The pharmacological management of cancer pain

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The optimal management of cancer pain requires a familiarity with a range of therapeutic options including antineoplastic therapies, analgesic pharmacotherapy, anaesthetic, neurosurgical, psychological and rehabilitation techniques. Successful pain management is characterised by the implementation of the techniques with the most favourable therapeutic index for the prevailing circumstances along with provision for repeated evaluations so that a favourable balance between pain relief and adverse effects is maintained. Currently available techniques can provide adequate relief to the vast majority of patients.

For the large majority of patients, pain management involves the administration of specific analgesic approaches. Anaesthetic and neurosurgical techniques should be considered for the patient who has not obtained satisfactory pain relief. In all cases, these analgesic treatments must be skilfully integrated with the management of other symptoms.

There is an universal agreement that analgesic pharmacotherapy remains the mainstay of cancer pain management. However, controversy has arisen regarding the validity and application of the 'Three step analgesic ladder' of the World Health Organization (WHO) which advocated three basic steps of therapy according to the severity of the presenting pain problem (Fig. 1) [1]. Despite the fact that data from a series of validation studies demonstrated that this approach, combined with appropriate dosing guidelines, provides adequate relief to 70–90% of patients [2–7], a review of these studies concluded that there was a lack of evidence for the long-term efficacy of this approach [8]. Additionally, the recent production of low dose formulations of pure opioid agonists traditionally used for severe pain and the introduction of other agents such as tramadol, has blurred the distinction between steps 2 and 3.

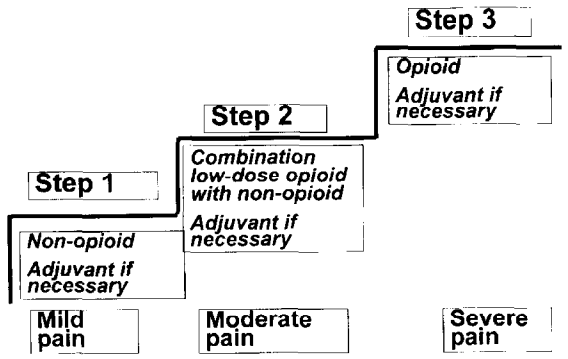

Fig. 1. The classic three-step ladder.

Systemic analgesic pharmacotherapy

Non-opioid analgesics

The non-opioid analgesics (aspirin, acetaminophen and the non-steroidal anti-inflammatory drugs — NSAIDs) are useful alone for mild to moderate pain (Step 1 of the analgesic ladder) and provide additive analgesia when combined with opioid drugs in the treatment of more severe pain [9]. They are useful in a broad range of pain syndromes of diverse mechanisms, but there is no data to support therapeutic superiority to alternative options in a particular setting other than inflammation [9]. Unlike opioid analgesics, the non-opioid analgesics have a 'ceiling' effect for analgesia and produce neither tolerance nor physical dependence.

The non-opioid analgesics constitute a heterogeneous group of compounds that differ in chemical structure, but share many pharmacological actions (Table 1). The NSAID drugs are competitive blockers of cyclooxygenase. It has recently been found that there are at least two isoforms of cyclooxygenase with distinct roles in analgesia and toxicity [10]. Cyclooxygenase-1 is responsible for the synthesis of the protective prostaglandins, which preserve the integrity of the stomach lining and maintain normal renal function in a compromised kidney and cyclooxygenase-2 is an inducible enzyme involved in inflammation, pain and fever. Recently, a range of relatively selective cyclooxygenase-2 inhibitors

Table 1
Commonly used non-opioid analgesics

Chemical class	Generic name
Cox-2 specific	meloxicam nemesulide rofecoxib celecoxib
Non-acidic	acetaminophen
Acidic salicylates	aspirin diflunisal choline magnesium trisalicylate salsalate
Proprionic acids	ibuprofen naproxen fenoprofen ketoprofen flurbiprofen suprofen
Acetic acids	indomethacin tolmentin sulindac diclofenac ketorolac
Oxicams	piroxicam
Fenemates	mefenamic acid meclofenamic acid

including, meloxicam, nemesulide, rofecoxib and celecoxib have been introduced and approved as analgesics. These agents are equianalgesic with the non-selective inhibitors and they are associated with less mucosal and renal morbidity [11–13].

Safely administering non-opioid analgesics requires familiarity with their potential adverse effects [14–17]. Aspirin and the other NSAID's have a broad spectrum of potential toxicity; bleeding diathesis due to inhibition of platelet aggregation, gastroduodenopathy (including peptic ulcer disease), and renal impairment are the most common [16]. Particular caution is required in the administration of these agents to patients at increased risk of adverse effects, including the elderly and those with blood clotting disorders, predilection to peptic ulceration, impaired renal function, and concurrent corticosteroid therapy. Data from randomised trials supports the use of either omeprazole [18], pantoprazole, misoprostol [19] or high dose famotidine (80 mg/day) [20] as the preferred agent for the prevention of NSAID-related peptic ulceration. In some countries, a combined formulation of diclofenac and misoprostol is available as a convenient and cost-effective option [21,22].

Acetaminophen rarely produces gastrointestinal toxicity and there are no adverse effects on platelet function; hepatic toxicity is possible, however, and patients with chronic alcoholism and liver disease can develop severe hepatotoxicity at the usual therapeutic doses [23].

The optimal administration of non-opioid analgesics requires an understanding of their clinical pharmacology. There is no certain knowledge of the minimal effective analgesic dose, ceiling dose or toxic dose for any individual patient with cancer pain. Based on clinical experience, an upper limit for dose titration is usually set at 1.5–2 times the standard recommended dose of the drug in question. Since failure with one NSAID can be followed by success with another, sequential trials of several NSAIDs may be useful to identify a drug with a favourable balance between analgesia and side-effects.

Opioid analgesics: basic pharmacology

A trial of systemic opioid therapy should be administered to all cancer patients with pain of moderate or greater severity regardless of the pain mechanism. Although somatic and visceral pain appear to be relatively more responsive to opioid analgesics than neuropathic pain, a neuropathic mechanism does not confer 'opioid resistance', and appropriate dose escalation will identify many patients with neuropathic pain who can achieve adequate relief [24,25].

Optimal use of opioid analgesics requires a sound understanding of the general principles of opioid pharmacology, the pharmacological characteristics of each of the commonly used drugs, and principles of administration, including: drug selection, routes of administration, dosing and dose titration and the prevention and management of adverse effects.

Important principles in opioid drug therapy

Classification

Opioid compounds can be divided into agonist, agonist–antagonist and antagonist classes based on their interactions with the various receptor subtypes (Table 2). In the management of cancer pain, the pure agonists are most commonly used. The mixed agonist–antagonist opioids (pentazocine, nalbuphine and butorphanol) and the partial agonist opioids (buprenorphine and probably dezocine) play a minor role in the management of cancer pain, because of the existence of a ceiling effect for analgesia, the potential for precipitation of withdrawal in patients physically dependent on opioid agonists, and in

Table 2
Classification of opioid analgesics

Agonists	Partial agonists	Agonist/antagonists
morphine	buprenorphine	pentazocine
codeine	dezocine	butorphanol
oxycodone		nalbuphine
heroin		
oxymorphone		
meperidine		
levorphanol		
hydromorphone		
methadone		
fentanyl		
sufentanil		
alfentanil		
propoxyphene		

the case of mixed agonist–antagonists, the problem of dose-dependent psychotomimetic side-effects that exceed those of pure agonist drugs [26].

Dose response relationship

The pure agonist drugs do not have a ceiling dose; as the dose is raised analgesic effects increase in a semi log-linear function, until either analgesia is achieved or the patient develops dose-limiting adverse effects such as nausea, vomiting, confusion, sedation, myoclonus or respiratory depression.

The equianalgesic dose ratio

Relative analgesic potency of opioid is commonly expressed in terms of the equianalgesic dose ratio. This is the ratio of the dose of two analgesics required to produce the same analgesic effect. By convention, the relative potency of each of the commonly used opioids is based upon a comparison to 10 mg of parenteral morphine [27]. Equianalgesic dose information (Table 3) provides guidelines for dose selection when the drug or route of administration is changed.

Several principles are critical in interpreting the data presented in equianalgesic dose tables. The commonly quoted values do not reflect the substantial variability that is observed in both single dose and multidose cross over studies. Numerous variables may influence the appropriate dose for the individual patient, including pain severity, prior opioid exposure (and the degree of cross-tolerance this confers), age, route of administration, level of consciousness, and genetically determined metabolic or receptor heterogeneity. For most agents, the equianalgesic dose relationship to morphine is linear, for methadone however, the relationship appears to be curvilinear with the equianalgesic dose ratio falling as the dose of prior morphine increases: at low doses of morphine (30–300 mg oral morphine) the equianalgesic ratio for oral methadone to oral morphine is 1 : 4–1 : 6 and at high doses (>300 mg oral morphine) it is 1 : 10–1 : 12 [28].

Selecting an appropriate opioid

The factors that influence opioid selection in chronic pain states include pain intensity, pharmacokinetic and formulatory considerations, previous adverse effects and the presence of co-existing disease.

Traditionally, patients with moderate pain have been conventionally treated with a combination product containing acetaminophen or aspirin plus codeine, dihydrocodeine, hydrocodone, oxycodone and propoxyphene. The doses of these combination products can be increased until the maximum dose of the non-opioid co-analgesic is attained (e.g. 4000 mg acetaminophen). Recent years have witnessed the proliferation of new opioid formulations that may improve the convenience of drug administration for patients with moderate pain. These include controlled release formulations of codeine, dihydrocodeine, oxycodone, morphine and tramadol in dosages appropriate for moderate pain.

Patients who present with strong pain are usually treated with morphine, hydromorphone, oxycodone, oxymorphone, fentanyl or methadone. Of these, the short half-life opioid agonists (morphine, hydromorphone, fentanyl, oxycodone or oxymorphone) are generally favoured because they are easier to titrate than the long half-life drugs which require a longer period to approach steady-state plasma concentrations. Morphine is generally preferred since it has a short half-life and is easy to titrate in its immediate release form, and it is also available as a controlled release preparation that allows an 8–12 hour dosing interval.

If the patient is currently using an opioid that is well tolerated, it is usually continued unless difficulties in dose titration occur or the required dose cannot be administered conveniently. A switch to an alternative opioid is considered if the patient develops dose-limiting toxicity which precludes adequate relief of pain without excessive side-effects or if a specific formulation, not available with the current drug, is either needed or may substantially improve the convenience of the opioid administration.

Some patients will require sequential trials of several different opioids before a drug which is

Table 3
Opioid agonist drugs

Drug	Dose (mg) equianalgesic to 10 mg IM morphine		Half life (hr)	Duration of action (hr)	Comments
	IM	PO			
Codeine	130	200	2–3	2–4	Usually combined with a nonopioid.
Oxycodone	7–10	15–20	2–3	2–4	
Propoxyphene	100	50	2–3	2–4	Usually combined with nonopioid. Norpropoxyphene toxicity may cause seizures.
Morphine	10	30	2–3	3–4	Multiple routes of administration and formulations available. M6G accumulation in renal failure.
Hydromorphone	2–3	7.5	2–3	2–4	Multiple routes of administration and formulations available.
Methadone	1–3	2–6	15–190	4–8	Plasma accumulation may lead to delayed toxicity. Dosing should be initiated on a PRN basis.
Pethidine	75	300	2–3	2–4	Low oral bioavailability. Norpethidine toxicity limits utility. Contraindicated in patients with renal failure and those receiving MAO inhibitors.
Oxymorphone	1	10 (PR)	2–3	3–4	No oral formulation available. Less histamine release.
Fentanyl transdermal system		Empirically transdermal fentanyl 100 μg/h = 2–4 mg/h intravenous morphine		48–72	Patches available to deliver 25, 50, 75 and 100 μg/hr

M6G: Morfine-6-glucuronide (metabolite of morphine); PRN: pro re na'ta: as needed; MAO: monoamine oxidase; PR: per rectum; IM: intramuscular; PO: orally.

effective and well tolerated is identified [29,30]. This strategy has been variably labelled opioid-rotation, or opioid-switching. The existence of incomplete cross-tolerance to various opioid effects (analgesia and side-effects) may explain the utility of these sequential trials. It is strongly recommended that clinicians be familiar with at least 3 opioid drugs used in the management of severe pain and have the ability to calculate appropriate starting doses using equianalgesic dosing data when switching between drugs.

Selecting the appropriate route of systemic opioid administration

Opioids should be administered by the least invasive and safest route capable of providing adequate analgesia. Usually, the oral route is preferred. Alternative routes are necessary for patients who have impaired swallowing or gastrointestinal dysfunction, those who require a very rapid onset of analgesia, and those who are unable to manage either the logistics or side-effects associated with the oral route.

The development of transdermal fentanyl has provided a convenient a non-invasive alternative to oral administration. Transdermal patches capable of delivering 25, 50, 75 and 100 μg/hr are available. The dosing interval for each patch is usually 72 hours [31], but some patients require a 48 hour schedule [32]. Recent data from controlled studies indicate that the transdermal administration of fentanyl is associated with a lesser incidence of constipation than oral morphine and is often preferred [33–35].

Other non-invasive routes are less commonly used. Rectal suppositories containing oxycodone, hydromorphone, oxymorphone and morphine have been formulated, and controlled-release morphine tablets can also be administered per rectum [36,37]. The potency of opioids administered rectally is approximately equivalent to that achieved by the oral route [38].

The sublingual route has limited value due to the lack of formulations, poor absorption of most drugs,

and the inability to deliver high doses or prevent swallowing of the dose. An oral transmucosal formulation of fentanyl, which incorporates the drug into a candy base, has recently been approved for use in the management of breakthrough pain [39].

Invasive routes

A parenteral route may be considered when the oral route is precluded or there is need for rapid onset of analgesia, or a more convenient regimen. Repeated parenteral bolus injections, which may be administered by the intravenous (IV), intramuscular (IM) or subcutaneous (SC) routes, provides the most rapid onset and shortest duration of action. Parenteral boluses are most commonly used to treat very severe pain, in which case doses can be repeated at an interval as brief as that determined by the time to peak effect, until adequate relief is achieved [40]. Repeated bolus doses without frequent skin punctures can be accomplished through the use of an indwelling IV or SC infusion device such as a 25–27 gauge infusion device (a 'butterfly') which can be left under the skin for up to a week [41].

Continuous parenteral infusions are useful for many patients who cannot be maintained on oral opioids. Long-term infusions may be administered IV or SC In practice, the major indication for continuous infusion occurs among patients who are unable to swallow or absorb opioids. Continuous infusion is also used in some patients whose high opioid requirement renders oral treatment impractical. Ambulatory patients can easily use continuous SC infusion. A range of pumps is available varying in complexity, cost, and ability to provide patient-controlled 'rescue doses' as an adjunct to a continuous basal infusion [41]. Opioids suitable for continuous SC infusion must be soluble, well absorbed and nonirritant. Extensive experience has been reported with heroin, hydromorphone, oxymorphone, morphine and fentanyl. Methadone appears to be relatively irritating and is not recommended. To maintain the comfort of an infusion site, the SC infusion rate should not exceed 3–5 cc/hr. Patients who require high doses may benefit from the use of concentrated solutions. A high concentration hydromorphone (10 mg/cc) is available commercially and the organic salt of morphine, morphine tartrate, is available in some countries as an 80 mg/cc solution.

Changing routes of administration

The switch between oral and parenteral routes should be guided by knowledge of relative potency (Table 3) to avoid subsequent over-dosing or under-dosing. In calculating the equianalgesic dose, the potencies of the IV, SC, and IM routes are considered equivalent. In recognition of the imprecision in the accepted equianalgesic doses and the risk of toxicity from potential overdose, a modest reduction in the equianalgesic dose is prudent.

Scheduling of opioid administration

The schedule of opioid administration should be individualised to optimise the balance between patient comfort and convenience. 'Around the clock' dosing and 'as needed' dosing both have a place in clinical practice.

'Around the clock' dosing with 'rescue doses'

'Around the clock' dosing provides the chronic pain patient with continuous relief by preventing the pain from recurring. Controlled release preparations of opioids can lessen the inconvenience associated with the use of 'around the clock' administration of drugs with a short duration of action. Patients should also be provided a so-called 'rescue dose,' which is a supplemental dose offered on an 'as needed' basis to treat pain that breaks through the regular schedule [42].

The frequency with which the rescue dose can be offered depends on the route of administration and the time to peak effect for the particular drug. Oral rescue doses are usually offered up to every 1–2 hours and parenteral doses can be offered as frequently as every 15–30 minutes. Clinical experience suggests that the initial size of the rescue dose should be equivalent to approximately 50–100% of the dose administered every four hours for oral or parenteral bolus medications, or 50–100% of the hourly infusion rate for patients receiving continuous infusions. Alternatively, this may be calculated as 5–15% of the 24-hour baseline dose. The magnitude of the rescue dose should be individualised and some patients with low baseline pain, but severe exacerbations may require rescue doses that are substantially higher [43]. The drug used for the rescue dose is usually identical to that administered on a scheduled basis.

This approach provides a method for safe and rational stepwise dose escalation, which is applicable to all routes of opioid administration. Patients who are requiring more than 4–6 rescue doses per day should generally undergo escalation of the baseline dose. The quantity of the rescue medication consumed can be used to guide the dose increment.

Alternatively, each dose increment can be set at 33–50% of the pre-existing dose. In all cases, escalation of the baseline dose should be accompanied by a proportionate increase in the rescue dose, so that the size of the supplemental dose remains a constant percentage of the fixed dose.

'As-needed' (PRN) dosing

Opioid administration on an 'as needed' basis, without an 'around the clock' dosing regimen, may provide additional safety during the initiation of opioid therapy, particularly when rapid dose escalation is needed or therapy with a long half-life opioid such as methadone or levorphanol is begun. 'As needed' dosing may also be appropriate for patients who have rapidly decreasing analgesic requirement or intermittent pains separated by pain-free intervals.

Patient controlled analgesia (PCA)

Patient controlled analgesia (PCA) generally refers to a technique of parenteral drug administration in which the patient controls an infusion device that delivers a bolus of analgesic drug 'on demand' according to parameters set by the physician. Long-term PCA in cancer patients is most commonly accomplished via the subcutaneous route using an ambulatory infusion device [44]. In most cases, PCA is added to a basal infusion rate and acts essentially as a rescue dose [44]. Rare patients have benefited from PCA alone to manage episodic pains characterised by an onset so rapid that an oral dose could not provide sufficiently prompt relief.

Dose selection and titration

Selecting a starting dose

A patient who is relatively nontolerant, having had only some exposure to an opioid typically used on the second rung of the 'analgesic ladder' for moderate pain, should generally begin one of the opioids typically used for severe pain at a dose equivalent to 5–10 morphine IM every four hours [38]. If morphine is used, a PO : IM relative potency ratio of 2 : 1–3 : 1 is conventional [38].

Dose adjustment

Inadequate relief should be addressed through gradual escalation of dose until adequate analgesia is reported or excessive side-effects supervene. Because opioid response increases linearly with the log of the dose, a dose increment of less than 30–50% is not likely to significantly improve analgesia. The absolute dose is immaterial as long as administration is not compromised by excessive side-effects, inconvenience, discomfort or cost.

Rate of dose titration

The rate of dose titration depends on the severity of the pain, the medical condition of the patient and the goals of care. Patients who present with very severe pain are sometimes best managed by repeated parenteral administration of a dose every 15–30 minutes until pain is partially relieved. Patients with moderate pain may not require a loading dose of the opioid, but rather the initiation of a regular dose with provision for rescue doses and gradual dose titration. In this situation, dose increments of 30–50% can be administered at intervals greater than that required to reach steady state following each change. The dose of morphine (tablets or elixir), hydromorphone or oxycodone can be increased on a twice daily basis, and the dose of controlled release oral morphine or transdermal fentanyl can be increased every 24–48 hours.

The problem of tolerance

When the need for dose escalation arises, disease progression [45,46], increasing psychological distress or changes in the pharmacokinetics of an analgesic drug are much more common than true analgesic tolerance. True analgesic tolerance, which could compromise the utility of treatment, can only be said to occur if a patient manifests the need for increasing opioid doses in the absence of other factors (e.g. progressive disease) that would be capable of explaining the increase in pain.

Management of opioid adverse effects

Successful opioid therapy requires that the benefits of analgesia and other desired effects clearly outweigh treatment-related adverse effects. Thus, a detailed understanding of adverse opioid effects and the strategies used to prevent and manage them are essential skills for all involved in cancer pain management.

Adverse drug interactions

In patients with advanced cancer, side-effects due to drug combinations are common. The potential for

additive side-effects and serious toxicity from drug combinations must be recognised. The sedative effect of an opioid may add to that produced by numerous other centrally-acting drugs, such as anxiolytics, neuroleptics and antidepressants [47]. Likewise, drugs with anticholinergic effects probably worsen the constipatory effects of opioids. As noted previously, a severe adverse reaction, including excitation, hyperpyrexia, convulsions and death has been reported after the administration of meperidine to patients treated with a monoamine oxidase inhibitor [48].

Gastrointestinal side-effects

The gastrointestinal adverse effects of opioids are common. In general, they are characterised by having a weak dose response relationship.

Constipation

Constipation is the most common adverse effect of chronic opioid therapy [49]. The likelihood of opioid-induced constipation is so great that laxative medications should be prescribed prophylactically to most patients.

Nausea and vomiting

Opioids may produce nausea and vomiting through both central and peripheral mechanisms. These drugs stimulate the medullary chemoreceptor trigger zone, increase vestibular sensitivity and have effects on the gastrointestinal tract (including increased gastric antral tone, diminished motility and delayed gastric emptying). With the initiation of opioid therapy, patients should be informed that nausea can occur and that it is usually transitory and controllable. Routine prophylactic administration of an antiemetic is not necessary, except in patients with a history of severe opioid-induced nausea and vomiting, but patients should have access to an antiemetic at the start of therapy if the need for one arises. Anecdotally, the use of prochlorperazine and metoclopromide has usually been sufficient.

Central nervous system side-effects

The CNS side-effects of opioids are generally dose related. The specific pattern of CNS adverse effects is influenced by individual patient factors, duration of opioid exposure and dose.

Sedation

Initiation of opioid therapy or significant dose escalation commonly induces sedation that persists until tolerance to this effect develops, usually in days to weeks. It is useful to forewarn patients of this potential, and thereby reduce anxiety and encourage avoidance of activities, such as driving, that may be dangerous if sedation occurs [50]. Some patients have a persistent problem with sedation, particularly if other confounding factors exist. These factors include the use of other sedating drugs or coexistent diseases such as dementia, metabolic encephalopathy or brain metastases. Both dextroamphetamine and methylphenidate have been widely used in the treatment of opioid-induced sedation [51]. Treatment with methylphenidate or dextroamphetamine is typically begun at 2.5 mg to 5 mg in the morning, which is repeated at midday if necessary to maintain effects until evening. Doses are then increased gradually if needed. Few patients require more than 40 mg per day in divided doses. This approach is relatively contraindicated among patients with cardiac arrhythmias, agitated delirium, paranoid personality and past amphetamine abuse.

Confusion and delirium

Mild cognitive impairment is common following the initiation of opioid therapy or dose. Similar to sedation, however, pure opioid-induced encephalopathy appears to be transient in most patients, persisting from days to a week or two. Although persistent confusion attributable to opioid alone occurs, the aetiology of persistent delirium is usually related to the combined effect of the opioid and other contributing factors, including electrolyte disorders, neoplastic involvement of central nervous system, sepsis, vital organ failure and hypoxemia [51]. A stepwise approach to management (Table 4) often culminates in a trial of a neuroleptic drug. Haloperidol in low doses (0.5–1.0 mg PO or 0.25–0.5 mg IV or IM) is most commonly recommended because of its efficacy and low incidence of cardiovascular and anticholinergic effects.

Respiratory depression

When sedation is used as a clinical indicator of CNS toxicity and appropriate steps are taken, respiratory depression is rare. When, however, it does occur it is always accompanied by other signs of CNS depression, including sedation and mental clouding. Respiratory compromise accompanied by tachypnoea and anxiety is never a primary opioid event.

Table 4
Examples of stepwise dose escalation of morphine sulphate administered as oral immediate release preparation, oral controlled release and continuous infusion

Oral immediate release morphine sulphate		
Step[a]	mg q4hr ATC	Rescue dose mg
1	15	7.5 PRN q1hr
2	30	15.0 PRN q1hr
3	45	22.5 PRN q1hr
4	60	30.0 PRN q1hr
5	90	45.0 PRN q1hr
Oral controlled release morphine sulphate (immediate release rescue dose)		
Step[a]	mg ATC	Immediate release rescue dose mg
1	30 q12	7.5 PRN q1hr
2	30 q8	15.0 PRN q1hr
3	60 q12	15.0 PRN q1hr
4	100 q12	30.0 PRN q1hr
5	100 q8	45.0 PRN q1hr
Continuous morphine infusion		
Step[a]	mg/hr	Rescue dose mg
1	3	2.0 PRN q30min
2	5	2.5 PRN q30min
3	7	3.5 PRN q30min
4	10	5.0 PRN q30min
5	15	7.5 PRN q30min

[a] Suggested indications for progression from one step to the next include:(1) requirement of >2 rescue doses in any 4 hour interval or (2) requirement of >6 rescue doses in 24 hours.
ATC: anatomical chemical therapeutics classification.
PRN: pro re na'ta: as needed.
q: every.
hr: hour.

With repeated opioid administration, tolerance appears to develop rapidly to the respiratory depressant effects of the opioid drugs, consequently clinically important respiratory depression is a very rare event in the cancer patient whose opioid dose has been titrated against pain.

The ability to tolerate high doses of opioids is also related to the stimulus related effect of pain on respiration in a manner that is balanced against the depressant opioid effect. Opioid-induced respiratory depression can occur, however, if pain is suddenly eliminated (such as may occur following neurolytic procedures) and the opioid dose is not reduced [52].

When respiratory depression occurs in patients on chronic opioid therapy, administration of the specific opioid antagonist, naloxone, usually improves ventilation. This is true even if the primary cause of the respiratory event was not the opioid itself, but rather, an intercurrent cardiac or pulmonary process. A response to naloxone, therefore, should not be taken as proof that the event was due to the opioid alone and an evaluation for these other processes should ensue.

Naloxone can precipitate a severe abstinence syndrome and should be administered only if strongly indicated. If the patient is bradypneic but readily aroused, and the peak plasma level of the last opioid dose has already been reached, the opioid should be withheld and the patient monitored until improved. If severe hypoventilation occurs (regardless of the associated factors that may be contributing to respiratory compromise), or the patient is bradypneic and not aroused, naloxone should be administered. To reduce the risk of severe withdrawal following a period of opioid administration, dilute naloxone (1 : 10) should be used in doses titrated to respiratory rate and level of consciousness. In the comatose patient, it may be prudent to place an endotracheal tube to prevent aspiration following administration of naloxone.

Multifocal myoclonus

All opioid analgesics can produce myoclonus. Mild and infrequent myoclonus is common. In occasional patients, however, myoclonus can be distressing or contribute to breakthrough pain that occurs with the involuntary movement. If the dose cannot be reduced due to persistent pain, consideration should be given to either switching to an alternative opioid [29] or to symptomatic treatment with a benzodiazepine (particularly clonazepam or midazolam), dantrolene or an anticonvulsant [51].

Other effects

Urinary retention

Opioid analgesics increase smooth muscle tone and can occasionally cause bladder spasm or urinary retention (due to an increase in sphincter tone). This is an infrequent problem that is usually observed in elderly male patients. Tolerance can develop rapidly, but catheterisation may be necessary to manage transient problems.

Adjuvant analgesics

The term 'adjuvant analgesic' describes a drug that has a primary indication other than pain but is analgesic in some conditions. In the cancer population, these drugs may be combined with primary analgesics in any of the three steps of the 'analgesic ladder' to improve the outcome for patients who cannot otherwise attain an acceptable balance between relief and side-effects. The potential utility of an

adjuvant analgesic is usually suggested by the characteristics of the pain or by the existence of another symptom that may be amenable to a non-analgesic effect of the drug.

There is great inter-individual variability in the response to all adjuvant analgesics. Although patient characteristics, such as advanced age or co-existent major organ failure, may increase the likelihood of some (usually adverse) responses, neither favourable effects nor specific side-effects can be reliably predicted in the individual patient. Furthermore, there is remarkable intra-individual variability in the response to different drugs, including those within the same class. These observations suggest the potential utility of sequential trials of adjuvant analgesics. The process of sequential drug trials, like the use of low initial doses and dose titration, should be explained to the patient at the start of therapy to enhance compliance and reduce the distress that may occur if treatments fail.

In the management of cancer pain, adjuvant analgesics can be broadly classified based on conventional use. Four groups are distinguished:

(1) Multipurpose adjuvant analgesics.
(2) Adjuvant analgesics used for neuropathic pain.
(3) Adjuvant analgesics used for bone pain.
(4) Adjuvant analgesics used for visceral pain.

Multipurpose adjuvant medications

Corticosteroids

Corticosteroids are among the most widely used adjuvant analgesics [53]. They have been demonstrated to have analgesic effects, to significantly improve quality of life; and to have beneficial effects on appetite, nausea, mood and malaise in the cancer population. Painful conditions that commonly respond to corticosteroids include: raised intracranial pressure headache, acute spinal cord compression, superior vena cava syndrome, metastatic bone pain, neuropathic pain due to infiltration or compression by tumour, symptomatic lymphoedema, and hepatic capsular distention [53]. The mechanism of analgesia produced by these drugs may involve anti-oedema effects, anti-inflammatory effects, and a direct influence on the electrical activity in damaged nerves [54]. The most commonly used drug is dexamethasone, a choice that gains theoretical support from the relatively low mineralocorticoid effect of this agent. Dexamethasone also has been conventionally used for raised intracranial pressure and spinal cord compression.

Patients with advanced cancer who experience pain and other symptoms may respond favourably to a relatively small dose of corticosteroid (e.g. dexamethasone 1–2 mg twice daily). In some settings, however, a high dose regimen may be appropriate. For example, patients with spinal cord compression, an acute episode of very severe bone pain or neuropathic pain that cannot be promptly reduced with opioids may respond dramatically to a short course of relatively high doses (e.g. dexamethasone 100 mg, followed initially by 96 mg per day in divided doses) [55]. This dose can be tapered over weeks, concurrent with initiation of other analgesic approaches, such as radiotherapy.

Although the effects produced by corticosteroids in patients with advanced cancer are often very gratifying, side-effects are potentially serious and increase with prolonged usage [56]. The most common adverse effects include oropharyngeal candidiasis, oedema or cushingoid habitus; dyspepsia, weight gain, neuropsychological changes and ecchymoses, hyperglycaemia and myopathy. The risk of peptic ulcer is approximately doubled in patients chronically treated with corticosteroids, and co-administration of corticosteroid with aspirin or a NSAID further increases the risk of gastroduodenopathy and is not recommended [57]. Active peptic ulcer disease, systemic infection and unstable diabetes are relative contraindications to the use of corticosteroids as adjuvant analgesics.

Topical local anaesthetics

Topical local anaesthetics can be used in the management of painful cutaneous and mucosal lesions, and as a premedication prior to skin puncture. An eutectic mixture of 2.5% lidocaine and 2.5% prilocaine (EMLA) is effective in reducing pain associated with venipuncture, lumbar puncture, and arterial puncture. It has also been used for painful ulcerating skin lesions. Viscous lidocaine is frequently used in the management of oropharyngeal ulceration. Although the risk of aspiration appears to be very small, caution with eating is required after oropharyngeal anaesthesia.

Adjuvants used for neuropathic pain

Neuropathic pains are generally less responsive to opioid therapy than nociceptive pain and in many cases the outcome of pharmacotherapy may be improved by the addition of an adjuvant analgesic.

Antidepressant drugs are commonly used to manage continuous neuropathic pains and the evidence for analgesic efficacy is greatest for the tertiary amine tricyclic drugs, such as amitriptyline, doxepin and imipramine [58]. The secondary amine tricyclic

antidepressants (such as desipramine, clomipramine and nortryptyline) have fewer side-effects and are preferred when concern about sedation, anticholinergic effects or cardiovascular toxicity is high [58]. The selective serotonin uptake inhibitor antidepressants are much less effective in the management of neuropathic pain and are generally not recommended for this purpose.

The starting dose of a tricyclic antidepressant should be low, e.g. amitriptyline 10 mg in the elderly and 25 mg in younger patients. Doses can be increased every few days and the initial dosing increments are usually the same size as the starting dose. When doses have reached the usual effective range (e.g. amitriptyline 75–150 mg), it is prudent to observe effects for a week before continuing upward dose titration. It is reasonable to continue upward dose titration beyond the usual analgesic doses in patients who fail to achieve benefit and have no limiting side-effects. Plasma drug concentration, if available, may provide useful information and should be followed during the course of therapy.

Selected anticonvulsant drugs appear to be analgesic for the lancinating dysesthesias that characterise diverse types of neuropathic pain [59]. Although most practitioners prefer to begin with carbamazepine because of the very good response rate observed in trigeminal neuralgia [59], this drug must be used cautiously in cancer patients with thrombocytopenia, those at risk for marrow failure (e.g. following chemotherapy), and those whose blood counts must be monitored to determine disease status. If carbamazepine is used, a complete blood count should be obtained prior to the start of therapy, after two and four weeks, and then every 3–4 months thereafter. A leucocyte count below 4000 is usually considered to be a contraindication to treatment, and a decline to less than 3000, or an absolute neutrophil count of less than 1500 during therapy should prompt discontinuation of the drug. Other anticonvulsant drugs may also be useful and published reports and clinical experience support trials with gabapentin, phenytoin, clonazepam and valproate [59]. When anticonvulsant drugs are used as adjuvant analgesics it is recommended that dosing follow the dosing guidelines customarily employed in the treatment of seizures.

Occasionally, systemically administered local anaesthetic drugs may be useful in the management of neuropathic pains characterised by either continuous or lancinating dysesthesias. It is reasonable to undertake a trial with an oral local anaesthetic in patients with continuous dysesthesias who fail to respond adequately, or who cannot tolerate, the tricyclic antidepressants, and in patients with lancinating pains refractory to trials of anticonvulsant drugs and baclofen. Mexiletine is the safest of the oral local anaesthetics [60,61] and is preferred. Analgesic response to a trial of intravenous lidocaine (5 mg/kg, over 45 minutes) may predict for likelihood of response to oral mexiletine [62]. Dosing with mexiletine should usually be started at 100–150 mg per day. If intolerable side-effects do not occur, the dose can be increased by a like amount every few days, until the usual maximum dose of 300 mg three times per day is reached.

Less compelling data supports the use of clonidine, baclofen, calcitonin and subcutaneously administered ketamine [63].

Adjuvant analgesics used for bone pain

The management of bone pain frequently requires the integration of opioid therapy with multiple ancillary approaches. Although a meta-analysis of NSAID therapy in cancer pain that reviewed data from 1615 patients in 21 trials found no specific efficacy in bone pain and analgesic effects equivalent only to 'weak' opioids [9], some patients appear to benefit greatly from the addition of such a drug. Corticosteroids are often advocated in difficult cases [53].

Bisphosphonates are analogues of inorganic pyrophosphate that inhibit osteoclast activity and reduce bone resorption in a variety of illnesses. Controlled and uncontrolled trials of i.v. pamidronate in patients with advanced cancer have demonstrated significant reduction of bone pain [64]. The analgesic effect of pamidronate appears to be dose and schedule dependent, a dose response is evident at doses between 15 and 30 mg/week and it has been noted that 30 mg every 2 weeks is less effective than 60 mg every 4 weeks [64]. Similar effects have been observed with orally administered clodronate [65].

Radiolabelled agents that are absorbed into areas of high bone turnover have been evaluated as potential therapies for metastatic bone disease. It has the advantages of addressing all sites of involvement and relatively selective absorption, thus limiting radiation exposure to normal tissues. Excellent clinical responses with acceptable haematological toxicity have been observed with a range of radiopharmaceuticals. The best studied and most commonly used radionuclide is strontium-89. Large, prospectively randomised clinical trials have demonstrated its efficacy as a first-line therapy [66] or as an adjuvant to external-beam radiotherapy [67]. This approach is contraindicated with patients who have a platelet count less than 60,000 or a WCC <2.4 and is not advised for patients with very poor performance

status [68]. Using another approach, bone-seeking radiopharmaceuticals that link a radioisotope with a bisphosphonate compound have been synthesised. Positive experience has been reported with samarium-153-ethylenediaminetetramethylene phosphonic acid, and rhenium-186-hydroxyethylidene diphosphonate.

Adjuvant analgesics for visceral pain

There are limited data that support the potential efficacy of a range of adjuvant agents for the management of bladder spasm, tenesmoid pain and colicky intestinal pain. Oxybutynin chloride, a tertiary amine with anticholinergic and papaverine-like, direct muscular antispasmodic effects, is often helpful for bladder spasm pain [69] as is flavoxate [70]. Based on limited clinical experience and in vitro evidence that prostaglandins play a role in bladder smooth-muscle contraction, a trial of NSAIDs may be justified for patients with painful bladder spasms [71]. Limited data supports a trial of intravesical capsaicin [72,73].

There is no well established pharmacotherapy for painful rectal spasms. A recent double blinded study demonstrated that nebulised salbutamol can reduce the duration and severity of attacks [74]. There is anecdotal support for trials of diltiazem [75,76], clonidine [77], chlorpromazine [78] and benzodiazepines [79].

Colicky pain due to inoperable bowel obstruction has been treated empirically with intravenous scopolamine (hyoscine) butylbromide [80–82] and sublingual scopolamine (hyoscine) hydrobromide [83]. Limited data supports the use of octreotide for this indication [84].

Sedation as pain therapy

Through the vigilant application of analgesic, cancer pain is often relieved adequately without compromising the sentience or function of the patient beyond that caused by the natural disease process itself. Occasionally, however, this cannot be achieved and pain is perceived to be 'refractory' [85]. In deciding that a pain is refractory, the clinician must perceive that the further application of standard interventions are either (1) incapable of providing adequate relief, (2) associated with excessive and intolerable acute or chronic morbidity, or (3) unlikely to provide relief within a tolerable time-frame. In this situation, sedation may be the only therapeutic option capable of providing adequate relief. This approach is described as "sedation in the management of refractory symptoms at the end of life" [85].

The justification of sedation in this setting is that it is goal appropriate and proportionate. At the end of life, when the overwhelming goal of care is the preservation of patient comfort, the provision of adequate relief of symptoms must be pursued even in the setting of a narrow therapeutic index for the necessary palliative treatments [86–88]. In this context, sedation is a medically indicated and proportionate therapeutic response to refractory symptoms, which cannot be otherwise relieved. Appeal to patients' rights also underwrites the moral legitimacy of sedation in the management of otherwise intolerable pain at the end of life. Patients have a right, recently affirmed by the Supreme Court, to palliative care in response to unrelieved suffering [86].

Once a clinical consensus exists that pain is refractory, it is appropriate to present this option to the patient or their surrogate. When presented to a patient with refractory symptoms, the offer of sedation can demonstrate the clinician's commitment to the relief of suffering. This can enhance trust in the doctor-patient relationship and influence the patient's appraisal of their capacity to cope. Indeed, patients commonly decline sedation, acknowledging that pain will be incompletely relieved but secure in the knowledge that if the situation becomes intolerable to them, this option remains available. Other patients reaffirm comfort as the predominating consideration and request the initiation of sedation.

The published literature describing the use of sedation in the management of refractory pain at the end of life is anecdotal and refers to the use of opioids, neuroleptics, benzodiazepines, barbiturates and propofol [85]. In the absence of relative efficacy data, guidelines for drug selection are empirical. Irrespective of the agent or agents selected, administration initially requires dose titration to achieve adequate relief, followed subsequently by provision of ongoing therapy to ensure maintenance of effect.

Conclusion

The goal of analgesic therapy in the cancer population is to optimise analgesia with the minimum of side-effects and inconvenience. Currently available techniques can provide adequate relief to a vast majority of patients. Most will require ongoing pain treatment, and analgesic requirements often change as the disease progresses. Patients with refractory pain, or unremitting suffering related to other losses or distressing symptoms, should have access to spe-

cialists in pain management or palliative medicine who can provide an approach capable of addressing these complex problems.

References

1 World Health Organization. Cancer Pain Relief. World Health Organization, Geneva, 1986.
2 Takeda F. Japanese field-testing of WHO guidelines. PRN Forum 1985, 4: 4–5.
3 Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. Cancer 1987, 59: 850–856.
4 Walker VA, Hoskin PJ, Hanks GW, White ID. Evaluation of WHO analgesic guidelines for cancer pain in a hospital-based palliative care unit. J Pain Symptom Manage 1988, 3: 145–149.
5 Schug SA, Zech D, Dorr U. Cancer pain management according to WHO analgesic guidelines. J Pain Symptom Manage 1990, 5(1): 27–32.
6 Goisis A, Gorini M, Ratti R, Luliri P. Application of a WHO protocol on medical therapy for oncologic pain in an internal medicine hospital. Tumori 1989, 75: 470–472.
7 Grond S, Zech D, Schug SA, Lynch J, Lehmann KA. Validation of World Health Organization guidelines for cancer pain relief during the last days and hours of life. J Pain Symptom Manage 1991, 6: 411–422.
8 Jadad AR, Browman GP. The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation [see comments]. JAMA 1995, 274: 1870–1873.
9 Eisenberg E, Berkey CS, Carr DB, Mosteller F, Chalmers TC. Efficacy and safety of nonsteroidal antiinflammatory drugs for cancer pain: a meta-analysis. J Clin Oncol 1994, 12: 2756–2765.
10 Vane JR, Bakhle YS, Botting RM. Cyclooxygenases 1 and 2. Annu Rev Pharmacol Toxicol 1998, 38: 97–120.
11 Lefkowith JB. Cyclooxygenase-2 specificity and its clinical implications. Am J Med 1999, 106(5B): 43S–50S.
12 Ehrich EW, Dallob A, De Lepeleire I, Van Hecken A, Riendeau D, Yuan W et al. Characterization of rofecoxib as a cyclooxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. Clin Pharmacol Ther 1999, 65: 336–347.
13 Hawkey CJ. COX-2 inhibitors. Lancet 1999, 353(9149): 307–314.
14 Bennett WM, Henrich WL, Stoff JS. The renal effects of nonsteroidal anti-inflammatory drugs: summary and recommendations. Am J Kidney Dis 1996, 28(1 Suppl 1): S56–62.
15 Laine L. Nonsteroidal anti-inflammatory drug gastropathy. Gastrointest Endosc Clin N Am 1996, 6: 489–504.
16 Lehmann T, Day RO, Brooks PM. Toxicity of antirheumatic drugs. Med J Aust 1997, 166: 378–383.
17 Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs–differences and similarities. N Engl J Med 1991, 324: 1716–1725.
18 Hawkey CJ. Progress in prophylaxis against nonsteroidal antiinflammatory drug-associated ulcers and erosions. Omeprazole NSAID Steering Committee. Am J Med 1998, 104: 67S–74S; discussion 79–80S.
19 Valentini M, Cannizzaro R, Poletti M, Bortolussi R, Fracasso A, Testa V et al. Nonsteroidal antiinflammatory drugs for cancer pain: comparison between misoprostol and ranitidine in prevention of upper gastrointestinal damage. J Clin Oncol 1995, 13: 2637–2642.
20 Taha AS, Hudson N, Hawkey CJ, Swannell AJ, Trye PN, Cottrell J et al. Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs [see comments]. N Engl J Med 1996, 334: 1435–1439.
21 Plosker GL, Lamb HM. Diclofenac/misoprostol. Pharmacoeconomic implications of therapy. Pharmacoeconomics 1999, 16: 85–98.
22 McKenna F. Diclofenac/misoprostol: the European clinical experience. J Rheumatol Suppl 1998, 51: 21–30.
23 Makin AJ, Williams R. Acetaminophen-induced hepatotoxicity: predisposing factors and treatments. Adv Intern Med 1997, 42: 453–483.
24 Portenoy RK, Foley KM, Inturrisi CE. The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions [see comments]. Pain 1990, 43(3): 273–286.
25 Hanks GW, Forbes K. Opioid responsiveness. Acta Anaesthesiol Scand 1997, 41(1 Pt 2): 154–158.
26 Hanks GW. The clinical usefulness of agonist-antagonistic opioid analgesics in chronic pain. Drug Alcohol Depend 1987, 20: 339–346.
27 Houde RW, Wallenstein SL, Beaver WT. Evaluation of analgesics in patients with cancer pain. In: Lasagna L (Ed.), International Encycloped of Pharmacology and Therapeutics. Pergamon Press, New York, 1966, pp. 59–67.
28 Ripamonti C, Groff L, Brunelli C, Polastri D, Stravakis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain. What is the equianalgesic dose ratio. J Clon Oncol 1998, 16: in press.
29 Cherny NJ, Chang V, Frager G, Ingham JM, Tiseo PJ, Popp B et al. Opioid pharmacotherapy in the management of cancer pain: a survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. Cancer 1995, 76: 1283–1293.
30 de Stoutz ND, Bruera E, Suarez-Almazor M. Opioid rotation for toxicity reduction in terminal cancer patients. J Pain Symptom Manage 1995, 10: 378–384.
31 Varvel JR, Shafer SL, Hwang SS, Coen PA, Stanski DR. Absorption characteristics of transdermally administered fentanyl. Anesthesiology 1989, 70: 928–934.
32 Jeal W, Benfield P. Transdermal fentanyl. A review of its pharmacological properties and therapeutic efficacy in pain control. Drugs 1997, 53: 109–138.
33 Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. J Pain Symptom Manage 1997, 13: 254–261.
34 Donner B, Zenz M, Tryba M, Strumpf M. Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain. Pain 1996, 64: 527–534.
35 Payne R, Mathias SD, Pasta DJ, Wanke LA, Williams R, Mahmoud R. Quality of life and cancer pain: satisfaction and side effects with transdermal fentanyl versus oral morphine. J Clin Oncol 1998, 16: 1588–1593.
36 Kaiko RF, Fitzmartin RD, Thomas GB, Goldenheim PD. The bioavailability of morphine in controlled-release 30-mg tablets per rectum compared with immediate-release 30-mg rectal suppositories and controlled-release 30-mg oral tablets. Pharmacotherapy 1992, 12: 107–113.
37 Maloney CM, Kesner RK, Klein G, Bockenstette J. The rectal administration of MS Contin: clinical implications of use in end stage cancer. Am J Hosp Care 1989, 6: 34–35.

38 European Association for Palliative Care. Morphine in cancer pain: modes of administration. Expert Working Group of the European Association for Palliative Care. BMJ 1996, 312: 823–826.

39 Simmonds MA. Oral transmucosal fentanyl citrate produces pain relief faster than medication typically used for breakthrough pain in cancer patients (Meeting abstract). Proc Annu Meet Am Soc Clin Oncol 1997, 16: A180.

40 Hagen NA, Elwood T, Ernst S. Cancer pain emergencies: a protocol for management. J Pain Symptom Manage 1997, 14: 45–50.

41 Coyle N, Cherny NI, Portenoy RK. Subcutaneous opioid infusions at home. Oncology (Huntingt) 1994, 8(4): 21–7; discussion 31–2, 37.

42 Cleary JF. Pharmacokinetic and pharmacodynamic issues in the treatment of breakthrough pain. Semin Oncol 1997, 24(5 Suppl 16): S16–13-9.

43 Lyss AP. Long-term use of oral transmucosal fentanyl citrate (OTFC) for breakthrough pain in cancer patients (Meeting abstract). In: Proc Annu Meet Am Soc Clin Oncol 1997, p A144.

44 Ripamonti C, Bruera E. Current status of patient-controlled analgesia in cancer patients. Oncology (Huntingt) 1997, 11: 373–80, 383–4; discussion 384–386.

45 Paice JA. The phenomenon of analgesic tolerance in cancer pain management. Oncol Nurs Forum 1988, 15: 455–460.

46 Schug SA, Zech D, Grond S, Jung H, Meuser T, Stobbe B. A long-term survey of morphine in cancer pain patients. J Pain Symptom Manage 1992, 7: 259–266.

47 Pies R. Psychotropic medications and the oncology patient. Cancer Pract 1996, 4: 164–166.

48 Browne B, Linter S. Monoamine oxidase inhibitors and narcotic analgesics. A critical review of the implications for treatment. Br J Psychiatry 1987, 151: 210–212.

49 Fallon M, O'Neill B. ABC of palliative care. Constipation and diarrhoea. BMJ 1997, 315(7118): 1293–1296.

50 Vainio A, Ollila J, Matikainen E, Rosenberg P, Kalso E. Driving ability in cancer patients receiving long-term morphine analgesia. Lancet 1995, 346(8976): 667–670.

51 Portenoy RK. Management of common opioid side effects during long-term therapy of cancer pain. Ann Acad Med Singapore 1994, 23(2): 160–170.

52 Wells CJ, Lipton S, Lahuerta J. Respiratory depression after percutaneous cervical anterolateral cordotomy in patients on slow-release oral morphine [letter]. Lancet 1984, 1(8379): 739.

53 Watanabe S, Bruera E. Corticosteroids as adjuvant analgesics. J Pain Symptom Manage 1994, 9(7): 442–445.

54 Devor M, Govrin-Lippmann R, Raber P. Corticosteroids suppress ectopic neural discharge originating in experimental neuromas. Pain 1985, 22(2): 127–137.

55 Sorensen S, Helweg-Larsen S, Mouridsen H, Hansen HH. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomised trial. Eur J Cancer 1994, 30A(1): 22–27.

56 Twycross R. The risks and benefits of corticosteroids in advanced cancer. Drug Saf 1994, 11(3): 163–178.

57 Ellershaw JE, Kelly MJ. Corticosteroids and peptic ulceration. Palliat Med 1994, 8(4): 313–319.

58 McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. Pain 1996, 68(2–3): 217–227.

59 McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. BMJ 1995, 311(7012): 1047–1052.

60 Ruskin JN. The cardiac arrhythmia suppression trial (CAST). N Engl J Med 1989, 321(6): 386–388.

61 (CAST) Cardiac Arrhythmia Suppression Trial Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989, 321(6): 406–412.

62 Galer BS, Harle J, Rowbotham MC. Response to intravenous lidocaine infusion predicts subsequent response to oral mexiletine: a prospective study. J Pain Symptom Manage 1996, 12(3): 161–167.

63 Lipman AG. Analgesic drugs for neuropathic and sympathetically maintained pain. Clin Geriatr Med 1996, 12(3): 501–515.

64 Strang P. Analgesic effect of bisphosphonates on bone pain in breast cancer patients: a review article. Acta Oncol 1996, 5(50): 50–54.

65 Ernst DS, Brasher P, Hagen N, Paterson AH, MacDonald RN, Bruera E. A randomized, controlled trial of intravenous clodronate in patients with metastatic bone disease and pain. J Pain Symptom Manage 1997, 13(6): 319–326.

66 Robinson RG, Preston DF, Schiefelbein M, Baxter KG. Strontium 89 therapy for the palliation of pain due to osseous metastases. JAMA 1995, 274(5): 420–424.

67 Porter AT, McEwan AJ, Powe JE, Reid R, McGowan DG, Lukka H et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. Int J Radiat Oncol Biol Phys 1993, 25(5): 805–813.

68 Schmeler K, Bastin K. Strontium-89 for symptomatic metastatic prostate cancer to bone: recommendations for hospice patients. Hosp J 1996, 11(2): 1–10.

69 Paulson DF. Oxybutynin chloride in control of post-transurethral vesical pain and spasm. Urology 1978, 11(3): 237–238.

70 Baert L. Controlled double-blind trail of flavoxate in painful conditions of the lower urinary tract. Curr Med Res Opin 1974, 2(10): 631–635.

71 Abrams P, Fenely R. The action of prostaglandins on smooth muscle of the human urinary tract in vitro. British Journal of Urology 1976, (47): 909–915.

72 Lazzeri M, Beneforti P, Benaim G, Maggi CA, Lecci A, Turini D. Intravesical capsaicin for treatment of severe bladder pain: a randomized placebo controlled study. J Urol 1996, 156(3): 947–952.

73 Barbanti G, Maggi CA, Beneforti P, Baroldi P, Turini D. Relief of pain following intravesical capsaicin in patients with hypersensitive disorders of the lower urinary tract. Br J Urol 1993, 71(6): 686–691.

74 Eckardt VF, Dodt O, Kanzler G, Bernhard G. Treatment of proctalgia fugax with salbutamol inhalation. Am J Gastroenterol 1996, 91(4): 686–689.

75 Boquet J, Moore N, Lhuintre JP, Boismare F. Diltiazem for proctalgia fugax [letter]. Lancet 1986, 1(8496): 1493.

76 Castell DO. Calcium-channel blocking agents for gastrointestinal disorders. Am J Cardiol 1985, 55(3): 210B–213B.

77 Swain R. Oral clonidine for proctalgia fugax. Gut 1987, 28(8): 1039–1040.

78 Patt RB, Proper G, Reddy S. The neuroleptics as adjuvant analgesics. J Pain Symptom Manage 1994, 9(7): 446–453.

79 Hanks GW. Psychotropic drugs. Postgrad Med J 1984, 60(710): 881–885.

80 Ventafridda V, Ripamonti C, Caraceni A, Spoldi E, Messina L, De Conno F. The management of inoperable gastroin-

testinal obstruction in terminal cancer patients. Tumori 1990, 76(4): 389–393.
81 De Conno F, Caraceni A, Zecca E, Spoldi E, Ventafridda V. Continuous subcutaneous infusion of hyoscine butylbromide reduces secretions in patients with gastrointestinal obstruction. J Pain Symptom Manage 1991, 6(8): 484–486.
82 Baines MJ. ABC of palliative care. Nausea, vomiting, and intestinal obstruction. BMJ 1997, 315(7116): 1148–1150.
83 Baines MJ. Management of intestinal obstruction in patients with advanced cancer. Ann Acad Med Singapore 1994, 23(2): 178–182.
84 Mercadante S. The role of octreotide in palliative care. J Pain Symptom Manage 1994, 9(6): 406–411.
85 Cherny NI, Portenoy RK. Sedation in the management of refractory symptoms: guidelines for evaluation and treatment. J Palliat Care 1994, 10(2): 31–38.
86 Burt RA. The Supreme Court speaks — not assisted suicide but a constitutional right to palliative care. N Engl J Med 1997, 337(17): 1234–1236.
87 President's Commission for the Study of Ethical Problems in Medical and Biomedical and Behavioral Research. Deciding to Forgo Life Sustaining Treatment: Ethical and Legal Issues in Treatment Decisions. U.S. Government Printing Office, Washington, 1983.
88 American Medical Association. Good care of the dying patient. Council on Scientific Affairs, American Medical Association. JAMA 1996, 275(6): 474–478.