

Difficult-to-Manage Cancer Pain



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Clinician: all pain is difficult-to-manage unless you:

1. understand that pain is somato-psychic
2. carefully evaluate the patient's pains
3. use appropriate non-drug treatments
4. use the right drugs in the right doses at the right time intervals

Clinician: all pain is difficult-to-manage unless you:

5. are aware that the effective dose of morphine varies
6. are aware that cancer pains often respond poorly to opioids alone
7. closely monitor & vigorously treat side effects, notably nausea and vomiting, and constipation

Patient: factors associated with poor pain relief prognosis

- Major psychological distress
- Neuropathic pain
- Episodic pain
- Need to increase opioid dose several times per week
- History of alcohol or drug abuse

Bruera et al 1995 JPSM 10: 348-355

Patient: impact of risk factors for a poor pain relief prognosis

In a series of nearly 300 patients:

No risk factor → 93% good response

1+ risk factor → 55% good response

Bruera et al 1995 JPSM 10: 348-355

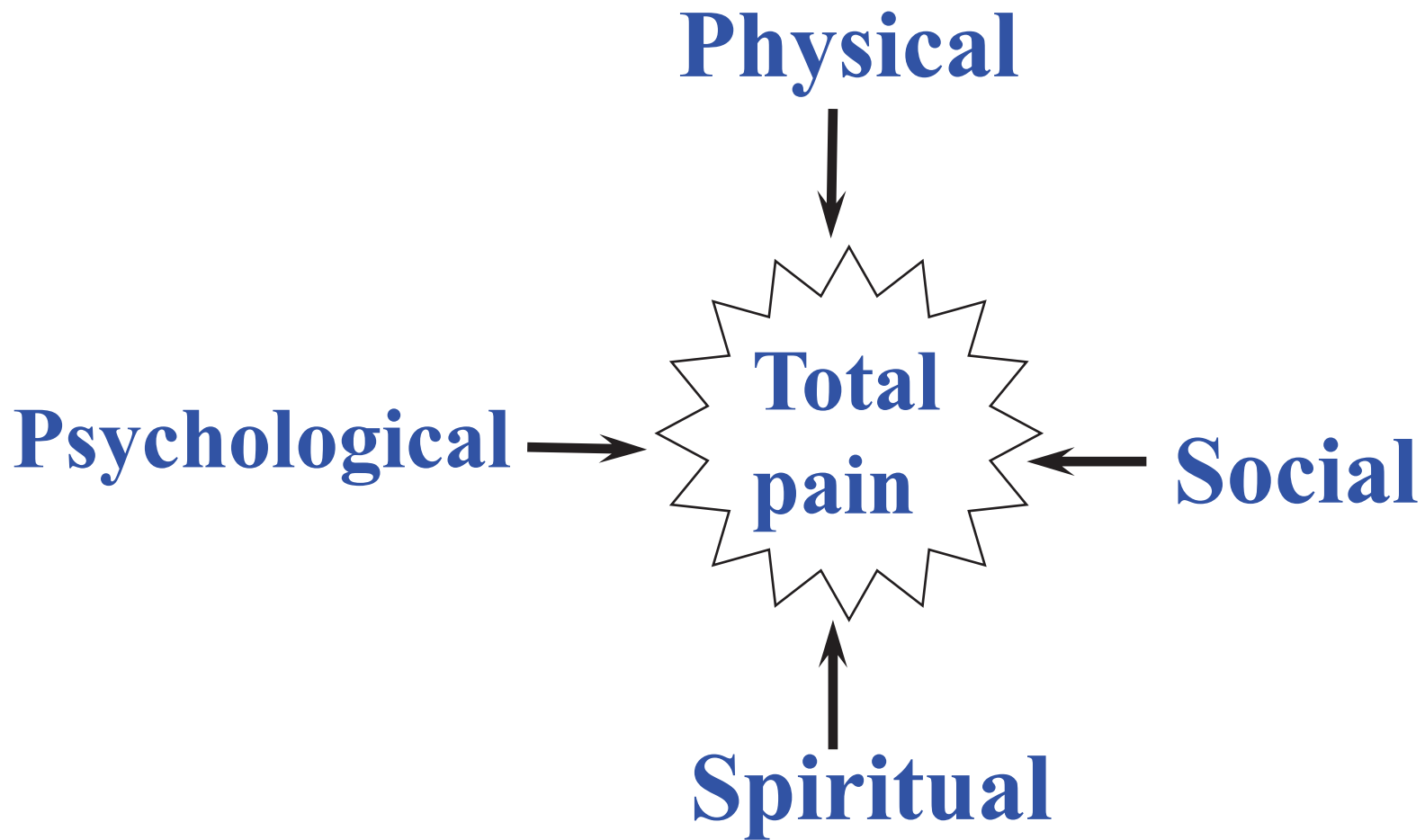
Pain

A physical and emotional experience...

International Association for the Study of Pain

‘A somato-psychic phenomenon’

Pain is modulated by mood, morale,
and meaning



Physical

Other symptoms
Adverse effects of treatment
Insomnia and chronic fatigue



Psychological

Anger at delays in diagnosis
Anger at therapeutic failure
Disfigurement
Fear of pain and/or death
Feelings of helplessness



Social

Worry about family and finances
Loss of job prestige and income
Loss of social position
Loss of role in family
Feelings of abandonment
and isolation



Spiritual

Why has this happened to me?
Why does God allow me to suffer like this?
What's the point of it all?
Is there any meaning or purpose in life?
Can I be forgiven for past wrongdoing?

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Pain in advanced cancer

Multiple pains

Multiple causes

Multiple mechanisms

Multiple causes

cancer

concurrent
disorder

treatment

debility

Multiple mechanisms

Pathological

nociceptive

neuropathic

Functional (Muscle)

somatic (cramp)

visceral (colic)

Top 10 pains in advanced cancer

Cancer

1. Bone
2. Visceral
3. Neuropathic
4. Soft tissue

Twycross & Fairfield 1982 Pain 14: 303-310

Top 10 pains in advanced cancer

Cancer

Bone

Visceral

Neuropathic

Soft tissue

Non-cancer

Immobility

Constipation

Myofascial

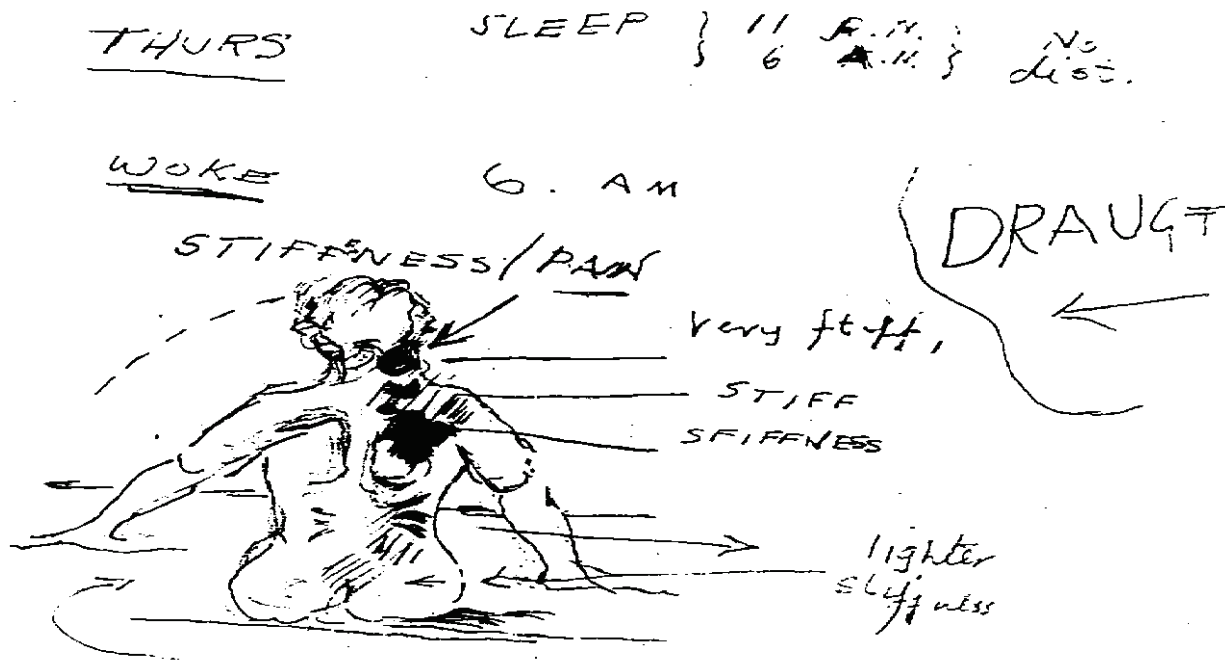
Cramp

Oesophagitis

Degeneration of spine

Twycross & Fairfield 1982 Pain 14: 303-310

Evaluation



Probability
Pattern recognition
*Imagination before
more investigation*

Man with cancer of pancreas

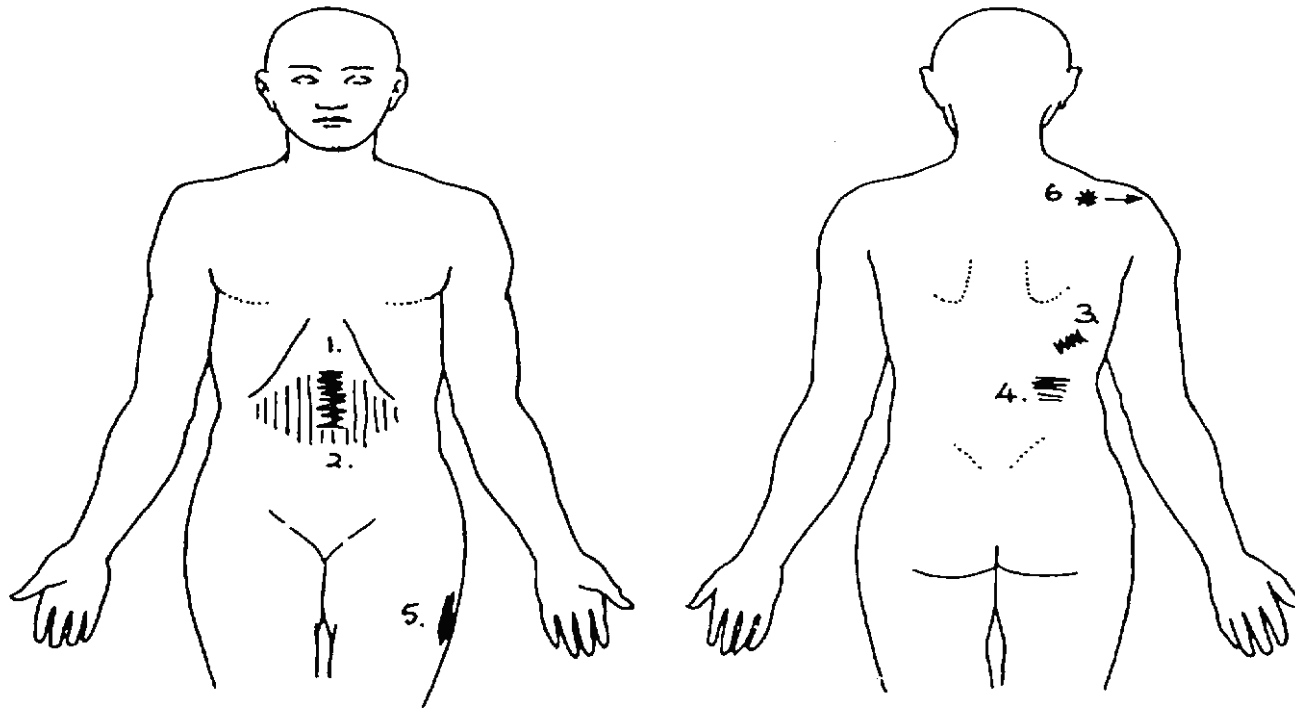
Evaluation

63 year-old woman with upper abdominal pain; laparotomy = inoperable cancer of pancreas.

10 days post-operatively still in pain despite morphine 25mg PO q4h.

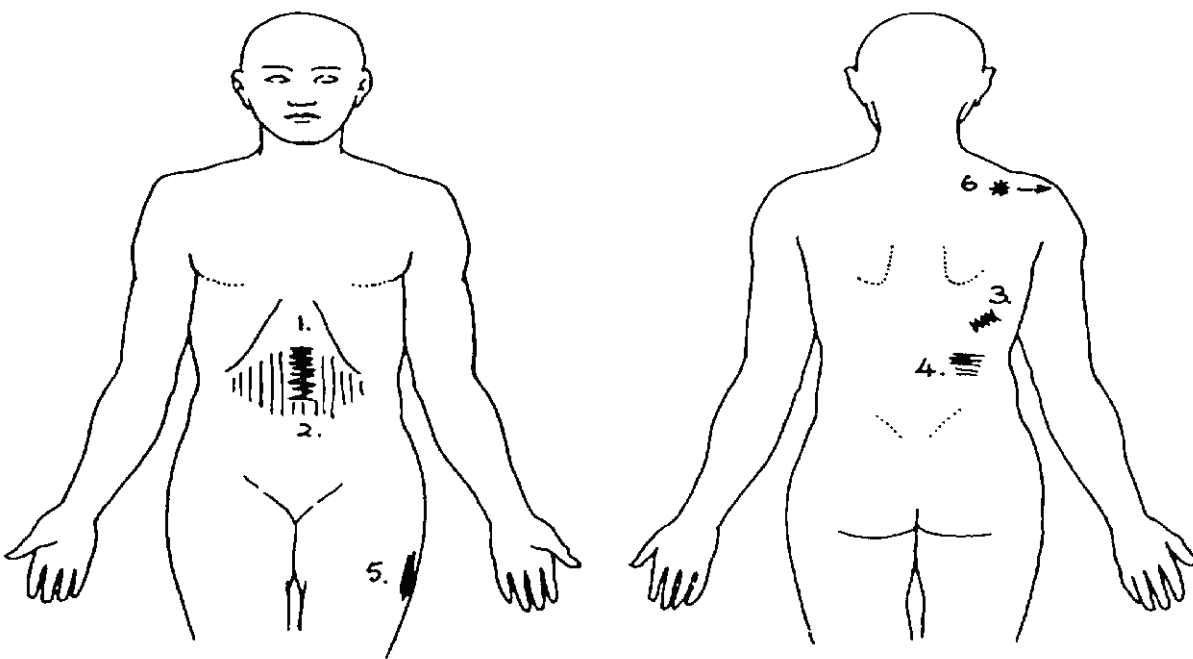
Drowsy, distressed & insomnia

Evaluation



63 year-old woman 10 days after laparotomy

10 days after laparotomy



1. incision [stitching]
2. cancer?
3. fractured rib
4. muscle spasm
5. nerve compression
6. trigger point

Initial advice

- Nurses advised about rib pain
- NSAID prescribed
- Dose of morphine...

Initial advice

- Nurses advised about rib pain
- NSAID prescribed
- Dose of morphine *reduced* to 15mg q4h and 30mg at bedtime
- Night sedative prescribed
- Laxative prescribed; enema next day

Further advice

Morphine *reduced* further:

after 3 days = *5mg q4h*

and *15 mg at bedtime*

Symptom management

‘EEMMA’

Evaluation

Explanation

Management

Monitoring

Attention to detail

Explanation

Reduces fear → reduces pain

Management makes sense to patient

Improves compliance with treatment

Explanation

Mr BC 59; recurrent cancer of larynx

Constant pain in the neck

Excruciating pain radiates up
to the temple every 15-20 minutes

Management

Correct the correctable

radiotherapy

orthopaedic surgery

Non-drug treatment

physical (heat, cold, massage)

psychological

nerve destruction (e.g. coeliac plexus)

Drug treatment

analgesics

Principles of analgesic use

‘By the mouth’

‘By the clock’

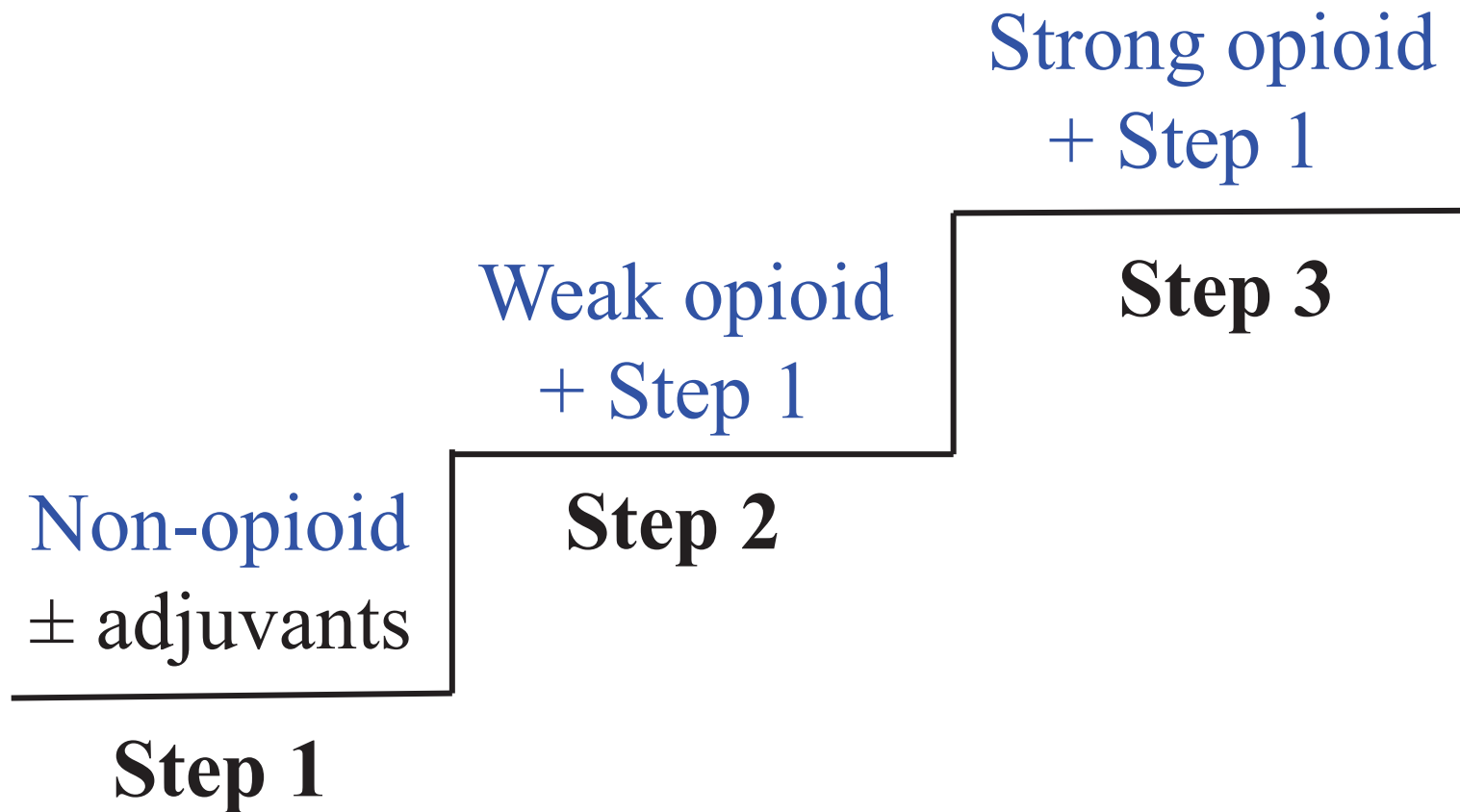
‘By the ladder’

‘Individual dose titration’

‘Use adjuvant drugs’

**The right drugs by the right route in the
right doses at the right time intervals**

WHO Analgesic Ladder



Adjuvant analgesics

Corticosteroids

Antidepressants

Anti-epileptics

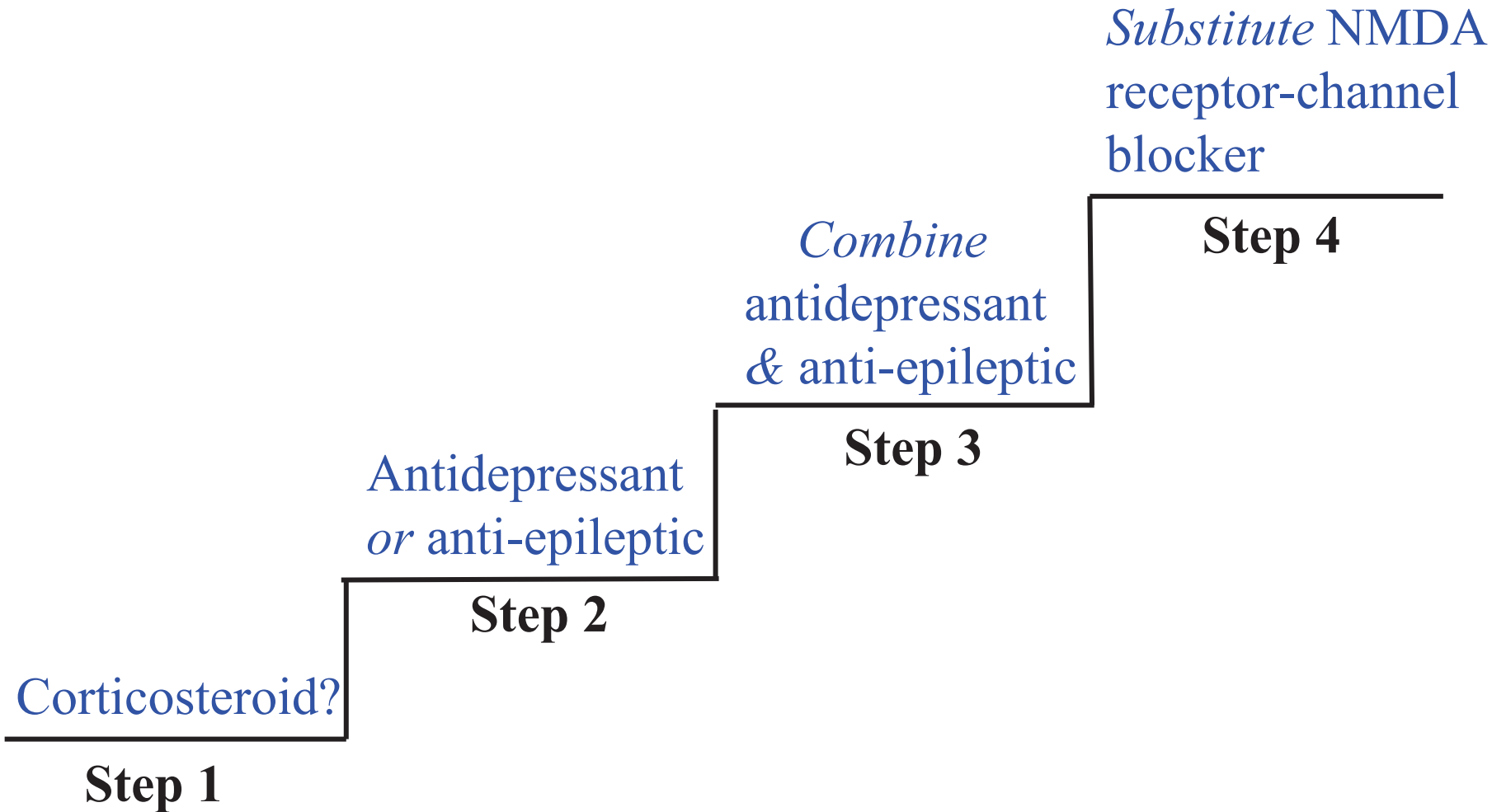
NMDA-receptor channel
blockers

Antispasmodics

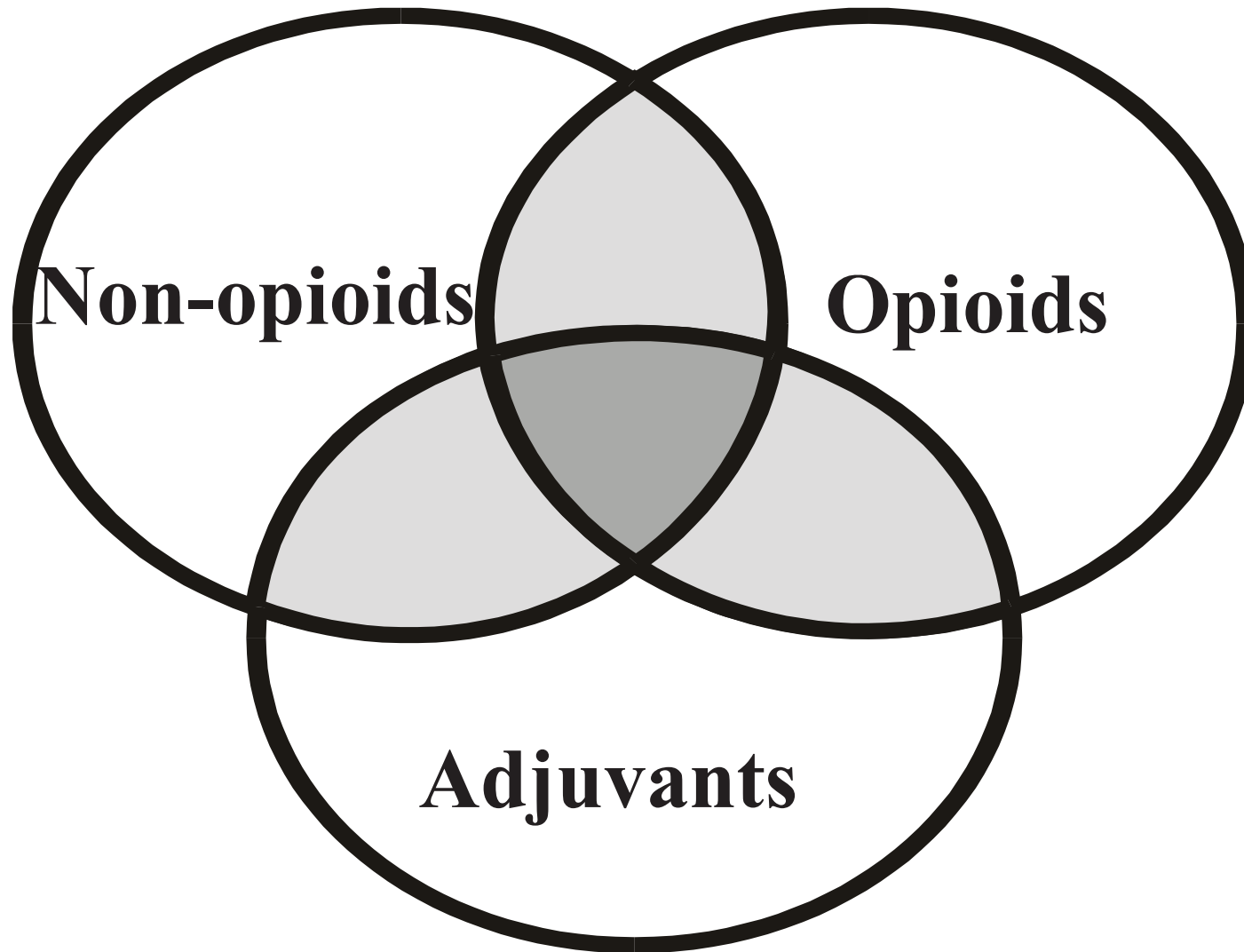
Muscle relaxants

Bisphosphonates

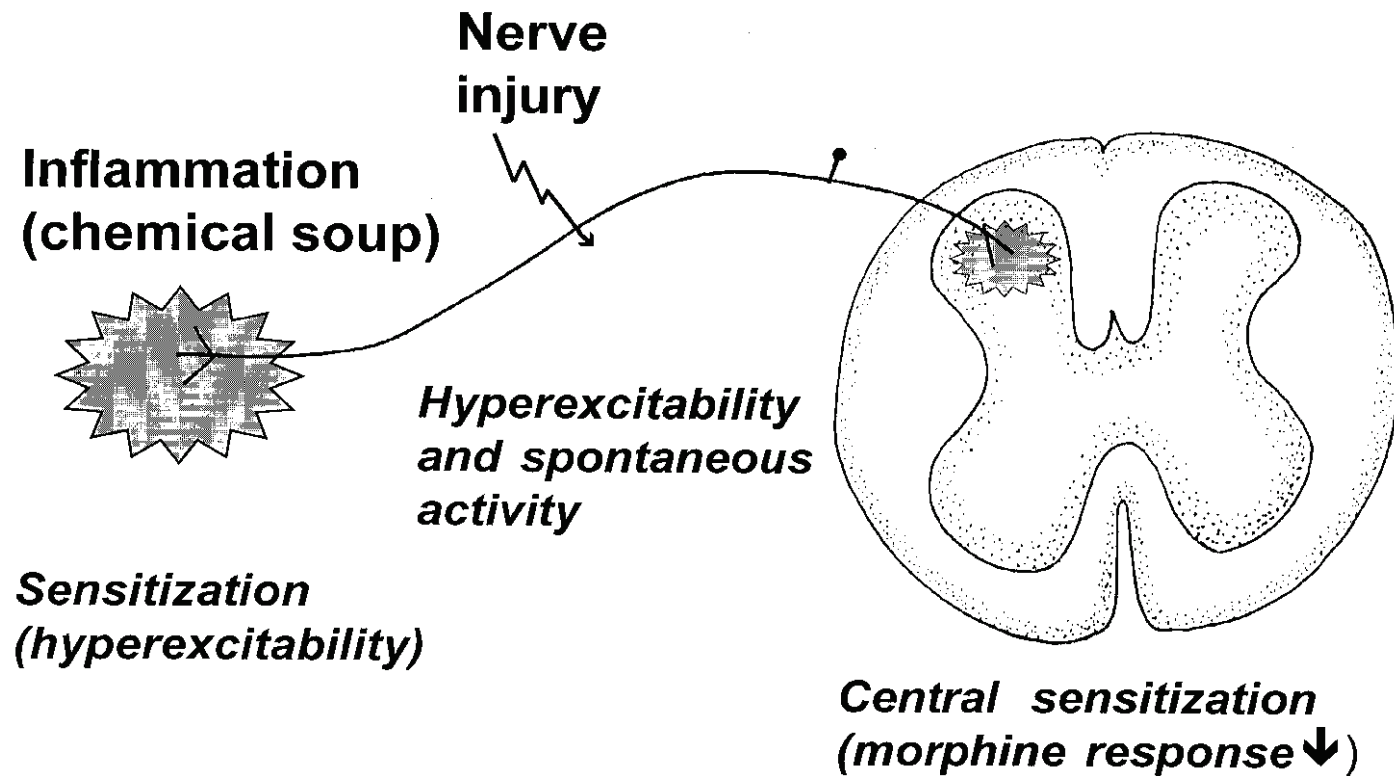
Drugs for neuropathic pain



Broad-Spectrum Analgesia



Nerve Sensitization



Hyperalgesia

1. Nerve damage
2. Inflammation
3. Chronic pain of any kind
4. Opioids!!

Case history

Mrs CD 58, mastectomy 3 years ago

Severe pain in her back when active

Bone scan = multiple metastases

Codeine 60mg q.i.d. → some relief but constipated & intermittently nauseated.

Case history

Mrs JK 82, inoperable cancer R. kidney

Severe pain in R. lumbar region.

Exacerbated by activity; needs to rest after 20 minutes.

Propoxyphene-paracetamol 2 tabs q.i.d.
reduces the pain to a dull ache for several hours.

Sometimes takes an extra dose in the night.

Opioid-induced neurotoxicity

Also called ‘neuropsychiatric toxicity’

Daeninck & Bruera 1999. Acta Anaesthesiol Scand 43: 924-938

Opioid-induced neurotoxicity

Somnolence

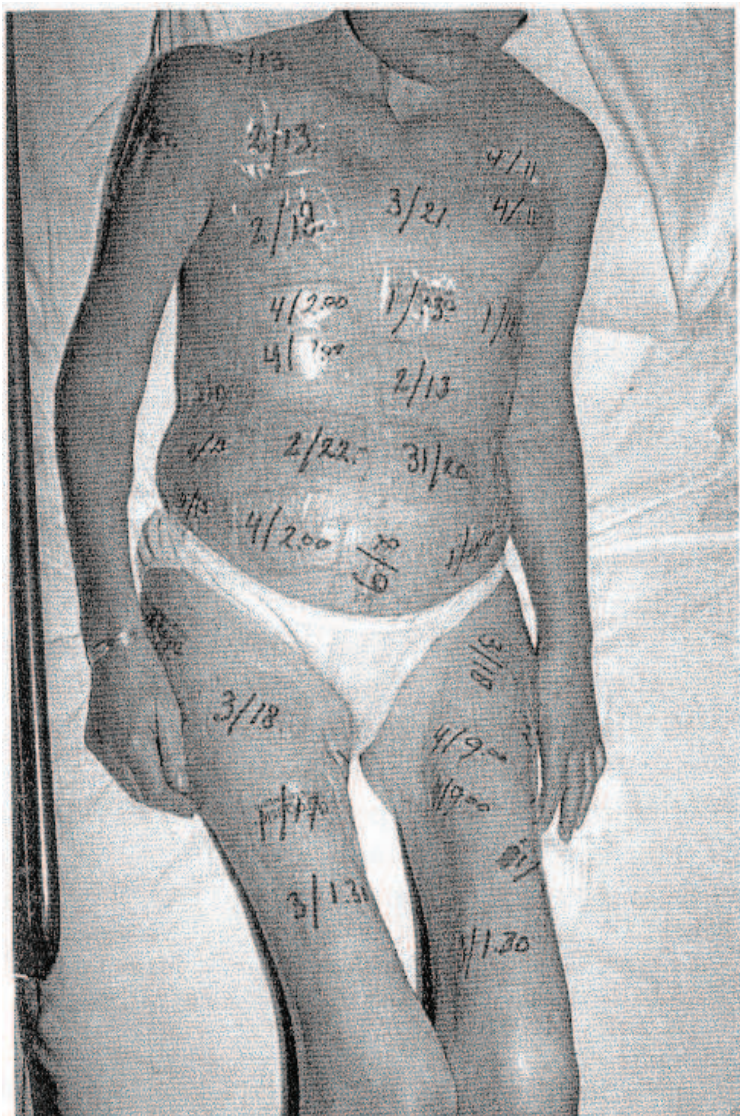
Cognitive impairment (delirium)

Hallucinosi

Myoclonus

Hyperalgesia

[Seizures]



A case of therapeutic madness

35 patches of
fentanyl 100mcg/h

Inefficacy of high-dose
fentanyl in neuropathic pain.
*Bleeker et al. 2001 European
Journal of Pain 5: 325-31*

Opioid-induced pain

Case history (1)

39 year-old man with testicular cancer.

L2 destruction + paraparesis + pain.

IT analgesia: morphine, LA, clonidine
+ IV PCA hydromorphone

Equivalent to oral morphine 86 grams/day

Opioid-induced pain

Case history (2)

Admitted to PCU; increase in IV hydromorphone → more pain.

IV midazolam 20mg/h added.

IT morphine → 1150mg/day +
IV phenytoin, IV dexamethasone,
IV ketamine, IV fentanyl

Opioid-induced pain

Case history (3)

? Opioid-induced hyperalgesia:

IT morphine reduced → 19mg/day
by 6h = more comfortable

24h = hydromorphone reduced

48h = all non-IT medication stopped

(Used oral morphine for episodic pain)

Died in comfort 6 weeks later at home

Pain

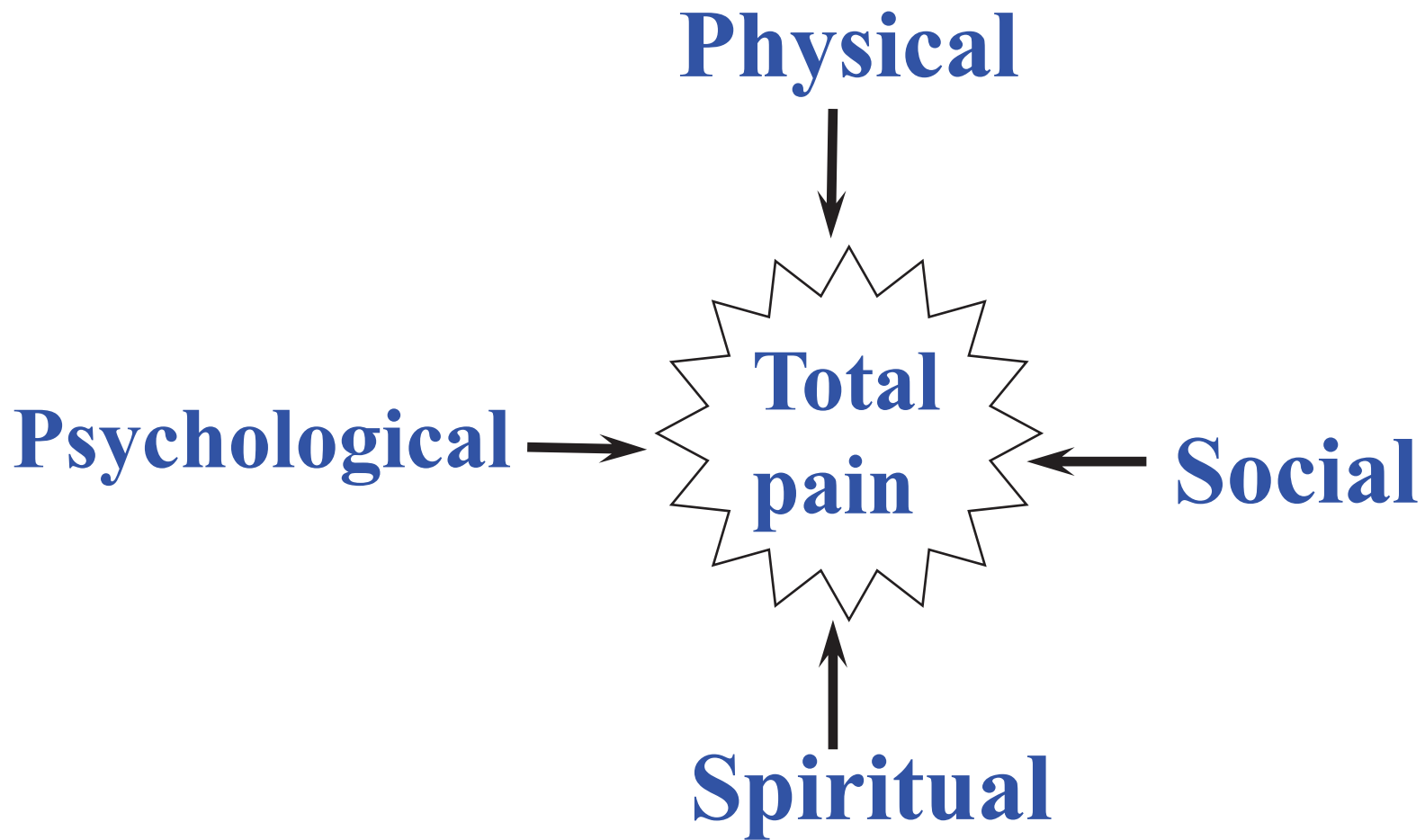
‘a somato-psychic phenomenon’

pain is modulated by:

mood

morale

meaning



Somatization

Case history (1)

79 year-old woman with cancer of pancreas.

Pain controlled with SR morphine 30mg b.i.d.

Somatization

Case history (2)

Pain controlled with SR morphine 30mg b.i.d.

Then: intense abdominal colic for several hours every 2-3 days → great distress.

Investigations: constipation... but not possible to reduce the dose of morphine...

Eventually accepted functional nature of pain.

Somatization

Case history (3)

A few days later, excruciating pain in left lumbar region related to a trigger point.

Initially, treated with massage.

Later, LA injected into trigger point;
after 1-2 days colic started again

Non-abandonment

‘Slowly, I learn about the importance of powerlessness; I experience it in my own life and I live with it in my work.

The secret is not to be afraid of it – not to run away. The dying know we are not God.

All they ask is that we do not desert them.’

Sheila Cassidy 1988

Remember

- Relief is not ‘all or none’
- Movement-related pain may continue to limit activity
- Old pains may recur & new pains develop

Realistic expectations

3-Step Pain Relief

1. pain-free night
2. comfort at rest during the day
3. comfort when active, *e.g.*
weight-bearing, walking

Reframe goal

Primary goal of pain management:
helping patients move from being
overwhelmed by their pain to
gaining mastery over their pain

‘Good enough’ relief

‘I still have some pain, but it doesn’t worry me any more’

‘It’s still there, but it’s not what you’d call pain’

‘I can get on with things and forget it now’

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Clinician: all pain is difficult-to-manage unless you:

5. are aware that the effective dose of morphine varies
6. are aware that cancer pains often respond poorly to opioids alone
7. closely monitor & vigorously treat side effects
8. are optimistic and have a sense of urgency



Thank you for listening

Factors involved in difficult-to-manage pain

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Introduction

In this article I shall focus on patients with advanced cancer. Although certain types of pain tend to be more difficult to manage, in practice the same type of pain can be straightforward to manage in one patient but difficult in another. Over 2000 years ago, Aristotle described pain as a 'passion of the soul'. He emphasised that pain is not just a physical sensation by omitting it from his list of the five senses (sight, hearing, smell, taste, touch). This fundamental truth is incorporated in the definition of pain adopted by the International Association for the Study of Pain:

'Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.' (IASP, 1986)

In other words, pain is a *somato-psychic experience*, and will inevitably be modulated by a person's mood, morale, and the perceived meaning of the pain (Box A). Continuing severe pain for which the doctor offers no

coherent explanation, associated with progressive physical deterioration, conveys the non-verbal message to the cancer patient that death is certain to be agonising. However, only about 2/3 of pains in advanced cancer are caused directly by the cancer. (Twycross, 1982; Twycross, 1996) It follows that to be able to tell someone that, 'This particular pain is not caused by the cancer' reduces the negative impact of the pain, and thereby decreases its intensity. Indeed, no explanation by the doctor and no opportunity for discussion is probably a major cause of difficult-to-manage pain in advanced cancer (Box B).

Broadly speaking, success in cancer pain management depends on health professionals, including doctors, who:

- appreciate that pain is a somato-psychic phenomenon
- carefully evaluate the cause(s) of pain
- when appropriate, combine non-drug treatment with drug treatment
- use the right drugs in the right doses at the right time intervals
- are aware that the effective dose of a strong opioid varies widely
- are aware that some pains respond poorly to opioid analgesics, and be familiar with the use of a range of adjuvant analgesics
- closely monitor patients and energetically treat undesirable drug effects, particularly constipation and nausea and vomiting

Even so, certain factors undoubtedly can make pain more difficult to manage. (Bruera, 1995; Laval, 1997) In one study, the following were found to predict a

Box A: Factors affecting pain intensity

Pain increased	Pain decreased
Discomfort	Relief of other symptoms
Insomnia	Sleep
Fatigue	Understanding
Anxiety	Companionship
Fear	Creative activity
Anger	Relaxation
Sadness	Reduction in anxiety
Depression	Elevation of mood
Boredom	Analgesics
Mental isolation	Anxiolytics
Social abandonment	Antidepressants

Box B: Common reasons for unrelieved pain

Associated with patient or family

Belief that pain in cancer is inevitable and untreatable.

Failure to contact doctor.

Patient misleads doctor by 'putting on a brave face'.

Patient fails to take prescribed medication as does not 'believe' in tablets.

Belief that analgesics should be taken only 'if absolutely necessary'.

Non-compliance because of fears of 'addiction'.

Non-compliance because of a belief that tolerance will rapidly develop, and will leave nothing 'for when things get really bad'.

Patient stops medication because of undesirable effects and does not notify doctor.

Associated with doctor or nurse

Doctor ignores the patient's pain, believing it to be inevitable and untreatable.

Failure to appreciate the severity of the patient's pain, often because of a failure to get behind the patient's 'brave face'.

Doctor prescribes an analgesic which is too weak to relieve the pain.

Prescription of an analgesic to be taken *p.r.n.* (*pro re nata*, 'as required').

Failure to appreciate that standard doses are not relevant for cancer pain.

Failure to give a patient adequate instructions about how the prescribed analgesics should be used to obtain maximum benefit.

Because of lack of knowledge about relative analgesic potency, the doctor either reduces or fails to increase the analgesic dose when transferring from one opioid to another.

Fear that patient will become 'addicted' if a strong opioid is prescribed.

Belief that morphine should be reserved until patient is 'really terminal' (moribund), and continues to prescribe inadequate doses of less effective drugs.

Failure to monitor the patient's progress.

Lack of knowledge about adjuvant analgesics for use when opioids are ineffective.

Failure to use non-drug measures when appropriate.

Failure to give psychological support to the patient and family.

poorer pain relief prognosis:

- major psychological distress
- neuropathic pain
- episodic pain
- the need to increase the opioid dose several times per week
- a history of alcohol or drug abuse

In a series of nearly 300 patients, 93% of those without any of these features achieved good pain control, whereas in those with one or more of these features the figure was only 55%. (Bruera, 1995)

Evaluation of pain

The following case history illustrates the importance of thorough clinical evaluation, linked with appropriate explanation to the patient.

Case history 1

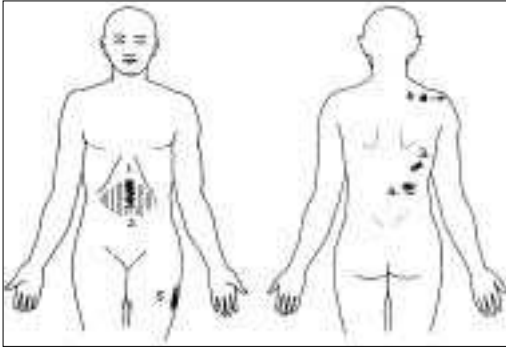
A 63 year-old woman with a history of upper abdominal pain was found at laparotomy to have cancer of

the pancreas with liver metastases. When seen 10 days post-operatively by a palliative care doctor she was receiving morphine 25 mg by mouth every 4 hours. This failed to provide adequate relief. She was drowsy, distressed and complained of insomnia. Clinical evaluation demonstrated the presence of six different pains (Figure 1).

It was explained to her that:

- some of her pains were muscular
- the pain in her chest wall was probably caused by a rib fracture
- her abdominal incision would probably continue to be uncomfortable on movement for several weeks, but would improve progressively
- some of the abdominal pain was probably caused by constipation
- some pains respond better to anti-inflammatory drugs and non-drug measures than to morphine.

The following measures were taken:



1. Intermittent stabbing pain (postoperative wound pain)
2. Diffuse upper abdominal discomfort (probably constipation – colonic pain)
3. Rib pain (? fracture)
4. Muscle spasm
5. Meralgia paraesthetica
6. TP pain (supraspinatus)

Figure 1: Pain chart of a 63-year old woman with cancer of the pancreas 10 days postoperatively. TP, myofascial trigger point

- the nurses were advised about the nature of the rib pain
- a non-steroidal anti-inflammatory drug (NSAID) was prescribed
- the dose of morphine was *reduced* to 15 mg every 4 hours in the daytime with 30 mg at bedtime
- a night sedative was prescribed
- a laxative was prescribed, and an enema planned for the following day.

The next day she was dramatically improved following a good night, and had minimal pain. The dose of morphine was reduced further and, after three days, she was taking only 5mg every 4 hours with 15 mg at bedtime.

This case history emphasises the following points:

- not all pains in cancer are malignant in origin
- cancer patients with pain often have more than one pain
- muscular pains may be as intense as (or even more intense than) much pain caused directly by cancer
- some pains, however intense, do not benefit from the use of incremental doses of morphine
- thorough clinical evaluation is necessary before starting treatment
- explanation is essential before starting treatment
- re-evaluation may lead to further changes in treat-

ment in the light of initial results and/or undesirable drug effects.

When evaluating a patient's pain, it is important to consider whether the pain is nociceptive (associated with tissue distortion or tissue injury) or neuropathic (associated with nerve compression or nerve injury). Pain in an area of abnormal or absent skin sensation is always neuropathic. It may be solely neuropathic (e.g. chronic postoperative scar pain, post-herpetic neuralgia) or, more often in cancer, mixed nociceptive-neuropathic (e.g. intrapelvic recurrence with lumbosacral plexopathy). In addition to being neurodermatomal in distribution, nerve injury pain is often burning in character and associated with cutaneous hypersensitivity (allodynia). There may also be spontaneous stabbing (lancinating) pain.

Use of analgesics

Analgesics can be divided into three classes:

- non-opioid (antipyretic)
- opioid
- adjuvant

Non-opioid and opioid analgesics both act peripherally and centrally. (Geisslinger, 2000; Stein, 1993) The principles governing analgesic use include: (World Health Organization, 1986)

- *By the mouth*, the oral route is the standard route for analgesics, including morphine and other strong opioids
- *By the clock*, persistent pain requires preventive therapy. Analgesics should be given regularly and prophylactically at pharmacologically appropriate intervals, and as needed (p.r.n.); as needed medication alone is irrational and inhumane (Figure 2)
- *By the ladder*, use the analgesic ladder (Figure 3). Generally, if a combination of an NSAID and a weak opioid fails to provide adequate relief, move to Step 3, and not sideways to another weak opioid
- *Individual dose titration*, the right dose is the one which relieves the pain; doses should be titrated upwards until the pain is relieved or undesirable effects prevent further escalation
- *Use adjuvant drugs*, in the context of the analgesic ladder these include:
 - other drugs which relieve pain in specific situ-

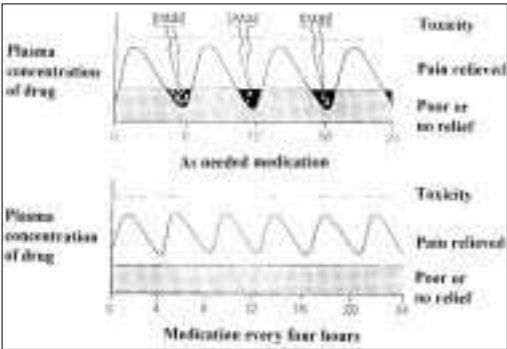


Figure 2: ‘As needed’ administration compared with morphine regularly every 4 hours

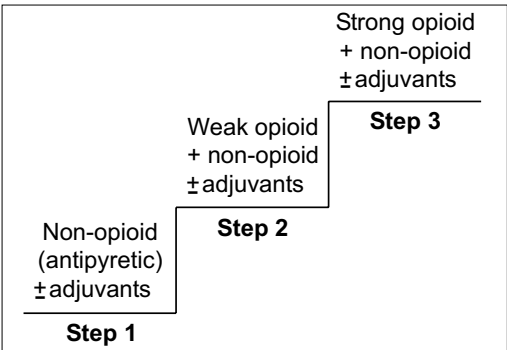


Figure 3: The World Health Organization analgesic ladder for cancer pain

- ations
- drugs to control the undesirable effects of analgesics
- concurrently prescribed psychotropic medication, e.g. anxiolytics.

A key concept underlying the analgesic ladder is *broad-spectrum analgesia*, i.e. drugs from each of the three classes of analgesic are used appropriately, either singly or in combination, to maximise their impact (Figure 4). Relief with morphine and other opioids is often limited by the development of central sensitisation (Figure 5).

A cancer tends to provoke a local inflammatory reaction with the release of prostaglandins, various cytokines and other chemical mediators of inflammation. These sensitise the free nerve endings involved in nociception. The result is enhanced nociception and secondary sensitisation of the dorsal horn of the spinal cord - and a decreased response to opioids. Some-

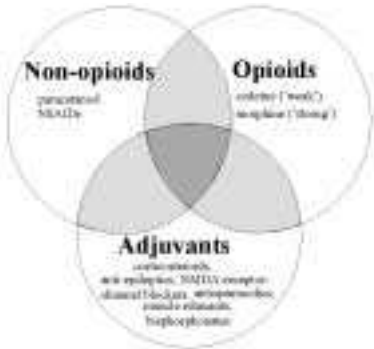


Figure 4: Broad-spectrum analgesia

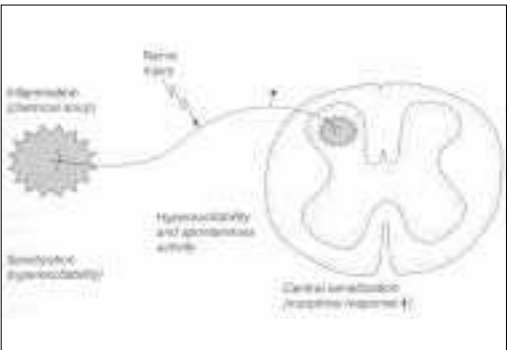


Figure 5: Peripheral sensitisation leads to central sensitisation and a reduced response to opioids

times, with further escalation of the opioid dose, pain control is achieved but often it is not. In this circumstance, the best approach is to counter the inflammation responsible for the sensitisation by prescribing an anti-inflammatory drug in conjunction with morphine (or other strong opioid) as part of a broad-spectrum attack on the pain. (Shah, 2001) Unfortunately, the value of NSAIDs in cancer pain management is not universally recognised.

Dorsal horn sensitisation also occurs in association with nerve injury pain, though via a different mechanism. (Dickenson, 2001) When the pain is caused purely by nerve destruction (e.g. by diabetic neuropathy) there is no inflammation, and an NSAID is unlikely to help. In nerve destruction caused by cancer, there will however be two sensitising mechanisms involved – that secondary to the neurophysiological perturbation which follows nerve injury and also the effect of the inflammation. Thus, in nerve injury pain

in cancer, it is important to use both an NSAID (or corticosteroid) and a strong opioid before adding or switching to adjuvant analgesics.

It must always be remembered that the use of analgesics and pain management are not synonymous. Indeed, drug treatment can never be more than one part of a multimodality approach to management (Box C). The fact that pain is a somato-psychic experience immeasurably widens the scope for intervention. Pain management will extend to factors such as anxiety, depression, fatigue, boredom and loneliness. Too much reliance on morphine and too little attention to the psychological dimension of pain can, all too easily, result in intractable pain.

Neuropathic pain

Neuropathic pain responds to a variable extent to opioid drugs; occasionally very well but often only to a very limited extent. (Rowbotham, 2001; Rowbotham, 2003) Patients with central pain after a stroke are perhaps the least likely to find them helpful. (Rowbotham, 2003) It is important to establish guidelines for the use of adjuvant analgesics for neuropathic

pain which is poorly responsive to opioids. (Dworkin, 2003; Mendell, 2003; Twycross, 2001; Twycross, 2002) Several drugs are necessary because none helps in all cases. The best achieve more than 50% relief in about 70% of patients. (Sindrup, 2001) The most commonly used drugs for cancer neuropathic pain which responds poorly to a combination of an NSAID and an opioid are the tricyclic antidepressants (commonly amitriptyline) and the anti-epileptics (gabapentin is being used increasingly). (Backonja, 2001; Dworkin, 2003; Sindrup, 2001)

In seemingly intractable situations, methadone (possessing both broad-spectrum opioid and non-opioid properties) (Morley, 1998; Blackburn, 2002; Twycross, 2002; Morley, 2003; www.palliatedrugs.com) or ketamine (an NMDA-receptor-channel blocker) (Jackson, 2001; Twycross, 2002; Mercadante, 2003; www.palliatedrugs.com) should be considered. Alternatively, if readily available, long-term spinal analgesia (epidural or intrathecal) with morphine and bupivacaine \pm clonidine can be used. (Twycross, 2002) The impact of these third-line treatments is sometimes dramatic. For example, a

Box C: Pain management in cancer

Modification of the pathological process	Psychological
Radiation therapy	Relaxation
Hormone therapy	Cognitive-behavioural therapy
Chemotherapy	Psychodynamic therapy
Surgery	
Analgesics	Interruption of pain pathways
Non-opioid (antipyretic)	Local anaesthesia
Opioid	lidocaine
Adjuvant	bupivacaine
corticosteroids	Neurolysis
antidepressants	chemical, e.g. alcohol, phenol
anti-epileptics	cryotherapy
NMDA-receptor-channel blocker	thermocautulation
muscle relaxants	Neurosurgery
antispasmodics	cervical cordotomy
bisphosphonates	
Non-drug methods	Modification of way of life and environment
Physical	Avoid pain-precipitating activities
massage	Immobilisation of the painful part
heat pads	cervical collar
TENS	surgical corset
	slings
	Orthopaedic surgery
	Walking aid
	Wheelchair
	Hoist

patient with severe pain despite taking several grams per day of morphine by mouth, becoming pain-free on a daily dose of methadone 20-30 mg. (Davis, 2000; Morley, 1998; Morley, 2003)

Beyond the ladder

Spinal analgesia is generally classified as 'beyond the ladder', together with local anaesthesia, neurolytic blocks, (Wilsey, 2002) neurosurgery, (Jackson, 1999; Jones, 2003) and orthopaedic surgery (Box C). In many centres, only about 5% of patients require neuroablative or orthopaedic interventions. Most patients with bone pain will receive palliative radiotherapy, and a small number will have further palliative oncological treatment as part of pain management.

However, some patients continue to experience pain on movement despite the appropriate use of analgesics, radiotherapy, spinal analgesia, and nerve blocks. Here, the situation is often improved by suggesting modifications to a patient's way of life and environment. The involvement of a physiotherapist and an occupational therapist is important in these circumstances.

Episodic pain

Episodic pain is a term used to describe a transient exacerbation or recurrence of pain in someone who has adequately relieved background pain for most of the time. (Portenoy, 1990) The main types of episodic pain are:

- *incident (predictable) pain*, related to movement or activity (the majority), e.g. weight-bearing, walking, coughing, swallowing, defaecation, dressing change
- *spontaneous (unpredictable) pain*, unrelated to movement or activity (the minority).

Episodic pain may be functional (e.g. tension headache) or pathological, and either nociceptive or neuropathic. In one group of palliative care services, episodic pain occurred in about 40% of patients, on average 1.5 times a day. (Gomez-Batiste, 2002) Compared to spontaneous pain, patients were less likely to take additional analgesia for incident pain, possibly because of its predictability and shorter duration.

A detailed history and examination with, if necessary, further investigation should identify the cause of the

episodic pain, the exacerbating and relieving factors, and the impact on the patient – and lead onto the selection of the most appropriate treatment.

For example, if the patient has severe oesophagitis because of acid reflux from the stomach, and swallowing causes pain, administration of a local anaesthetic solution or gel may provide short-term relief. More definitive measures such as metoclopramide to minimise further acid reflux, and a proton-pump inhibitor (e.g. lansoprazole) to reduce gastric acid would also be necessary.

Because episodic pain is generally severe, an additional dose of an opioid is often recommended, e.g. morphine by mouth. (Hanks, 2001) Practice differs, but most centres recommend either 1/6 or 1/10 of the total daily dose of morphine. However, a standard fixed-dose is unlikely to suit all patients and all pains, particularly because the intensity and the impact of episodic pain vary considerably. Further, episodic pain has a relatively rapid onset and short duration whereas oral morphine has a relatively slow onset of action (20-30 minutes) and relatively long duration of effect (3-6 hours). (Collins, 1998)

The use of an opioid with a high bio-availability, a rapid onset of action and a relatively short duration of effect, and which can be administered by a convenient route and provide rapid absorption should improve the management of episodic pain. Injections provide rapid onset of analgesia but are not always feasible. (Walker, 2002) Other non-oral routes of administration include transmucosal, sublingual, intranasal and inhaled. (Walker, 2002) Opioids which are lipophilic and which can be formulated in a small volume are the best choices for these routes, e.g. transmucosal fentanyl. (Coluzzi, 2001; Twycross, 2002) In one trial, a reduction in pain score of >33% was reported after 15 minutes by 42% of patients with transmucosal fentanyl and 32% with morphine. (Coluzzi, 2001) At the end of the trial, 94% of the patients opted to continue with transmucosal fentanyl, rather than morphine. This is somewhat surprising given the modest difference in relief at 15 minutes, and the fact that it generally takes 8-10 minutes, sometimes longer, of rubbing movements up and down the cheeks to extract all the fentanyl from the 'lozenge on a stick'. Even for a fit person, this is a tiring activity.

Available therapeutic options for episodic pain are

likely to increase in the near future; both the range of opioids available and the variety of delivery systems. (Duncan, 2002; Pavis, 2002) Meanwhile, moving from a rigid system based on a fixed ratio of supplementary morphine to a more individual approach may well result in significant improvement for many patients.

Other predictive factors for 'difficult-to-manage' pain

Two other factors reported in the study of factors associated with a poor pain relief prognosis were:

- the need to increase the opioid dose several times a week
- a history of alcohol or drug abuse. (Bruera, 1995)

The first factor relates to both intrinsic 'opioid unresponsiveness' (Box D) and to patients with major psychological distress (*see later*). The second factor relates to the psychological coping mechanisms used by a person when life becomes severely challenging. If someone uses analgesics in the same way as they have used drugs and/or alcohol (as an attempt to escape reality by 'drowning their sorrows'), there will be a high risk of somatisation and wildly inappropriate use of *p.r.n.* medication. With drug addicts it is best to have a formal written contract about the supply of opioids so as to reduce the risk of 'drug chaos'. (Hansen, 1999)

Box D: Opioid unresponsive pain in cancer: A clinical classification

A pain can be said to be unresponsive to opioids if there is little or no relief despite escalating the opioid dose to the maximum tolerated level.

Pseudo-unresponsive

Under-dosing

Poor alimentary absorption (*rare*)

Poor alimentary absorption because of vomiting

Ignoring psychological aspects of care

Semi-responsive

Soft tissue

Muscle infiltration } associated with local inflammation

Bone metastasis

Neuropathic (many)

Raised intracranial pressure

Activity-related

Unresponsive

Muscle spasm

Opioid-induced pain

Opioids and their metabolites can cause neurotoxicity, particularly when given in high doses or to susceptible patients. In florid cases, neurotoxicity manifests as myoclonus (muscle twitching), allodynia (skin pain provoked by a non-noxious stimulus, e.g. light touch), hyperalgesia (a painful stimulus becomes relatively more painful) and, more rarely, seizures. (Kaiko, 1983; Sjogren, 1993; De-Conno, 1991; Hagen, 1997) Sometimes these are compounded by drowsiness and delirium. The reported incidence of neurotoxicity varies widely, depending partly on definition. (Bruera, 1996) However, opioid-induced pain is rare.

Neurotoxicity was first reported several decades ago in association with pethidine, (Kaiko, 1983) but nowadays it is seen mainly with morphine. This may be because morphine is the most widely used strong opioid for cancer pain or because its main metabolite, morphine-3-glucuronide, is more neurotoxic than other opioids and their metabolites. (Labella, 1979) The following case history is a dramatic example of opioid neurotoxicity.

Case history 2

A 39 year-old man with testicular cancer developed sudden severe back pain and lower limb dysfunction. CT demonstrated bone destruction in L2 vertebra with associated neural compression. Increasing doses of oral and intravenous (IV) opioids failed to relieve the pain. Spinal analgesia (epidural followed by intrathecal) was no better despite the combined use morphine, local anaesthetic and clonidine, as well as IV hydromorphone. When transferred to a palliative care unit, he was receiving daily the equivalent of 86 *grams* of oral morphine. Increasing the amount of IV hydromorphone to 80 mg/h, and 40 mg every 15 min *p.r.n.*, was accompanied by increasing pain. IV midazolam 20 mg/h was added. He repeatedly said that he would prefer to die rather than continue to experience the unbearable pain. Further measures included increasing the intrathecal morphine to 1150 mg/day, and adding IV phenytoin, IV dexamethasone, IV ketamine and IV fentanyl. With all this he began to have short periods of sleep and intermittent periods of pain relief. It was suggested that he might be suffering from opioid-induced hyperalgesia. The dose of intrathecal morphine was reduced 60-fold, from 6 mg/ml to 0.1 mg/ml (19 mg/day), while the other

medication remained unchanged. Within 6 hours the patient reported greater comfort, and subsequently stopped administering *p.r.n.* doses. The hydromorphone was reduced after 24 hours, and stopped after 48 hours; all other analgesics and adjuvant were discontinued over the next 24 hours. He remained comfortable on intrathecal local anaesthetic, clonidine and morphine 17 mg/day. He used oral morphine for break-through pain. He died in comfort at home 6 weeks later. (Wilson, 2003)

Although unusual because of the extra-ordinary doses of both intrathecal morphine and IV hydromorphone, this case history is an excellent example of opioid-induced hyperalgesia. The authors state that the case history also illustrates the truth of the adage that pain is a physiological antagonist of the central depressant effects of morphine. Despite receiving daily the equivalent of over 200 grams of oral morphine, he remained, awake, lucid, and involved in his management. However, the primary reason for his continued wakefulness was probably the presence of extremely high concentrations of non-analgesic neuro-excitatory metabolites, principally morphine-3-glucuronide and hydromorphone-3-glucuronide. (Gong, 1992; Smith, 2000)

Early reports of morphine-induced neurotoxicity related to either intrathecal or high-dose IV administration. However, subsequent reports demonstrated that neurotoxicity can occur with 'normal' oral or parenteral doses (Table 1). (Sjogren, 1994)

Suffering

Suffering can be defined as a state of severe distress

Table 1: Morphine-induced allodynia in four patients [Sjogren, 1994]

Age (yrs.)	Gender	Diagnosis	Pain therapy
19	F	Glioblastoma	IV morphine 20g/day levomepromazine benzodiazepines
68	F	Breast cancer	IM morphine 960mg/day levomepromazine benzodiazepines
10	M	Astrocytoma	m/r morphine 300mg/day IMmorphine 150mg/day
55	F	Breast cancer	m/r morphine 60mg/day amitriptyline

caused by events which threaten the integrity of a person. (Cassell, 1983; Cassell, 1991) Suffering and pain are not synonymous. Thus, what I as an observer may think *must* be a major cause of suffering for the patient may not be so. (Cassell, 1983) However, people in pain commonly report suffering from pain when:

- they feel out of control
- the cause is unknown
- the pain is intractable
- the intensity of the pain is overwhelming
- the meaning of the pain for them is that the cancer is progressing inexorably and that they will soon die.

Thus, when evaluating a new patient, it can be helpful to ask, 'And what causes you the most suffering?'

Relief of pain and other distressing symptoms is rightly seen as the primary goal of palliative care, and competent symptom management means that patients can generally expect to be almost free of pain. (WHO, 1990) A high measure of relief can also be expected with many other symptoms. However, if no longer distracted and exhausted by unrelieved pain, patients may become distressed emotionally and spiritually as they contemplate their approaching death. Few do this with equilibrium. Most defend themselves psychologically in various ways, but some are overwhelmed with anguish, rage, or fear about what is happening to them. This is likely to exacerbate pain and other symptoms. Sometimes a patient cannot openly acknowledge their distress and, instead, expresses it through a symptom such as pain.

Case history 3

A 79 year-old woman, previously exceptionally fit, developed epigastric pain. When investigated she was found to have cancer of the pancreas. The pain was initially readily controlled by slow-release morphine 30 mg every 12 hours. She then began to experience intense central abdominal colic for several hours every 2-3 days. Between attacks she was her normal vivacious self. When the pain was present she would moan and groan and express feelings such as 'I can't go on', 'I'd rather die than have this pain', 'If I were a dog you'd put me down'. At times she was inconsolable. The pain appeared to be functional rather than organic, and radiological investigations demonstrated

only constipation. It was not possible to reduce the dose of morphine because a reduction was followed within 1-2 days by another severe episode of pain - which needed more morphine to control it. Eventually it seemed that the patient accepted that the pain was functional and not caused by the cancer. However, within a few days, she began to experience intermittent attacks of cramp in the left quadratus lumborum muscle related to a myofascial trigger point. This was explained to her and she was treated with local massage whenever she had an attack. Because the attacks continued, she was treated by local injection of bupivacaine into the trigger point. Then, within a few days, she began to experience functional intestinal pains again. Although visited regularly by a psychologist, she remained locked in her recurring anguish, and most of her final months were spent in bed in a palliative care unit.

This case history is a good example of a common problem in patients with unresolved fears, unexpressed anger and emotional conflicts. Functional abdominal pain may well have been her way of expressing negative emotions throughout her life. If this was so, it was not surprising that it proved impossible to prevent her recurring episodes of agonising pain. The situation eventually developed into a vicious downward spiral of more morphine, more laxatives and more sedatives until the patient finally died. Such situations are extremely demanding for everyone involved. They engender feelings of failure and of guilt. Good communication between all the carers is essential in order to clarify goals (which may change) and to provide ongoing mutual support. In contrast, other people work through great psycho-spiritual distress, and achieve a remarkable measure of acceptance and peace, as demonstrated in the following account.

Case history 4

A 34 year-old woman had widely disseminated breast cancer. In the past, she had two still-born children, but now had a 3 year-old son. While relatively well she had coped with her situation by intellectualisation, and had made all the necessary arrangements for her approaching death. However, as she weakened it was clear that she had not come to terms with her illness psychologically. Now she was asking, 'Why all this? Why me?' She grieved about her past bereave-

ments; she wanted to be able to collect her son from the playschool, and to cuddle him, but could no longer do so. She lamented her increasing dependence and feared the possible future loss of control over physical functions. Her grief was compounded by overwhelming intractable pain. She said, 'I am resigned to the fact that this is my lot. It is the pain I cannot accept. Dying is all right, but there is no reason for this pain, no purpose in it. I am no longer angry with God for my fate, but why this pain?' Oral morphine in doses up to 1500mg/24h was ineffective. Episodes of shattering pain continued and she was miserable and often withdrawn. The slightest movement caused her to cringe in pain. For relief, large and frequent doses of IV diazepam were required. Epidural morphine was commenced at this stage and was continued for 5 weeks. Gradually she came to terms with her situation. As this occurred, her need for analgesia became less and eventually she was kept pain-free on morphine 10mg by mouth every four hours. She improved to the point where she could be wheeled down the road on an ambulance trolley to buy some chocolate for her son, and to visit a nearby art gallery the day before she died. (Lichter, 1991)

'Good enough' pain relief

When considering pain management, it is necessary to bear in mind that:

- pain relief is not an 'all or none' phenomenon
- all pains are not equally responsive to analgesics
- some pains continue to be brought on by weight-bearing and/or activity
- relief is not generally a 'once and for ever' exercise; old pains may re-emerge as the disease progresses and new pains develop.

When these points are taken into account, the primary goal of pain management can be redefined as helping patients move from a position in which they are overwhelmed by the pain to one in which they establish mastery over the pain. When a patient is overwhelmed by pain, the pain becomes all-embracing. When sufficiently improved, a patient may say:

'I still have the pain, but it doesn't worry me anymore.'

'It's still there, but it's not what you'd call pain.'

'I can get on with things and forget it now.'

Of course, the ultimate goal remains complete relief. But, in practice, partial relief is acceptable provided the patient is much more comfortable, mentally rested, and both patient and family are demonstrating 'mastery' of the situation. In this situation there is little need to pursue relentlessly the ultimate goal using neurolytic or neurosurgical techniques which do not guarantee success but may well be complicated by weakness, numbness or incontinence.

The concept of 'mastery over pain' is supported by studies using the Wisconsin Brief Pain Inventory. (Daut, 1982) When using the inventory, patients rate both pain intensity and how much the pain interferes with a range of activities, scored on a scale of 0-10. Patients with pain rated 1-3 record little impact on either activity or enjoyment of life.

Case history 5

A 66 year-old man with local spread of a bladder cancer became exhausted and greatly distressed because of insomnia caused by 'round-the-clock' frequency of micturition and by pain in the lower abdomen and legs. The frequency of micturition and insomnia were both corrected by appropriate drug treatment. However, despite increasing the morphine to above the maximum tolerated dose, he continued to experience 'a golf ball' sensation in the perineum, 'but it's not really painful', and intermittent pain in the right L5 dermatome. This was generally mild, but occasionally became more intense. Because lowering the dose of morphine did not make the pain worse, it was concluded that this particular pain was probably only partly responsive to opioids. Further, because the residual pain had only minimal impact on the patient's activity and enjoyment of life, it was decided not to recommend a nerve block or other invasive procedure at this stage.

The contrast between the man's condition at his initial assessment and subsequent reviews continued to be considerable, despite occasional trouble with constipation or frayed emotions. So, was his pain controlled or was it not? In absolute terms, no; but, in his estimation, yes.

Realistic expectations

Understandably, many cancer patients with long-standing pain have a low expectation of relief. Thus, when

first seen, all patients should be assured that the situation can be improved, and that it is generally possible to make good progress *within a week* in terms of pain relief. (Grond, 1996) With few exceptions, it is possible to achieve *at least* some improvement within 48 hours. However, it is generally wise to aim at 'graded relief'. Further, because some pains respond more readily to treatment than others, improvement must be evaluated in relation to each pain.

The initial target is a pain-free, sleep-full night. Some patients have not had a good night's rest for weeks or months and are exhausted and demoralised. To sleep through the night pain-free and wake refreshed is a boost to both the patient's and the doctor's morale. Next, one aims for relief at rest in bed or chair during the day, and finally for freedom from pain on movement. Even though the latter is not possible in some 10-15% of patients, relief at night and when resting during the day gives the patient new hope and incentive. This enables him to begin to live again despite limited mobility; freed from the nightmare of constant pain, the last weeks or months of life take on a new look.

However, the doctor and other carers must be determined to succeed, and be prepared to spend time evaluating and re-evaluating the patient's pain and other distressing symptoms. In addition, a balance is needed between 'marking time' therapeutically (capitalising on the impact of improved sleep and morale) and pressing on decisively with further initiatives. If this skill is not developed, the doctor and patient become trapped in the 'one step behind' syndrome. Most of the right things will be done, but always several days or weeks too late. (Fenton, 1992, Hunt, 1977)

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