side effects, with almost no analgesic effect, in some other people. Further research is needed to clarify this matter, and also to determine whether dihydrocodeine behaves in the same way.

The main reason that these drugs continue to be used at all is that, because they were introduced into clinical practice before regulatory mechanisms were well established, there is less "red tape" associated with their prescribing than with that of the strong opioids discussed later. Nevertheless, they are both

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[19] Codeine is usually marketed simply as codeine, though dihydrocodeine is often sold under various trade (brand) names.

[20] The term alkaloids refers to a large group of related chemicals, mainly found in plants, many of which have toxic or medicinal effects on animals.

capable of providing useful, though not very powerful, analgesic effects in a reasonable proportion of patients.

Tramadol

Tramadol[21] has quite a number of actions, and its pharmacology is very complex. As a weak opioid with many side effects, it is completely unsuitable for the management of nociceptive pain. Indeed, it has a particularly poor side effect profile (including induction of seizures at therapeutic dosage) and can cause many serious drug interactions (including the potentially fatal serotonin syndrome[22]).

Because escalation of its dosage is limited by severe toxicity, tramadol has a low addiction potential, and is therefore subject to fewer prescribing restrictions, in most jurisdictions, than are strong opioids. This fact, combined with very skilful marketing, often results in it being prescribed inappropriately for nociceptive pain, sometimes with disastrous results.

However, tramadol also has a variety of non-opioid actions, some of which can be of value for some patients with neuropathic pain. Therefore, although considerable expertise is needed to use it safely, it is a useful drug in some situations.

Other weak opioids

Most of the other weak opioids named above may very occasionally be helpful to a particular patient, but the combination of their weak analgesic effect and their numerous

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[21] The trade (brand) names of tramadol include Contramal, Dromadol, Mabron, Nobligan, Ralivia, Ryzolt, Siverol, Topalgic, Tradol, Tradolan, Tradonal, Tralodie, Tramadex, Tramadin, Tramadolor, Tramahexal, Tramake, Tramal, Tramed, Tramedo, Trexol, Tridural, Ultram, Zamadol, Zamudol, Zydol and Zytram.

[22] Serotonin syndrome is a medical emergency which can occur as a result of various drug interactions. The details of this very complex, very dangerous and potentially fatal condition are outside the scope of this booklet.

side effects usually severely limits (or in some cases completely precludes) their practical usefulness. Even codeine and dihydrocodeine, which are often thought of as being pretty harmless, usually cause significantly more unwanted side effects than an equivalent dose of morphine.

Strong Opioids

There are many opioids which possess a strong analgesic effect. The main examples used in the management of cancer pain are morphine, oxycodone, hydromorphone and fentanyl. Methadone and buprenorphine can also be useful in a few unusual circumstances, but are not suitable for most patients.

Dextromoramide, pethidine and diacetylmorphine (heroin) have been used in the past, and occasionally still are, but they possess no useful advantages over the previously mentioned drugs. Dextromoramide and pethidine also have very significant disadvantages, as discussed below, and diacetylmorphine is no longer available in most countries.

Morphine

Morphine[23] is a purified extract of the sap released when shallow cuts are made in the unripe seedpods of the common poppy *Papaver somniferum* (the same poppy which yields the poppy seeds used in various foods). Morphine has been commercially available for nearly two hundred years, and despite all the advances of modern pharmacology, it is still the most useful of all the available opioids.

The main reason that alternative opioids are sometimes needed is that not all patients can tolerate morphine. This might occur

[23] Morphine, as morphine hydrochloride, morphine sulphate or occasionally morphine tartrate, is marketed under many trade (brand) names, some of which will be listed later.

because of renal failure[24], hepatic failure[25], increased susceptibility to morphine side effects or allergy to morphine. Another reason, at the time of writing, is that morphine cannot be administered via an adhesive patch applied to the skin.[26]

Preparations of morphine for oral administration which have not been modified to produce extended (sustained) release are sometimes referred to as "immediate release" (IR) morphine; or, in the case of morphine sulphate, as "morphine sulphate immediate release" (MSIR). As discussed later, IR morphine is essential in some circumstances, but the longer acting formulations are more convenient in other circumstances.

Extended (sustained) release oral formulations sometimes include the syllable "dur" or "cont" in their trade names, or else use the suffix ER or SR to denote extended release or sustained release. However, most morphine trade names do *not* specify whether the morphine preparation has been formulated for immediate or sustained release, so this information has to be found elsewhere on the label, or in the Product Information.

As discussed later, the difference is extremely important, as immediate release and sustained release formulations of morphine (or any other medication) behave differently and can therefore not be directly substituted for each other. When changing from one to the other, the prescribing doctor has to change the size of each dose, and also the interval between doses, in order to achieve a safe and effective result.

Immediate release oral morphine is often provided in liquid form, which increases the flexibility of dosage, but also

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[24] The use of opioids in renal failure is discussed in Appendix 1.

[25] The use of opioids in hepatic failure is discussed in Appendix 2.

[26] Transdermal drug delivery from adhesive patches applied to the skin will be discussed later when describing fentanyl.

reduces accuracy somewhat, especially if the doses are measured with a spoon or medicine glass rather than a syringe. The use of liquid oral dose forms, such as "morphine mixture", makes it easier to adjust the dosage frequently until the correct dosage for "baseline analgesia"[27] has been established by "dose titration"[28]. After that, extended (sustained) release preparations are usually more convenient. This will all be discussed further under Optimal Use of Opioid Analgesics, below.

It is very important to remember that liquid oral morphine preparations are available in many different concentrations. This means that the actual dose of morphine depends on the concentration, as well as the volume, of liquid administered. For this reason, doses of morphine mixture given in hospitals are usually prescribed (and recorded) in milligrams, rather than millilitres, even though the dose itself then has to be calculated, and measured, in millilitres. For the same reason, patients living at home who are prescribed morphine mixture must make sure they understand exactly how to measure their doses.

Similarly, sustained release oral morphine is available in tablets and capsules of many different strengths. This means that the actual dose of morphine depends on the amount of morphine in each tablet or capsule as well as the number of tablets or capsules taken. This has the potential to cause confusion when the strength of tablets or capsules is changed,

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[27] In the context of cancer pain management, baseline analgesia means the continuous analgesia which controls a patient's chronic pain most of the time, but which may not prevent new pain, breakthrough pain or incident pain.

[28] Dose titration means gradually increasing (or, if necessary, decreasing) the dose until the desired effect is obtained. This is analogous, though not identical, to the meaning of titration in chemistry. Dose titration has traditionally been done using immediate release medications, but it can also be done (a little more slowly) with extended (sustained) release medications.

so patients and their carers must make absolutely sure that the new instructions are clearly understood.

As mentioned above, extended (sustained) release oral formulations of morphine (or in some cases oxycodone or hydromorphone, as discussed later) usually provide the most convenient way of maintaining baseline analgesia in patients who are able to swallow their medication, once the correct dosage for this purpose has been established. Even if tablets or capsules are too difficult to swallow, preparations which consist of small granules encased in a capsule, such as Kapanol, can still be taken by sprinkling the contents of the capsule over some soft or pureed food.

Some sustained release morphine tablets can also be inserted rectally[29], though this would constitute "off-label use"[30] in most jurisdictions. However, if morphine is to be used rectally, the doctor first needs to adjust the dosage[31]. An approximate starting dose might be somewhere between half and two thirds of the oral dose, but the dosage then usually needs to be adjusted further according to the patient's response.

Morphine is, of course, also available in ampoules for administration by injection or infusion. The ampoules usually contain morphine sulphate, but morphine tartrate, which is

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[29] In some countries, sustained release suppositories are available for this purpose.

[30] Off-label prescribing is the prescribing of a pharmaceutical substance in a way which does not constitute an officially approved indication at the time.

[31] The main reason that this dosage adjustment is necessary is that when a drug is given by mouth it is absorbed from the small intestine, and venous blood from the small intestine passes through the liver before reaching the rest of the body. This allows some inactivation to occur even before the drug has a chance to start working. However, the veins which collect blood from the rectum join the general circulation without this "first pass effect".

more soluble in water and therefore allows a larger dose to be given in the same volume of fluid, is sometimes convenient.

A subcutaneous injection of morphine is often used for rapid control of new pain, breakthrough pain or incident pain[32], as it reaches the bloodstream more quickly than morphine taken by mouth. (Intravenous injections work even more quickly, but they are also more likely to cause side effects, and may possibly result in excessive tolerance if given frequently.)

A continuous morphine infusion can be used to provide baseline analgesia when other methods of administration are not suitable. Continuous subcutaneous infusion is the most convenient, safe and well tolerated type of continuous infusion, but continuous intravenous infusion is preferred in some circumstances. (Sometimes, as discussed in Appendix 3, morphine is infused "epidurally" or "intrathecally", so that it affects the spinal cord directly. Very rarely, it is infused into a "cerebral ventricle", so that it affects the brain directly.)

Fentanyl

Fentanyl[33] is a strong synthetic opioid which was first synthesised in 1959. It has high potency,[34] a rapid onset of action and a short duration of action. It was originally used intravenously in anaesthesia, where it still plays an important role. However, it is poorly and inconsistently absorbed when swallowed, so tablets, capsules and mixtures are not available.

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[32] See the General Classification of types of pain under Facts about Pain.

[33] Trade (brand) names for various dose forms of fentanyl include Actiq, Durogesic, Duragesic, Fentora, Instanyl, Matrifen, Onsolis and Sublimaze.

[34] The term potency simply refers to the amount required for a given effect. Although fentanyl is very much more "potent" than morphine, this has nothing whatsoever to do with its effectiveness. It simply means that its equivalent dosage, by weight, is smaller than that of morphine.

Despite this disadvantage, other dose forms of fentanyl, developed over the last fifteen years, have made fentanyl very useful for some patients, both for baseline analgesia and for the relief of new, incident or breakthrough pain. Because its side effect profile is different to that of morphine, it can often be used successfully in patients who are intolerant of morphine.

One important advantage of fentanyl (in common with its less well known analogues, such as alfentanil, sufentanil and remifentanil) is that it causes less sedation, confusion and constipation than most other opioids. Another is that it can be used in the presence of renal or hepatic failure, as discussed in Appendix 1 and Appendix 2 respectively. However, morphine is still the most useful opioid for the majority of patients.

Short term fentanyl analgesia, which is useful for new pain, breakthrough pain or incident pain, can be given by injection, or alternatively by "transmucosal" absorption across the epithelial lining of the mouth. Available formulations of fentanyl for transmucosal delivery include lozenges (sometimes referred to as fentanyl lollipops), effervescent tablets, discs of buccal soluble film and buccal sprays. Various other short acting dose forms of fentanyl, including buccal tablets, buccal patches, nasal sprays and pulmonary inhalers, are also being evaluated.

Baseline fentanyl analgesia for the management of chronic pain can be provided by continuous subcutaneous infusion (or occasionally intravenous or epidural infusion) but transdermal absorption of fentanyl from an adhesive patch applied to the skin is usually the most convenient method for this purpose.

Fentanyl transdermal patches[35] work by gradually releasing fentanyl through the skin into the subcutaneous fat, and thence into the bloodstream, over about 72 hours, after which the

[35] Trade (brand) names for fentanyl transdermal patches include Durogesic, Duragesic and Matrifen.

patch is replaced with a new one. Patches of different sizes result in different blood levels, these remaining fairly stable after rising gradually for about 24 hours after applying the first patch and rising a little further with the second patch.

The rate of absorption of fentanyl from currently available fentanyl patches is dependent on a number of factors, including body temperature, skin type, amount of body fat, the anatomical site of placement of the patch and the brand of patch used. This means that estimation of the necessary initial dosage, when a doctor first prescribes fentanyl patches for a patient, is even more approximate than it is with most other methods of analgesia.[36]

An inevitable delay in the onset of analgesia, until the level of fentanyl in the bloodstream has stabilised after the application of the first two patches, is another factor which the doctor needs to take into account. However, as long as the patient is closely observed for signs of undertreatment or overdosage, excellent results can be achieved with fentanyl patches.

When switching to fentanyl patches from another opioid, or even from another route of fentanyl administration, the doctor's estimate of the equivalent dosage is also very approximate, due to variability in dosage equivalence in different patients.

When switching in the opposite direction, continuing release of fentanyl into the bloodstream after removal of the last patch (from a reservoir of fentanyl which always collects in the subcutaneous fat while a patch is on) is yet another factor which the doctor must consider. Therefore, whenever fentanyl patches are started *or* stopped, very frequent review of the patient by the medical and nursing staff members is absolutely essential until stable analgesia is achieved.

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[36] "Active" transdermal patches, controlled by heat or electrical signals, may provide better control of absorption rates in the fairly near future.

In practice, although morphine is still generally considered to be the best opioid analgesic to try first, for most cancer patients in most situations, the various available dose forms of fentanyl can often provide a better overall result for the following types of patients:

- patients who cannot swallow
- patients who are intolerant of other opioids
- patients with moderate or severe renal failure
- patients with severe hepatic failure

Oxycodone

Oxycodone[37] is a semisynthetic opioid derived from thebaine[38]. Its chemical structure is very similar to that of codeine, but it lacks the main disadvantages of that drug, its effects being almost identical to those of morphine. It has been used for nearly a hundred years and is sometimes the strong opioid which is best tolerated by a particular patient. (It is probably slightly better tolerated than morphine in the presence of renal failure, but it is rarely the best opioid to use in that situation.)

Although oxycodone is in fact a strong opioid, it was previously considered to be of medium strength, simply because its usual routes of administration (oral and rectal) made it relatively unsuitable for use at high dosage, due to the inconveniently large number of tablets or suppositories which would be required.[39] In addition, because of its non-threatening

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[37] Trade (brand) names for various dose forms of oxycodone include Endocodone, Endone, Oxycontin, Oxydose, Oxynorm, Percolone, Proladone, Roxicodone and Supeudol.

[38] Thebaine, like morphine, can be extracted from crude opium.

[39] This is rarely a problem with the extended (sustained) release oral dose forms of oxycodone, which are available in a wide range of strengths. It is also possible to give oxycodone by injection (marketed in some countries as Eukodol, Eucodol or Oxynorm injection) or as a nasal spray, but these dose forms are not widely available at the time of writing.

name, which sounds more like codeine than morphine, it is frequently employed at low dosage in the guise of a "weak" opioid (a role it plays much better than the weak opioids discussed earlier).

Immediate release dose forms of oxycodone can provide reasonably smooth baseline analgesia when taken at intervals of four to six hours. As in the case of morphine, extended (sustained) release oral dose forms of oxycodone can allow conveniently increased dosing intervals to be employed once the correct daily dosage has been established by titration.

Some sustained release oxycodone tablets can also be administered rectally, again usually at somewhat decreased dosage, if the patient is unable to swallow them, though there is less reported experience of this "off-label use" than is the case with rectal administration of extended (sustained) release morphine tablets.

Importantly, all of the precautions mentioned earlier in relation to different formulations and strengths of morphine also apply to oxycodone, and to all the other medications discussed in this booklet – as indeed they do to every medication in existence which is available in more than one formulation.

Hydromorphone

Hydromorphone[40], another chemically modified derivative of morphine, has also been used for nearly a hundred years, and is commercially available in most countries. It can be given orally, rectally or by injection or infusion, and it is occasionally the best alternative analgesic for patients who are unusually susceptible to the side effects of morphine. (Like oxycodone, it

[40] Trade (brand) names for various dose forms of hydromorphone (which is sometimes called dihydromorphinone or dimorphone) include Dilaudid, Hydal Retard, Hydromorph Contin, Hymorphan, Jurnista, Laudicon, Opidol, Palladone, Palladone SR and Sophidone.

is probably somewhat better tolerated than morphine in the presence of renal failure. However, as discussed in Appendix 1, other opioids are usually preferable in that situation.)

Hydromorphone has a somewhat shorter duration of action than morphine, but reasonably smooth baseline analgesia can be achieved when immediate release dose forms are given each four hours. These dose forms can also be used for the treatment of new pain, incident pain and breakthrough pain.

Extended (sustained) release forms of oral hydromorphone with a 12 hour, or in at least one case a 24 hour, duration are available in some countries, and these can conveniently be used for baseline analgesia once the correct daily dosage has been established. I have not seen any reports of "off-label" rectal administration of sustained release hydromorphone tablets, but hydromorphone suppositories are available in some countries.

Methadone

Methadone[41] is a synthetic opioid with effects similar to those of morphine, but with a very long, and inconsistently variable, duration of action. In addition to strong opioid analgesia, methadone has other actions which are sometimes helpful in cases of neuropathic, inflammatory or ischaemic pain[42]. It also has the advantage of not causing toxic metabolites to accumulate in the presence of renal failure.

However, due to unpredictable changes in its duration of action when it is given regularly, safe and effective methadone analgesia requires considerable experience and expertise. Even in expert hands, it should usually be reserved for neuropathic,

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[41] Trade (brand) names for various dose forms of methadone (or sometimes its isomer polamidon) include Amidone, Dolophine, Heptadon, Heptadone, Levo-Polamidone, Methadose, Physeptone, Polamidone and Symoron.

[42] See the Physiological Classification of types of pain under Facts about Pain.

inflammatory or ischaemic pain, or only tried when other opioids have not been successful.

Buprenorphine

Buprenorphine[43] is a strong opioid, with a short duration of action, which has been available for injection since the 1980s. More recently, it has become available in the form of adhesive patches for transdermal drug delivery, as discussed above in relation to fentanyl. However, the patches available in most countries, at the time of writing, can only provide weak baseline opioid analgesia, due to the relatively low doses of buprenorphine which they deliver.

Weak opioid analgesia is, of course, appropriate for some patients. However, in the case of the currently available patches, the blood levels can take from three to seven days to reach steady state levels, so finding the right dose is an impracticably slow process. Therefore, the buprenorphine patches available at the time of writing are rarely, if ever, used in the management of cancer pain.

Another important disadvantage of buprenorphine, regardless of the route of administration, is that it is a "mixed agonist and antagonist" at opioid receptors (meaning that it can block opioid effects, as well as stimulate them). It therefore has the potential to precipitate sudden opioid withdrawal in patients who have been receiving another opioid analgesic. In addition to the pain, which then of course returns, opioid withdrawal can be dangerous, or occasionally even fatal.

The disadvantages described above mean that, at the time of writing, buprenorphine has very little place in the management of cancer pain. In patients who are not already receiving

[43] Trade (brand) names for various dose forms of buprenorphine include Bupregesic, Buprenex, Buprigesic, Butrans, Morgesic, Norspan, Subutex, Temgesic and Transtec.

another opioid, it could be given by injection for new, breakthrough or incident pain, or by continuous infusion for baseline analgesia. However, doctors with experience in pain management rarely prescribe buprenorphine for cancer pain.

Dextromoramide

Dextromoramide[44] is a synthetic opioid which is structurally related to methadone, but has a very short duration of action. It is only available in a small (and decreasing) number of countries.[45] It has a rapid onset when given orally or sublingually, and as its effect lasts for little more than an hour, it can sometimes be useful for breakthrough or incident pain.

Even in those countries where it is available, variations in its absorption can be problematic, especially when switching between oral and sublingual dose forms. Importantly, it is quite impracticable for baseline analgesia, as it would need to be given approximately every single hour around the clock (day and night) to provide reasonably smooth blood levels. (Doctors sometimes forget this, and the results are uniformly disastrous.)

Pethidine (Meperidine)

Pethidine[46], which is known in some countries as meperidine (and also frequently referred to as demerol, after its best known trade name) was developed in 1932 as a potential anti-spasmodic agent, but was found to have analgesic, rather than antispasmodic, properties. It has a short duration of action, and

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[44] When it was more widely available, trade (brand) names for dextromoramide included Alcoid, Dimorlin, Errecalma, Jetrium, Linfadol, Palfadonna, Palfium, Palphium and Troxilan.

[45] Like diacetyl morphine (heroin), dextromoramide became very popular with opioid abusers, which led to its prohibition in many jurisdictions.

[46] Trade (brand) names for pethidine (meperidine) include Aldolan, Alodan, Centralgin, Cluyer, Demerol, Dispadol, Dolantin, Dolantina, Dolantine, Dolargan, Dolcontral, Dolestine, Dolosal, Dolsin, Isonipecaine, Lydol, Meperol, Mialgin, Opystan, Pethadol, Pethanol, Petidin and Piridosal.

a very poor side effect profile, and it therefore has virtually no place whatsoever in the management of cancer pain.

It certainly cannot be used to provide baseline analgesia for chronic pain, as it has toxic metabolites which accumulate even in the absence of renal impairment. If treatment was continued at a dosage and frequency sufficient to control moderate or severe pain, these metabolites would soon cause confusion, then delirium, convulsions and ultimately death.

However, some clinicians still use pethidine for the treatment of new pain, incident pain or breakthrough pain, and it is usually fairly well tolerated when used in that way. (It was once thought that pethidine was superior to morphine in the treatment of spasmodic pains, such as renal, biliary or intestinal colic, but that alleged advantage has since been disproved.)

Diacetylmorphine (Heroin)

Diacetylmorphine[47], also known as diamorphine (but more often referred to as heroin, after its original trade name) is simply the diacetyl derivative of morphine. It is slightly more potent than morphine, so the equivalent dosage is a little lower. It is also more soluble in water than morphine, so subcutaneous injections can be given in a smaller volume of fluid. However, its beneficial effects, side effects and interactions with other medications are identical to those of morphine.

Because it is no more effective as an analgesic than morphine, the fact that heroin is a prohibited substance in most countries has no deleterious effects whatsoever on the management of pain, whether due to cancer or any other cause. On the other hand, heroin purchased illegally would almost invariably have

[47] Trade (brand) names for diacetylmorphine (diamorphine) include or have included Diacephin, Diagesil, Diamorfina and various slight modifications of its first trade name, Heroin.

very deleterious effects, as it is always of unknown concentration, and often contains poisonous adulterants.

Co-analgesics (Adjuvants)

In the context of analgesia, the terms "co-analgesic" and "adjuvant" are very often used interchangeably, to refer to medications which are combined with an opioid to achieve a better result, as judged by the achievement of effective analgesia with minimal side effects. However, I have noticed that they sometimes seem to be used slightly differently, in that simple (non-opioid) analgesics are sometimes included under the umbrella of "co-analgesics", but are sometimes omitted under the umbrella of "adjuvants".

Co-analgesics are useful in most cases of cancer pain management, and are almost always essential when treating neuropathic pain (which was discussed under Facts about Pain). Indeed, they are sometimes more important than an opioid for this type of pain. In future, it may become possible to treat neuropathic cancer pain entirely with non-opioid medication. However, at the time of writing, neuropathic pain occurring in patients with advanced cancer usually requires a strong opioid as well as one or more adjuvant medications.

Adjuvants used for Neuropathic Pain

As discussed previously, neuropathic pain is much more resistant to standard analgesic approaches than is the more common nociceptive pain. Understanding of the mechanisms responsible for neuropathic pain is increasing each year, and important developments (such as the introduction of the "gabapentinoids" mentioned below) occur from time to time.

At the time of writing, it is often necessary for the doctor to try a number of different agents before the best treatment for a particular patient is discovered. Under the next few subheadings, I will say a little about various medications which

are sometimes used in the management of neuropathic pain. As usual, the medications mentioned in this context are marketed under quite a number of different trade (brand) names, but here I will only refer to them by their approved (generic) names.

Anticonvulsants

The members of a new class of anticonvulsant drugs called gabapentinoids (such as pregabalin and gabapentin) are being used increasingly for neuropathic pain, with very good results in many cases. Other fairly new anticonvulsants, such as lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam and zonisamide, have also been used. Older anticonvulsants, such as sodium valproate, carbamazepine and clonazepam, still remain useful for some patients.

Antidepressants

Low doses of early tricyclic antidepressants such as amitriptyline and imipramine may be effective in reducing neuropathic pain. However, the "secondary amine tricyclic drugs", such as nortriptyline and desipramine, are better tolerated by some patients. Newer antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs) paroxetine and citalopram, or the serotonin-noradrenaline reuptake inhibitors (SNRIs) venlafaxine and duloxetine, may also be effective, and are often better tolerated than tricyclic antidepressants.

Opioids with extra actions

A number of opioids have extra pharmacological actions which can be useful in the management of neuropathic pain. Methadone and Tramadol are probably the most important examples. Both of these opioids are difficult to use safely, but either may be helpful in some situations. These two opioids are particularly dangerous if a SSRI or SNRI (see above) is also being taken, or was recently ceased. In my opinion, their use

should always be supervised by a clinician with considerable experience and expertise in pain management.

Other Drugs

Although not specific to neuropathic pain, glucocorticosteroids and NSAIDs, which have been mentioned previously, may be very effective when compression or inflammation of nervous tissue is the mechanism causing the neuropathic pain. They are also sometimes tried when the mechanism is unclear. Major or minor tranquillisers may also be helpful in some cases, and agents such as lidocaine and capsaicin, applied to the skin over the region where pain is felt, also appear to help some patients.

Many other drugs have been tried for neuropathic pain, with variable success. Examples include mexiletine, tocainide, baclofen, clonidine, ziconotide and ketamine. (Some of these drugs are administered, either optionally or exclusively, by the "neuraxial" route, which is discussed briefly in Appendix 3.)

In some jurisdictions the cannabinoid tetrahydrocannabinol, which is the main active ingredient of marijuana, may legally be used for neuropathic pain, as well as for refractory nausea or vomiting, and this appears to be effective for some patients.

Adjuvants used for Bone Pain

Bone pain due to cancer is a very complex phenomenon. In addition to the expected nociception arising from local inflammation, tissue disruption, and interference with the local blood supply, damage to nerve fibres within trabeculated (spongy) bone can create a major neuropathic component. Consequently, the use of three or more medications is frequently necessary in order to control bone pain effectively.

Almost any of the analgesics and co-analgesics mentioned previously might be prescribed in some cases. In addition, interventions directed at the size and local effects of the tumour deposits might include any or all of radiotherapy, radioisotope

therapy, chemotherapy, hormone therapy and immunotherapy. Various types of immobilisation, ranging from gentle nursing through to specific orthopaedic procedures for pathological fractures, are also very important in relieving bone pain.

Especially in the case of breast cancer, prostate cancer and multiple myeloma, all of which frequently cause bone pain, medications which interfere with the normal reabsorption of bone can relieve the pain and reduce the risk of pathological fractures. These medications are called "osteoclast inhibitors", and are also used in other conditions, especially osteoporosis.

Adjuvants used for Nociceptive Pain

If simple analgesics are included under the "adjuvant" umbrella, as they often are, then a simple analgesic is usually the first adjuvant to consider for nociceptive pain, and may sometimes be the only one required. Simple analgesics were discussed above, so I will not say any more about them now.

The antidepressant medications discussed in connection with neuropathic pain may also be useful as "opioid-sparing" agents when treating nociceptive pain, allowing a lower dose of opioid to be used than would otherwise be necessary. Other strategies usually reserved for the treatment of neuropathic pain may also be needed occasionally when standard treatments are either contraindicated for some reason or are incompletely effective.

Various major tranquillisers, such as haloperidol, and various minor tranquillisers, such as diazepam, can also be used as adjuvants when treating nociceptive pain. Their value is greater when anxiety is a significant factor in lowering the pain threshold, but their use is not limited to that situation.

Finally, some medications chosen for more specific effects might sometimes be thought of as "adjuvants", though their action is really "reducing a local tumour effect", as discussed earlier. Examples include the use of an antispasmodic to relax

the "smooth muscle" spasm which causes intestinal or other colic, or a glucocorticosteroid such as dexamethasone to reduce raised intracranial pressure (which causes a severe headache).

Optimal Use of Opioid Analgesics

The optimal use of opioid analgesics is more complex than that of simple analgesics or co-analgesics, so I have given it a heading of its own. When prescribing an opioid for the relief of cancer pain, a patient's doctor has to do the following things:

1. Choose the most suitable opioid
2. Give it regularly and at the right intervals
3. Find the right dosage by "dose titration"[48]
4. Administer it by the most suitable route
5. Control any side effects which occur
6. Reassess every aspect of the regimen frequently

It is often very helpful if patients and their carers have a clear and fairly comprehensive understanding of what is being done and why, so I will go into some detail about each point.

1. The Right Opioid

This is very often morphine. However, when treating any given patient, substituting other opioids such as oxycodone, hydromorphone, fentanyl or methadone sometimes results in equivalent analgesia with fewer side effects. A similar effect can sometimes be achieved by using the same opioid in a different dose form, especially where this also involves a different route of administration. In recent years, this process

[48] As discussed previously, dose titration means gradually increasing (or, if necessary, decreasing) the dose until the desired effect is obtained.

of trying different opioids, though not in itself new, has been referred to by a new name, "opioid rotation".[49]

When opioid rotation is thought to be necessary, the prescribing doctor has to remember that "equianalgesic tables" (which list approximately equivalent doses for different analgesics and different routes of administration) can only provide very approximate information. Conversion to a different dose form or a different opioid is simply not an exact science. It is therefore necessary for the doctor to reassess the patient frequently after such a change has been made.

2. The Right Regimen

Whatever opioid is used, and regardless of its dosage and the route by which it is administered, *regular timing of doses is of crucial importance*. Because acute pain, which was discussed earlier under the general classification of pain, is more common than chronic pain, most people (including many doctors) have become used to thinking in terms of occasional, short term pain relief, on an "as required" basis.

This simply *does not work* for most cases of cancer pain. Whether it is labelled subacute pain or chronic pain, the fact remains that most of the pain caused by advanced cancer is present most or all of the time. Therefore, the ONLY way to relieve it with analgesic medication is to make sure that the medication is present in the bloodstream, at sufficient concentration, *all the time*.

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[49] Mercadante S. Opioid rotation for cancer pain: rationale and clinical aspects. *Cancer*. 1999 Nov 1;86(9):1856-66.

For this reason, the prescribing of "p.r.n." analgesia[50], which is often appropriate for patients who might experience an episode of acute pain from time to time, is *never* appropriate as a means of controlling chronic or subacute cancer pain. Instead, analgesic medication(s) used to control subacute or chronic cancer pain must be given at *regular* intervals *around the clock*.[51, 52]

For many analgesic agents, including morphine, the right interval for immediate release dose forms, whether used for dose titration or for continuing baseline analgesia, is about four hours. At high dosages, smoother control may be achieved if the doses are given each three hours. But vague instructions such as "four times a day" are simply disastrous, because *the interval between doses is just as important as the number of doses*.

In practice, it is often necessary to adjust doses within a range prescribed by the doctor when the patient was last reviewed. These adjustments should be made by someone who is on the spot. In hospitals, that usually means a member of the nursing staff. For patients living at home, the patient or a relative could make the adjustments, following the doctor's advice carefully.

In my experience, whether it is done in a hospital or at home, this approach to dose titration requires a medication chart specifically designed for the purpose, such as the morphine chart reproduced in Figure 1. However, when the dosage is stable, and especially if a sustained release dose form of the opioid is then used, this type of chart is no longer necessary.

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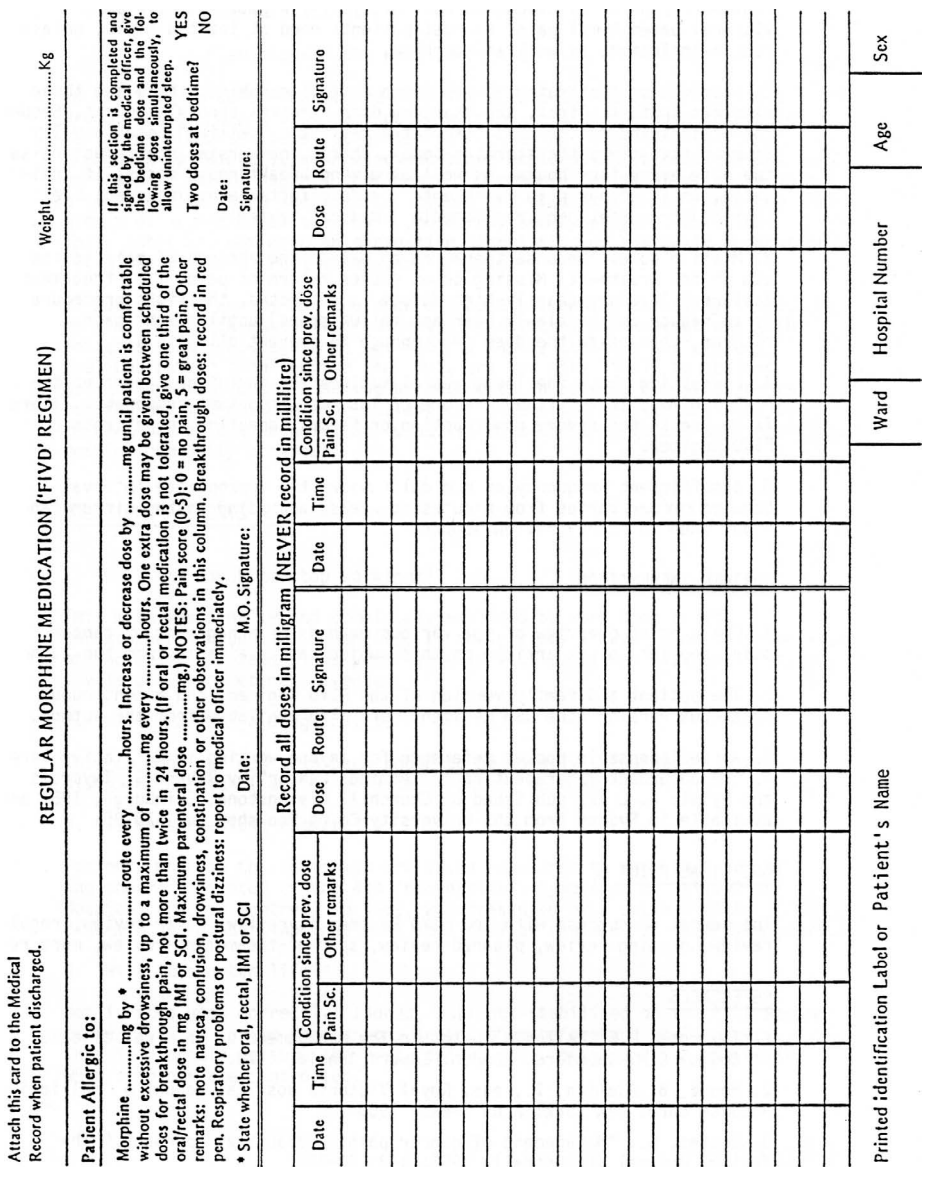
[50] P.r.n. is an abbreviation often used on prescriptions and medication charts. It stands for *pro re nata*, a Latin phrase which translates literally as "for an occasion that has arisen", but is used by doctors to mean "if needed". However, in the case of cancer pain, it usually stands for "pain relief never"!

[51] Tempest SM, Clarke IMC. The control of pain. I. By drugs; II. By non-drug methods. In: Wilkes E, ed. The dying patient. Lancaster: MTP Press Limited, 1982.

[52] Twycross RG. Relief of pain. In: Saunders C, ed. The management of terminal disease. London: Edward Arnold, 1978: 65-92.

Figure 1: A morphine titration chart



Attach this card to the Medical Record when patient discharged.

REGULAR MORPHINE MEDICATION ('FIVD' REGIMEN)

Weight .....Kg

Patient Allergic to:

Morphine .....mg by * .....route every .....hours. Increase or decrease dose by .....mg until patient is comfortable without excessive drowsiness, up to a maximum of .....mg every .....hours. One extra dose may be given between scheduled doses for breakthrough pain, not more than twice in 24 hours. (If oral or rectal medication is not tolerated, give one third of the oral/rectal dose in mg IMI or SCI. Maximum parenteral dose .....mg.) NOTES: Pain score (0-5): 0 = no pain, 5 = great pain. Other remarks: note nausea, confusion, drowsiness, constipation or other observations in this column. Breakthrough doses: record in red pen. Respiratory problems or postural dizziness: report to medical officer immediately.

* State whether oral, rectal, IMI or SCI

Date:

M.O. Signature:

If this section is completed and signed by the medical officer, give the bedtime dose and the following dose simultaneously, to allow uninterrupted sleep.

Two doses at bedtime? YES NO

Date:

Signature:

Record all doses in milligram (NEVER record in millilitre)

Date	Time	Condition since prev. dose		Dose	Route	Signature	Date	Time	Condition since prev. dose		Dose	Route	Signature
		Pain Sc.	Other remarks						Pain Sc.	Other remarks			

Printed identification Label or Patient's Name | Ward | Hospital Number | Age | Sex

Chart reproduced from Coates, G.T. 1987. The FIVD Regimen [fixed interval, variable dose morphine] 1987 Edition. Published by author.

3. The Right Dosage

The first and most important point to make about opioid dosage is that there is really no such thing as a "maximum dose" in the case of most strong opioids. While simple analgesics, weak opioids and adjuvants almost always have a maximum dose, which is not usually very much greater than the starting dose, the doses of most strong opioids can simply be increased according to need, with no absolute ceiling.

Some degree of physiological tolerance develops to any opioid with continuing use. Either an increase in physiological tolerance, or an increase in the severity of pain, may therefore necessitate an increase in opioid dosage. It is also true that *misuse* of any opioid, where the aim is to produce pleasure rather than control pain, can lead to psychological addiction. However, neither physiological tolerance nor psychological addiction pose significant problems when strong opioids are used properly in the management of cancer pain.[53, 54]

In my own palliative care practice, I prescribed doses of oral morphine as low as one milligram each six hours, and as high as 1,000 milligram (one gram) each four hours. The low end of this range was sometimes sufficient to relieve breathlessness in a frail patient with no prior exposure to opioid medication, and the high end was sometimes needed to control severe pain in a patient with considerable physiological tolerance.

Interestingly, some patients receiving very low doses reported drowsiness, while some patients receiving very high doses remained quite alert and fully ambulant. The lesson to be

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[53] Twycross RG. Clinical experience with diamorphine in advanced malignant disease. Int J Clin Pharmacol 1974; 9: 184.

[54] Twycross RG, Wald SJ. The long-term use of diamorphine in advanced cancer. In: Bonica JJ, Albe-Faescard D, eds. Advances in pain research and therapy. Vol. 1. New York: Raven Press, 1976: 653.

learned from such observations is that the right dose of a strong opioid is simply the dose that provides the desired effect.

That dose can only be determined by careful titration[55] of the dosage against the effects it causes, starting with a dose which can be expected, from past experience, to be well tolerated in all the particular circumstances involved. In the case of oral medication, it has been traditional to prescribe an immediate release dose form for this purpose, so that the effect of each dose can be assessed with a minimum of delay. However, dose titration can also be done (a little more slowly) with extended release medications, and this is sometimes more convenient.

Once the dosage required to provide effective baseline analgesia has been determined by titration using an immediate release dose form, that dosage can be expressed in terms of an amount per twenty-four hours. The doctor will then usually prescribe this amount in the form of extended (sustained) release tablets or capsules. These are more convenient for most patients, especially as they allow unbroken sleep without loss of analgesic effect. Of course, in patients who are unable to swallow, both dose titration and continuing treatment will be provided by one of the non-oral routes discussed below.

4. The Right Route

In most cases, the oral route of administration is the most convenient and comfortable, as long as the patient can swallow, retain and absorb the medication satisfactorily. When oral administration is not satisfactory, another route must, of course, be used. The general principle which guides the doctor is simply to find the most satisfactory route for each patient.

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[55] As mentioned earlier, dose titration means gradually increasing (or, if necessary, decreasing) the dose until the desired effect is obtained.

As previously discussed, some opioids can be given rectally, usually as suppositories, but occasionally in liquid or tablet form. This is often useful as a short term measure, but it is not usually a comfortable and convenient long term solution.

Subcutaneous injections given at regular intervals can also be useful as a short term measure, but blood levels fluctuate more than they do with oral doses, making it more difficult to achieve good pain control around the clock while minimising unwanted side effects. Doctors also try to avoid prescribing frequent injections because doing so can give the impression of a difficult situation, and may also cause some psychological and/or physical discomfort when they are administered.

The long term use of intravenous opioids is usually avoided whenever possible, partly because of the inevitable complications associated with venous cannulae, and partly because there is anecdotal evidence of excessive dose escalation when extra doses are frequently given intravenously.

In many cases, the most effective method of administration, when oral medication is not satisfactory, is for the doctor or nurse to place a fine needle in the subcutaneous fat under the surface of the skin, somewhere convenient, and fix it in position with a sterile adhesive dressing. One or more medications can then be administered through this needle as a slow continuous infusion. (The "syringe drivers" used for this purpose are discussed in Appendix 3, along with some less common types of administration used in special circumstances.)

As mentioned previously, the strong opioid fentanyl can provide continuous baseline analgesia via transdermal patches, often with very good results, but the currently available buprenorphine patches are rarely useful for cancer pain. Patches for the administration of various other analgesic or co-analgesic medications, as well as "active patches" from which

drugs could be delivered at more precisely controlled rates, will probably be very useful when they become available.

Very occasionally, an opioid is best administered by the "neuraxial" route, so that it acts directly on the spinal cord (or sometimes the brain). Other pain medications are also occasionally administered by this route. The neuraxial delivery of analgesia is briefly discussed in Appendix 3.

5. Control of Opioid Side-effects

The main side-effects of opioids are nausea, constipation and drowsiness. Respiratory depression is a potential risk, but is rarely a problem in practice if opioids are used correctly in the management of cancer pain.[56] (Depression of mood is, however, not uncommon after some weeks or months of regular opioid therapy, and should always be watched for.)

Other side effects which may require attention in some cases include mental confusion; emotional distress; unsteadiness; dizziness; fainting; headache; dry mouth; slow, fast or irregular pulse; palpitations; itch; rash; excessive sweating; and wheeze. (The latter is more often a reaction to preservatives than to the opioid itself, and is rare in the absence of a history of asthma.)

Although very rare, other acute allergic reactions are also possible. In addition, like all medications, opioids may interact with other medications or with pre-existing medical conditions, and such interactions may cause unwanted effects in some cases. (Problems specifically associated with kidney or liver failure are discussed in Appendix 1 and Appendix 2.)

Whenever it proves difficult to control opioid side effects, a change of opioid or dose form, as discussed under The Right Opioid, above, is then considered. The concurrent use of co-

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[56] Twycross RG. Relief of pain. In: Saunders C, ed. The management of terminal disease. London: Edward Arnold, 1978: 65-92.

analgesic agents, and of methods of pain management other than the use of analgesic medication, also helps in many cases, by enabling a lower dose of the opioid in question to be used.

Although it is not feasible in this booklet to go into detail about all of the possible opioid side effects which may occasionally occur, I will include a certain amount of information about the most common ones, under the subheadings which follow.

Nausea and Vomiting

Firstly, it must be remembered that nausea or vomiting (or indeed any other symptom) experienced by a cancer patient taking an opioid is not necessarily due either to the cancer *or* the opioid. Nausea and/or vomiting may be due to almost any abdominal, cerebral or inner ear condition, almost any infection, or a wide range of pharmaceutical, metabolic, endocrine, biochemical or psychological causes. However, as my topic is the treatment of nausea or vomiting as a side effect of an opioid, all I will say about alternative causes is that, as always, the doctor will need to make a diagnosis of the cause.

Nausea or vomiting within five minutes of a dose of morphine mixture is sometimes due to irritation of the stomach by additives such as alcohol, chloroform water or other preservatives. In this case, morphine mixture containing only morphine hydrochloride and purified water should be used. (This will usually keep for about a month at room temperature, and three or more months if refrigerated.)

However, opioids themselves can cause nausea and vomiting in a number of ways. Most often, they do so by stimulating a part of the brain called the "chemoreceptor trigger zone" (CTZ), which in turn stimulates the adjacent "true vomiting centre" (TVC). Sometimes, they stimulate the latter centre directly.

They can also affect the vestibule of the inner ear (thus imitating motion sickness) or slow down the emptying of the

stomach, or the movement of food through the small intestine. Finally, as discussed below, they have a powerful constipating effect on the large intestine. All of these effects can sometimes either cause, or worsen, nausea or vomiting.

Having determined that a patient's nausea and/or vomiting is partly or wholly due to opioid medication, an antiemetic which suppresses the CTZ is usually the first thing the doctor tries, and this is quite often all that is needed. A small regular dose of haloperidol[57] is often used for this purpose. Alternatives include metoclopramide and domperidone, which have a "prokinetic" effect[58] as well as suppressing the CTZ.

Sometimes, one of the above medications is started at the same time as the opioid, so that nausea or vomiting will be less likely to occur in the first place. This has the advantage of preventing an unpleasant symptom, but also the disadvantage of using a drug which may not be needed at all. In either case, the antiemetic can often be stopped quite soon, as opioid nausea quite often resolves spontaneously after some days.

When suppressing the CTZ is not effective (and especially when the opioid is not the only factor causing the symptom) a wide range of other medications may be prescribed to relieve the various causes of nausea and/or vomiting mentioned above.

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[57] Haloperidol is a major tranquilliser, and can cause a number of side effects, but it is usually well tolerated at low dosage. It also has a useful co-analgesic effect, often allowing the opioid dosage to be reduced.

[58] Prokinetics are drugs which promote the wavelike contractions called peristalsis, which move the contents of the gastro-intestinal tract onwards. Importantly, these drugs must be avoided in the presence of gastric outlet obstruction by tumour, when they can cause very severe vomiting. They must also be avoided if there is a bowel obstruction, when they can cause severe colic and also increase the risk of intestinal perforation.

Examples include antihistamines, such as promethazine or cyclizine, antiserotonin drugs (5-HT3 antagonists), such as ondansetron or tropisetron, anticholinergics, such as hyoscine or atropine, benzodiazepines, such as diazepam or oxazepam, and corticosteroids, such as dexamethasone or prednisone. The prokinetic effects of medications such as metoclopramide and domperidone, as mentioned above, may also be helpful in some cases, though counterproductive, or even dangerous, in others.

In refractory cases, the atypical neuroleptic drug olanzapine and the antidepressant medication mirtazapine have both been reported to help some patients. In addition, in some jurisdictions, the cannabinoid tetrahydrocannabinol, which is the main active ingredient of marijuana, may be used for refractory nausea or vomiting, as well as for neuropathic pain.

Constipation

There are various definitions of constipation, but its main features are infrequent and/or uncomfortable bowel motions, with a firm or hard stool consistency. There may also be a feeling of fullness in the lower bowel, or a sense of incomplete evacuation after moving the bowels. (In the case of faecal impaction, which is discussed below, some or all of these features are replaced by loose or liquid bowel motions, which have leaked past the impacted stool, often adding insult to injury by causing faecal incontinence.)

If preventive measures are neglected, constipation is almost invariable when an opioid is given regularly, regardless of the particular opioid used or the route of administration (although the latter factors can certainly influence its severity). However, opioid constipation can always be prevented by starting laxatives early and monitoring bowel function closely.

There are many, many causes of constipation apart from opioid analgesia, but only the latter cause is my current topic. It is also

very important to distinguish between constipation and bowel obstruction, but that is not my topic either. I will therefore restrict myself to a reminder that, if constipation is not responding to the treatment prescribed, the doctor must always be informed, so that other possible causes can be considered.

In the general population, the likelihood of constipation is greatly reduced by a diet high in fibre and not deficient in fat, a high fluid intake, and regular vigorous exercise. While these general principles should not be forgotten, some of them will not be practicable for some patients, and they are rarely sufficient to prevent or treat opioid constipation completely.

Incidentally, although the frequency and size of bowel motions is reduced somewhat in patients who are eating very little, low intake cannot be considered to be the cause of significant constipation, as food residues account for only a small proportion of the total stool volume. The rest is largely made up of dead epithelial cells shed by the mucosal lining layer of the intestine, dead and living bacteria, and water.

Principles of laxative therapy

Although a method of preventing opioid constipation by directly inhibiting its cause is currently being evaluated (see later), laxative therapy is still the mainstay for most patients at the time of writing. To prevent opioid constipation, laxative therapy should always be started on the same day as the opioid analgesia. It must then be titrated against bowel function, just as the opioid dosage itself is titrated against pain.

Laxatives can be broadly classified as stool softeners, intestinal lubricants, peristaltic stimulants, osmotic laxatives and bulking agents. (These terms are explained below.) However, many laxatives work in more than one of these ways. The best results are usually obtained by combining laxatives with different

modes of action. Importantly, some types of laxative are unsuitable for some patients, as will be discussed.

At the time of writing, the only common laxative which is usually classified as a **stool softener** (though sometimes as a lubricant) is dioctyl sodium sulfosuccinate (sometimes spelt sulphosuccinate). This laxative is often referred to by the simpler name docusate sodium, and was originally marketed in many countries under the brand name Coloxyl.

The commonest **intestinal lubricant** is liquid paraffin, which also softens stools and possibly promotes peristalsis to some extent. While liquid paraffin can be very helpful in some cases, it is very dangerous if it gets into the lungs, so it is never recommended for patients who have swallowing problems.

Peristaltic stimulants, as their name suggests, act by stimulating peristalsis.[59] If used to excess, they can therefore cause intestinal colic. They must not be used at all if there is a mechanical bowel obstruction or a weakened or inflamed area in the bowel, because powerful contractions might then cause a perforation. Common peristaltic stimulants include senna, bisacodyl and glycerol (also called glycerin or glycerine).

Osmotic laxatives, as their name implies, hold water in the bowel by osmosis[60]. This both softens the stool and increases its bulk, thus also tending to stimulate peristalsis. If given in a solution which has the same osmotic pressure as human blood, an osmotic laxative will not draw any more water from the bloodstream into the bowel, and it is then referred to as an "iso-osmotic" laxative. However, as the amount of water involved is

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[59] Peristalsis is the process of co-ordinated muscular contractions which effectively squeezes the contents of the intestine towards its lower end.

[60] Osmosis is the tendency for a solvent such as water to move through a semi-permeable membrane towards the side which has the more concentrated solution, thus gradually equalising the concentrations.

much less than the normal daily water requirement, this is usually a relatively minor advantage.

In the past, mineral salts such as sodium phosphate and magnesium sulphate have been used to create the osmotic effect, but their use can easily give rise to electrolyte[61] imbalances. At the time of writing, the most suitable osmotic laxative for prevention or treatment of opioid constipation (among other uses) appears to be macrogol (polyethylene glycol) 3350. A somewhat less effective alternative is lactulose[62]. One popular macrogol 3350 based laxative is Movicol, which also contains some sodium and potassium salts. When dissolved according to the manufacturer's directions, it is iso-osmotic, and it is also claimed to cause no net gain or loss of sodium or potassium.

Bulking agents may consist of soluble or insoluble plant fibre, or sometimes synthetic compounds with similar properties. Dietary fibre has quite complex effects on bowel function. Whether soluble or insoluble, the fibre naturally adds its own bulk to the stool. Insoluble fibre (also called roughage) also stimulates peristalsis. Soluble fibre also absorbs water, thus increasing its bulk further, forming a soft gelatinous substance.

Many dietary fibres are also excellent food for bacteria, which actually make up the largest single component of stool bulk in many cases. In addition, the soluble substances produced by the fermentation of undigested fibre in the colon attract water by osmosis, and the increase in bulk itself tends to stimulate

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[61] An electrolyte can be any solution that conducts electricity, but in the physiological context it refers to the various salts of sodium, potassium, calcium, magnesium, zinc etc which are present in solution in body fluids.

[62] Lactulose, a synthetic sugar, is sometimes referred to as soluble fibre. As discussed, soluble fibre has a variety of laxative effects, including osmosis. However, the laxative effect of lactulose is almost entirely osmotic.

peristalsis. Bulking agents are therefore very good examples of laxatives which act in more than one way.

Importantly, because bulking agents absorb water, leading to transfer of water from the bloodstream to the bowel if insufficient water is present in the bowel, they should only be used if the fluid intake is fairly good. Otherwise, they may not provide a laxative effect, but may instead worsen dehydration, and could cause a faecal impaction (which is discussed below).

Laxative therapy in practice

A simple practical approach to the prevention of opioid constipation, which is recommended by many doctors, is to start taking a small dose of dioctyl sodium sulfosuccinate, often combined with a peristaltic stimulant such as senna, when regular opioid analgesia is first introduced. The dosage is then increased as necessary, and one or more other laxative agents are added if needed. In order to know when it is necessary to increase the dose or add another laxative, *the frequency and consistency of the patient's bowel motions must be monitored*.

Whether the patient is at home or in hospital, the best way to monitor bowel motions is to maintain a "bowel chart" on which the date, approximate size and consistency of every bowel motion is recorded. This is hardly rocket science, but it is remarkable how often this basic essential of safe and effective opioid analgesia is carelessly completed, or even neglected altogether. The result of such neglect is almost always considerable unnecessary suffering for the patient.

A Possible Alternative

Although the laxatives mentioned above can always control opioid constipation if they are used properly, they do not directly prevent its cause. However, an opioid antagonist which prevented the effect of opioids on bowel motility, without significantly interfering with their analgesic effect, would

attack the problem at its source. At the time of writing, two opioid antagonists are being evaluated for this purpose.

The more promising of the two is a peripherally acting opioid antagonist called **methylnaltrexone**. This drug is poorly absorbed when taken by mouth, so most of it remains in the intestine. If it is given by injection, it does not cross the "blood-brain barrier". This is very important, because even a small amount of methylnaltrexone could interfere with the vitally important analgesic effects of opioids on the central nervous system if it were able to gain access to the brain and spinal cord.

Methylnaltrexone can be given orally or by injection for the treatment of opioid constipation when the response to laxatives is insufficient, and it appears to be very well tolerated. Its exact place in the management of opioid constipation is still being evaluated at the time of writing, but there seems little doubt that it can be very useful in some situations, and it is likely that its use will increase considerably over the next few years.

The less promising of the two is a peripherally *and* centrally acting opioid antagonist called naloxone. Naloxone reverses opioid effects in the brain as well as elsewhere, because, unlike methylnaltrexone, it *does* cross the "blood-brain barrier". An injection of naloxone can therefore be used to treat opioid overdoses, and it is very effective for that purpose.

However, naloxone is poorly absorbed when taken by mouth, and at low dosage the inhibitory effect of oral naloxone on opioid constipation can be much greater than its inhibitory effect on opioid analgesia. A tablet containing naloxone and an opioid in a fixed ratio is available in some countries, but for best results the two drugs should really be given separately, so that their dosage can be adjusted independently.

Unfortunately, even oral naloxone can precipitate severe opioid withdrawal in some circumstances, and that is not only painful

but potentially life threatening. At the time of writing, it therefore seems likely that methylnaltrexone will prove far more useful than naloxone as a direct inhibitor of opioid constipation.

Faecal Impaction

If constipation develops in spite of the precautions taken to prevent it (or because they were neglected) it may be possible to treat it with the same laxatives which can be used for its prevention. However, if there is associated rectal discomfort, or if there has been no bowel motion for three or more days, a gentle rectal examination should be performed by the doctor or nurse, in case a large stool is obstructing the rectum.

If the rectum is packed with stool, one or more evacuant suppositories[63] or "microenemas"[64] may help, especially if combined with an osmotic or lubricant laxative. If this approach is not effective, either a potable tap water enema or a disposable phosphate enema can be administered. (The latter must only be given by a very experienced person, as the phosphate solution can cause fatal rectal necrosis if the nozzle penetrates the lining of the anal canal or rectum.)

Giving a water enema suitable for the treatment of rectal impaction involves gradually instilling 250 to 500 millilitres of potable tap water into the rectum via a flexible enema tube. The enema should then be retained for some time if possible, to allow it to soften the stool. The procedure may need to be repeated one or more times before the problem is resolved.

In some cases, "manual removal" of stool from the rectum may be necessary. Using plenty of a lubricant, such as K-Y jelly or Vaseline, a well gloved index finger can be used to indent the stool and, with the finger slightly hooked, draw it out a little at

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[63] Examples are glycerol, Durolax and Coloxyl suppositories.

[64] An example is the 5ml Microlax enema.

a time. This will be more comfortable for the patient if extra analgesia is provided in advance of the procedure. Of course, it will be even more comfortable if it never becomes necessary.

Sometimes a faecal impaction in the rectum is suspected, but examination shows the rectum to be empty. This does not necessarily exclude impaction, as the retained stool may be higher up in the colon. In some cases, a high impaction can be felt through the abdominal wall, feeling rather like a large sausage, which can be indented by gentle sustained pressure from the examining fingers. A plain X-ray of the abdomen may also demonstrate the presence of a faecal impaction.

A high faecal impaction sometimes responds to laxative therapy, especially if osmotic and/or lubricant laxatives are used, but more often it needs to be treated by giving a very slow enema of two litres of potable tap water. (Such a large enema can *only* be given very slowly, otherwise it will be returned as quickly as it is given.) This procedure is usually carried out in a hospital, hospice or emergency room, but there is no reason that it could not be done by a nurse in the patient's home.

The best way to give a large enema is via an intravenous infusion set, or something similar, attached to a soft catheter which is inserted rectally so that its tip lies near the junction between the rectum and the sigmoid colon. The rate of infusion is then adjusted so that about two litres of water will be very gradually administered over two or more hours. In some cases, this may need to be repeated on one or more successive days.

Drowsiness and Confusion

Some degree of drowsiness should be expected during the first three or four days of regular opioid analgesia, and it is important for the patient and relatives to know this in advance.

Drowsiness may also recur at times of significant increase in dosage, but in most cases it is only a temporary inconvenience.

Occasionally, stimulants such as methylphenidate[65] appear to be helpful if opioid drowsiness is severe and persistent, though side effects (including confusion and other abnormal mental states) are quite common, and these could easily be mistaken for complications of the underlying cancer or side effects of other medications currently being used.

A newer stimulant, modafinil[66], has been suggested as an alternative to methylphenidate for the relief of opioid drowsiness, but its effectiveness for this purpose is still being evaluated. The use of stimulants to counteract fatigue or memory impairment, when these occur in association with opioid analgesia, has also been suggested, but at the time of writing their value in these roles has not been confirmed.

In a small proportion of cases, opioid drowsiness progresses to a confusional state. This is more common in elderly patients. Mild or moderate confusion may improve spontaneously over a day or so, just as drowsiness often does. Otherwise, strategies such as a change of opioid, optimisation of co-analgesic medication, review of other medications or conditions which may be contributing to the problem, or increased reliance on other methods of pain management, may become necessary.

Of course, confusion (which is sometimes called delirium or acute brain syndrome) is yet another condition which may occur as a feature or a complication of almost any illness, or as a side effect of many medications. Therefore, as always, it

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[65] Trade (brand) names for methylphenidate include Concerta, Metadate, Methylin and Ritalin.

[66] Trade (brand) names for modafinil include Alertec, Modafinilo, Modalert, Modavigil, Modiodal and Provigil.

cannot be assumed to be due to the opioid medication. Careful assessment by the doctor, usually followed by various investigations to aid in making a diagnosis, is an essential first step whenever any patient becomes confused.

6. Reassessment

All analgesic regimens need frequent reassessment by the doctors and nurses caring for the patient. Doses must be "titrated" upwards or downwards according to the patient's response. Residual pain, breakthrough pain, side effects of medications, and co-existing symptoms must be specifically enquired about. The suitability of any opioid in use, and the need for adjuvant medication(s) to improve the overall results, must be considered and reconsidered at frequent intervals.

WHAT ABOUT SYMPTOMS OTHER THAN PAIN?

There are, of course, many unpleasant symptoms other than pain, and most of them can sometimes be caused by cancer. These other symptoms, such as cough, breathlessness, hiccups, nausea, vomiting, constipation, diarrhoea, ulcerated lesions and generalised itching, can also be treated very effectively.

The general approach to the treatment of any symptom caused by a cancer is broadly similar to that which I have discussed in relation to cancer pain. If symptom control is not successful, referral to a Palliative Care (Palliative Medicine) specialist is always advisable. As this is a booklet about the treatment of cancer pain, the actual details of the treatment of other symptoms are outside its scope and will not be covered here.

APPENDIX 1: USE OF OPIOIDS IN RENAL FAILURE

Much of the information under this heading is not of direct relevance to patients and their carers, as the problems discussed will be addressed by the doctor. However, I have decided to provide the information in non-technical terms for the sake of completeness.

The metabolic products of most opioids are normally removed by the kidneys. They therefore tend to accumulate when renal function is reduced. Many of these metabolic products become toxic as their concentrations rise, causing muscle twitching and confusion, and in extreme cases convulsions, coma or even death.

It is not uncommon for patients who need opioid analgesia to also have some degree of renal failure, either as a result of their cancer, its treatment or some other illness. It is then necessary to watch carefully for the adverse effects caused by accumulation of toxic opioid metabolites. If they become significant, it may be necessary to change to an opioid which is better tolerated in renal failure.

Weak opioids

Weak opioids, if they are ever used at all, should not be administered to patients with a significant degree of renal failure. This is partly because their ratio of wanted to unwanted effects is relatively low to start with, and partly because that ratio deteriorates further as metabolic products which are normally removed by the kidneys accumulate in the bloodstream.

Pethidine

Pethidine (meperidine, demerol etc) is also completely unsuitable in renal failure (as it is in most other situations) because its metabolites are particularly toxic. Other strong opioids vary in their suitability for patients with renal failure, or for those undergoing renal dialysis, as discussed below.

Morphine, Oxycodone and Hydromorphone

Morphine is chiefly metabolised in the liver, and the resulting metabolites[67] are then excreted by the kidneys. They naturally accumulate in the bloodstream in renal failure, when they cause drowsiness, muscle twitching, hallucinations, and, at higher concentrations, convulsions, coma, and ultimately death.

Therefore, although morphine can be used cautiously in the presence of mild renal insufficiency, it often becomes unsuitable for continued use as renal function deteriorates. This is especially likely to be the case when the glomerular filtration rate[68] (GFR) is 10 ml/minute or less. Continued opioid analgesia will then usually need to be provided by a different opioid, as discussed later.

The hepatic metabolites of **oxycodone** and **hydromorphone** are probably somewhat better tolerated than those of morphine, but they also become toxic if their concentrations rise too much as a result of renal failure. When this occurs, these two opioids must also be replaced by an alternative opioid in order to maintain satisfactory opioid analgesia.

In the case of patients undergoing **renal dialysis**, morphine, oxycodone, hydromorphone and their metabolic products are usually reduced in concentration after each episode of dialysis. However, the degree of clearance varies with different dialysis systems, and is difficult or impossible to predict accurately.

In some cases, dialysis might cause failure of pain control, or even precipitate opioid withdrawal symptoms. In other cases, a reduction in opioid dosage might be necessary. Therefore,

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[67] The most important hepatic metabolites of morphine are morphine-3-glucuronide, morphine-6-glucuronide and normorphine.

[68] Glomerular filtration rate (GFR) is usually the best measure of renal function. A fairly accurate estimate of the GFR can be derived from a simple blood test, though its exact measurement is more difficult.

unless a dialysis patient's condition remains entirely satisfactory, one of the opioids discussed below may need to be substituted.

Fentanyl

Fentanyl is removed from the bloodstream mainly by being metabolised in the liver. Its metabolic products appear to be virtually inactive, as their accumulation in renal failure does not usually cause any clinically significant problems.

In most cases, fentanyl is therefore the ideal opioid for patients in whom renal failure is severe enough to result in side effects from the accumulation of toxic metabolic products of other opioids, such as morphine, oxycodone or hydromorphone.

Fentanyl is not removed by most dialysis filters, so failure of pain control, or an opioid withdrawal syndrome, does not usually occur as a result of renal dialysis. However, close monitoring of the patient is always essential, as dialysis systems vary, and information about drug clearance is limited.

Buprenorphine

Buprenorphine is well tolerated in renal failure and during renal dialysis, as its hepatic metabolites are virtually inactive and are also excreted into the bile. However, in view of the low concentrations achieved by the currently available patches, it would usually need to be administered by continuous infusion. Its ability to precipitate opioid withdrawal must, of course, also be taken into account by the prescribing doctor in patients who were recently, or are currently, taking another opioid.

Methadone

Methadone also has the advantages of having well tolerated hepatic metabolites, and of hepatic excretion of its metabolites into the bile. However, as discussed under Strong Opioids, methadone should only be prescribed by clinicians with considerable experience in its use because its duration of action is variable and unpredictable, even in healthy people.

APPENDIX 2:
USE OF OPIOIDS IN HEPATIC FAILURE

Much of the information under this heading is not of direct relevance to patients and their carers, as the problems discussed will be addressed by the doctor. However, I have decided to provide the information in non-technical terms for the sake of completeness.

It is not uncommon for patients who need opioid analgesia to also have some degree of liver failure, either as a result of cancer in the liver or because of some other illness affecting it. As most opioids are removed from the body chiefly by being metabolised in the liver, an increased amount of the parent drug, and a decreased concentration of its metabolites (which sometimes provide part of the analgesic effect), is the usual result when hepatic function is significantly reduced. (Fentanyl is an exception to this rule, as discussed below.)

Weak Opioids and Pethidine

As in the case of renal failure, neither weak opioids nor pethidine should be used in patients with hepatic failure, as their combination of a weak analgesic effect and plentiful, sometimes serious, side effects leaves very little room for manoeuvre.[69] Other opioids vary in their suitability for patients with hepatic failure, as discussed below.

Morphine, Oxycodone and Hydromorphone

Morphine, oxycodone and hydromorphone can usually be used cautiously in hepatic failure by means of downward adjustment of the dose and/or upward adjustment of the interval between

[69] This may be particularly important in the case of codeine, and possibly also dihydrocodeine, as some of their hepatic metabolites (especially morphine, in the case of codeine) may contribute significantly to their analgesic effect. However, the metabolism of codeine and dihydrocodeine remains very incompletely understood at the time of writing.

doses. However, dosage adjustment can be expected to become more difficult as liver function deteriorates further.

Fentanyl

Although fentanyl is metabolised in the liver, its metabolism appears to require very little residual liver function. Markedly reduced hepatic blood flow can interfere with the metabolism of fentanyl, but hepatic failure itself rarely results in fentanyl accumulation. For this reason, fentanyl, which is usually the opioid of choice in the presence of renal failure, is also, in most cases, the opioid of choice when hepatic failure is severe enough to preclude the safe and effective use of morphine, oxycodone or hydromorphone. In many cases, it is not even necessary to use reduced doses of fentanyl in the presence of hepatic failure, but, of course, this should not discourage frequent review of the patient's response.

Buprenorphine

Buprenorphine is metabolised in the liver, and its metabolites are excreted into the bile. (They are also, to a lesser extent, excreted by the kidneys.) There are some reports of acute liver toxicity associated with buprenorphine in the presence of liver disease, but information about its use in this situation is otherwise quite sparse. At the time of writing, I would suggest that buprenorphine, if it is ever used at all, should not be used in the presence of significant liver disease unless all other strong opioids are contra-indicated.

Methadone

Methadone, which is very difficult to use safely at the best of times, should not be used in the presence of significant hepatic failure unless absolutely no alternative exists. This is simply because the risk of excessive blood levels of methadone developing will be greater, and more unpredictable, than ever.

APPENDIX 3:
SPECIAL MEDICATION DELIVERY SYSTEMS

Much of the information under this heading is not of direct relevance to patients and their carers, as the problems discussed will be addressed by the doctor. However, I have decided to provide the information in non-technical terms for the sake of completeness.

Syringe Drivers

Syringe drivers are very useful for delivering medication by continuous infusion, often via a "butterfly" needle which is sited subcutaneously somewhere convenient, such as the anterior surface of the chest or abdomen. If a single analgesic medication is being infused continuously, extra doses of a predetermined size can be added to that infusion by the patient or nursing staff if breakthrough pain occurs, or if incident pain is expected, simply by pressing a button on the device.

A syringe of suitable size is filled with the medication which is to be administered, placed in the device, and connected to a butterfly needle by a flexible tube. After expelling air from the system, the butterfly needle is inserted subcutaneously at the chosen site and covered with sterile adhesive film, which keeps it in place and also protects the entry point from contamination.

The plunger of the syringe is then moved along very slowly by the drive mechanism of the device, over a number of hours, at a rate set by the doctor, nurse or pharmacist. This rate is, of course, calculated so that the medication in the syringe will be administered exactly as fast as is necessary in order to provide that particular patient's baseline analgesia.

Although this sounds simple, the end result depends on quite a number of steps, each of which must be carried out correctly in order to achieve the desired effect. Therefore, anyone who is responsible for the use of this type of medication delivery

system must obviously be familiar with the particular device in use, as well as the general principles involved, and must have received suitable training and supervised experience.

The devices themselves can be quite temperamental. There have been some welcome advances in their engineering in recent decades, but they are still far from foolproof, so close monitoring of their function is essential. If, for example, the plunger jams and therefore fails to advance at the set rate, baseline analgesia will fail, and the patient's pain will return. Alternatively, if the rate is set incorrectly high, the patient will receive a progressively worsening overdose of the medication.

When necessary, multiple medications can be combined in a single subcutaneous infusion, though more frequent re-siting of the subcutaneous needle is then usually necessary. Morphine sulphate, hyoscine, haloperidol, metoclopramide, promethazine and midazolam are usually compatible together in a syringe.

Importantly, when there is more than one medication in the syringe, extra opioid doses for breakthrough or incident pain cannot be given from that syringe, as an extra amount of each other medication in the syringe would be received by the patient, as well as the desired extra dose of opioid.

Some medications, such as diazepam and prochlorperazine, cause irritation when infused subcutaneously. Morphine tartrate (which has the sometimes considerable advantage of greater solubility than morphine sulphate) is inclined to form a precipitate when mixed with various other useful medications. The assistance of a pharmacist is therefore invaluable when more than one medication is to be loaded into the syringe.

Patient-Controlled Analgesia Pumps

Although Patient-Controlled Analgesia (PCA) is primarily used for post-operative pain management, usually by the intravenous or epidural route, the same type of pump can be used as an

alternative to a syringe driver when baseline analgesia is being provided by continuous subcutaneous infusion.

In addition, PCA itself is sometimes used as a temporary measure when a patient is admitted to hospital for the purpose of achieving rapid control of pain and then determining a suitable maintenance regimen. In this case, the intravenous route is often used initially, converting to a more suitable route for long term use when the correct dosage has been established.

As mentioned in the text of the booklet itself, the longer term use of intravenous opioids should be avoided whenever possible, partly because of the inevitable complications associated with venous cannulae, and partly because there is anecdotal evidence of excessive dose escalation when extra doses are frequently given intravenously.

Neuraxial Delivery Systems

Neuraxial administration usually means injection or infusion near the spinal cord, either inside (intrathecal) or just outside (epidural) its membranous coatings. However, the term can also be applied to an infusion into the cerebral ventricles (inside the brain).

Neuraxial delivery systems are sometimes used for the intrathecal administration of opioids, local anaesthetics and various other medications. The opioid most often chosen for intrathecal delivery is morphine. The local anaesthetic usually chosen for intrathecal delivery is bupivacaine. Two other agents which have an established role in intrathecal analgesia are the alpha-2 adrenergic receptor antagonist clonidine, and the $GABA_B$ receptor agonist baclofen. Various other medications, such as ketamine, midazolam and ziconotide, are also being evaluated for possible use as intrathecal analgesics.

The last agent mentioned, ziconotide, which is marketed under the trade name Prialt, is rather interesting. It is a synthetic analogue of a substance found naturally in a marine snail called

Conus magus. Its therapeutic action is the result of selective blockade of a neuronal transmission channel called the N-type voltage-sensitive calcium channel, so it is the first example of a new class of analgesics called N-type calcium channel blockers (NCCBs). Ziconotide could provide another option for patients whose pain has not been satisfactorily controlled by the methods currently in regular use, but it is too early to predict how often, or how effectively, it might come to be used.

However, it should be remembered that intrathecal infusions and other neuraxial delivery methods are only very occasionally appropriate in the management of cancer pain. They have the potential to provide very powerful analgesia with minimal drug side effects, but they also have risks of their own, some of which can be serious, so they should not be used if less invasive alternatives are available and effective.

When neuraxial analgesia really is necessary, a catheter can be tunnelled under the skin to a convenient site and connected to a suitable infusion pump. Totally implanted systems (with a subcutaneous portal for the addition of medications to a reservoir) are probably the only satisfactory way of providing long term neuraxial analgesia.

DECLARATION OF INTEREST

None

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