Management of cancer pain including interventions

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Management of cancer pain including interventions

- What is cancer pain?
- Common cancer pain syndromes at Royal Marsden
- Treatment of cancer pain
- Interventional treatments

What is cancer pain?

- ***"an unpleasant sensory and emotional experience in association with actual or potential tissue damage, or described in terms of such damage."***
- **Cancer Pain** caused by the disease itself or by treatments
- Pain can be **acute, chronic, breakthrough**
- **Chronic cancer pain** successfully treated in about 95% with drug and non-drug therapies
- Pain increases with disease progression
- Cancer pain is often **undertreated** (***BMJ, 1995, 51% inadequate***)
- Good cancer pain service = multidisciplinary

Cancer pain, 1985/6

The NEW ENGLAND JOURNAL of MEDICINE

Foley, NEJM, 1985

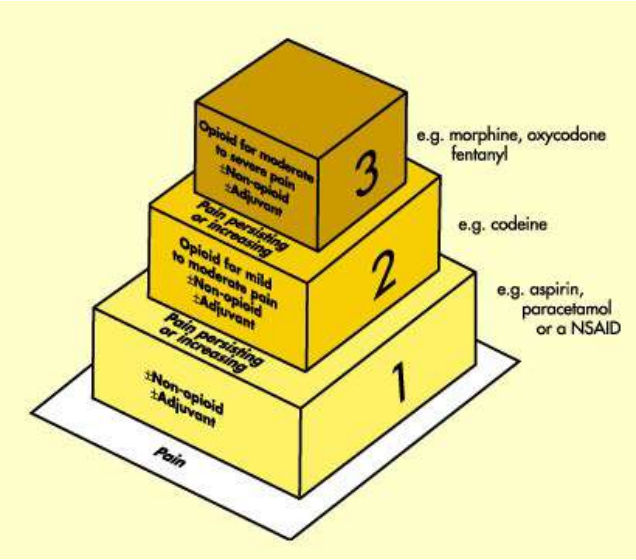
Pain is one of the most feared consequences of cancer.

Control of pain from cancer should be possible.

Pain management overshadowed by attempts at treating underlying disease

WHO ladder,1986

1. nonopioids
2. mild opioids +
3. strong opioids +



Prevalence of pain in patients with cancer: a systematic review of the past 40 year

Annals of Oncology, 2007, MHJ van den Beuken-van Everdingen

52 studies,> 6000 patients

Prevalence **of pain**

1. after curative treatment, **33%**
2. during anticancer treatment, **59%**
3. with advanced disease, **64%**

Conclusion:

Despite clear WHO recommendations, cancer pain still is a major problem.

Prevalence of undertreatment in cancer pain. A review of published literature

Annals of Oncology, 2008. S. Deandrea

- 26 studies, >1500 patients
- **Pain Management Index;** negative score in 43%
- **Conclusion:** Nearly one out of two patients with cancer pain is undertreated.
- AUDIT: proportion of patients who receive a painassessment

Classification of cancer pain

- **Cause:** tumour related, treatment related
- **Type:** neuropathic, nociceptive, psychological
- **Severity:** determines WHO stage

Is there any evidence that diagnosis of pain type influences treatment?

- **4 references indicate that pain diagnosis facilitates treatment**

(Grond, Assessment of cancer pain: prospective evaluation in 2266 patients with cancer, Pain, 1996)

Treatment of cancer- related neuropathic pain

1. **Dynamic pathophysiology** = ineffective treatments / spontaneous recovery & adaptation

2. **Neuropathic pain responds poorly to simple analgesics,** use adjuvants in the first instance

3. **Nerve compression** pain is more responsive to opioids than neural injury pain

Drug treatment according to mechanism

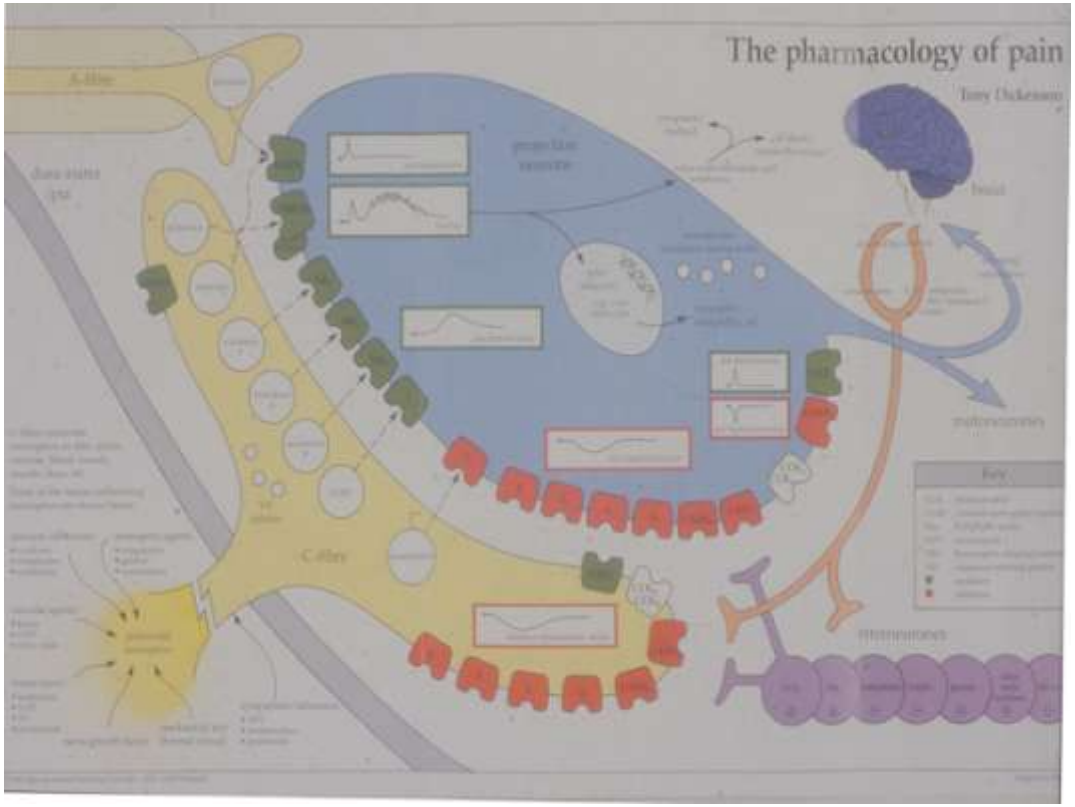
Mechanism	Symptom	Target	Drug
Sodium channel accumulation	Spontaneous pain, paraesthesia	Sodium channels	• Sodium channel blockers • Anti-epileptics • Blockers with greater analgesic than anticonvulsant index • Ion channel selective blockers
Central sensitisation	Tactile hyperalgesia Cold hyperalgesia Pin-prick hyperalgesia	NMDA Neurokinin NOS Protein kinase	• Ketamine, dextramethorphan, amatidine • Glycine site antagonists • Neurokinin, NOS + protein kinase antagonists
Peripheral sensitisation	Pressure hyperalgesia Thermal hyperalgesia Spontaneous pain	Vanilloid receptor Neurokinin Sodium channels Nerve growth factor	Capsaicin Neurokinin antagonist Sodium channel blockers
Alpha receptor expression Sympathetic sprouting	Spontaneous pain	Alpha receptor antagonists	Phentolamine Guanethidine
Increased transmission Reduced inhibition	Spontaneous pain hyperalgesia	Calcium channels GABA Adenosine	Opiates Gabapentin Clonidine Tricyclics

RCT evidence of effect of drugs on evoked pain

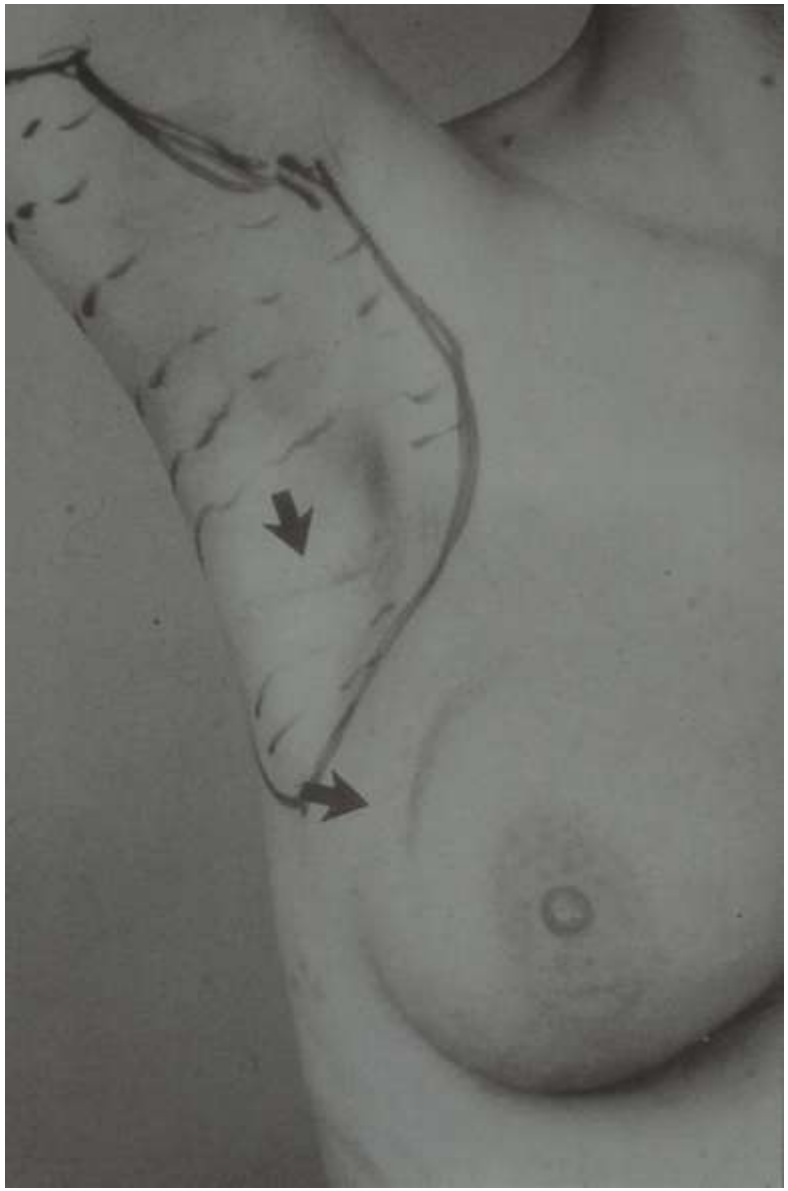
DRUG	EFFECT ON
Tramadol	Mechanical allodynia
Tricyclics	Mechanical allodynia
Gabapentin	Cold allodynia
Opioids	Hypersensitivity of skin
i.v. lidocaine	Mechanical allodynia
Topical lidocaine	Mechanical & thermal hyperalgesia

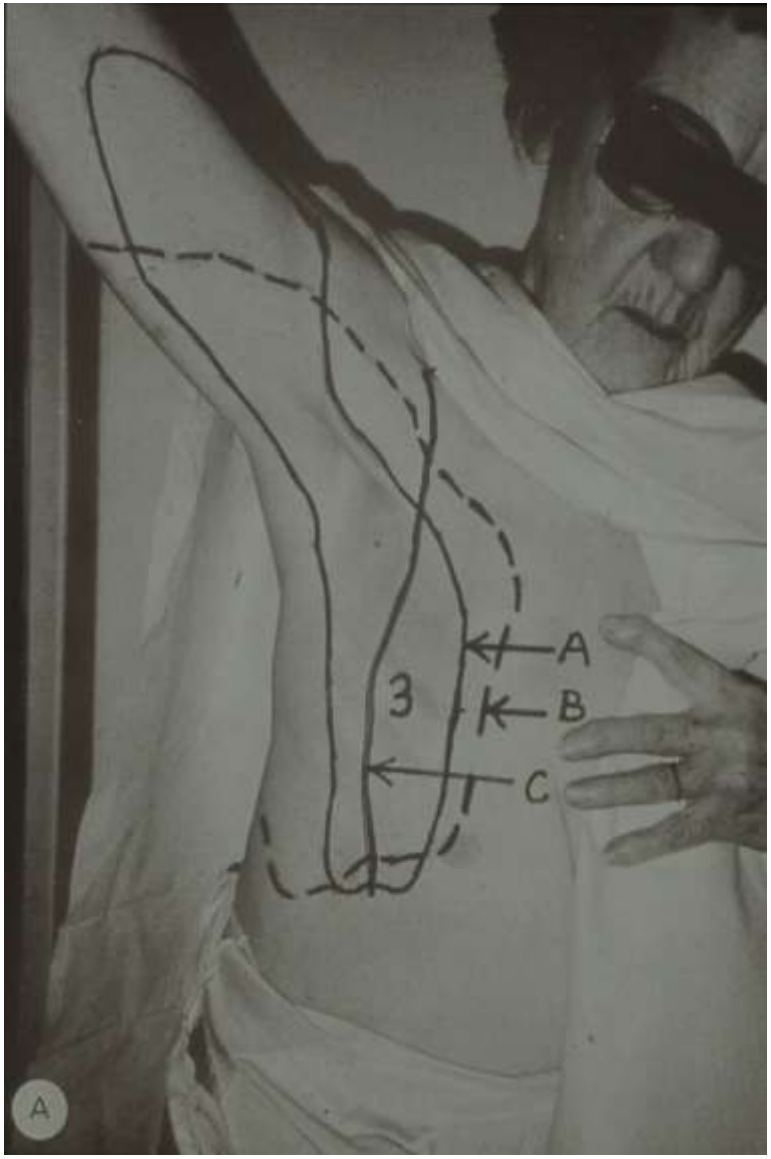
Common cancer pain syndromes at Royal Marsden

- Breast pain
- Amputations
- Head and neck
- Other cancer syndromes



Post surgical - breast




A
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B
C
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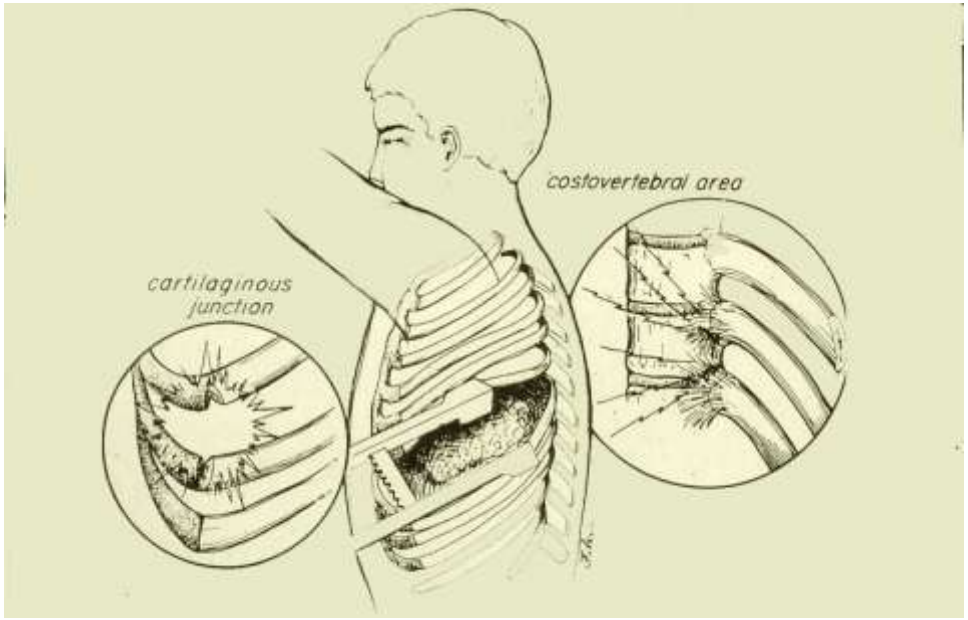
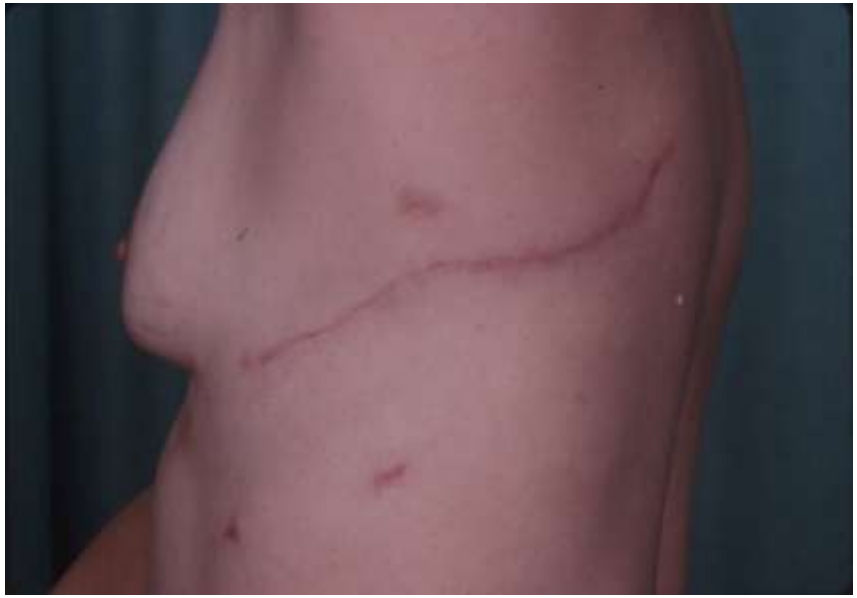
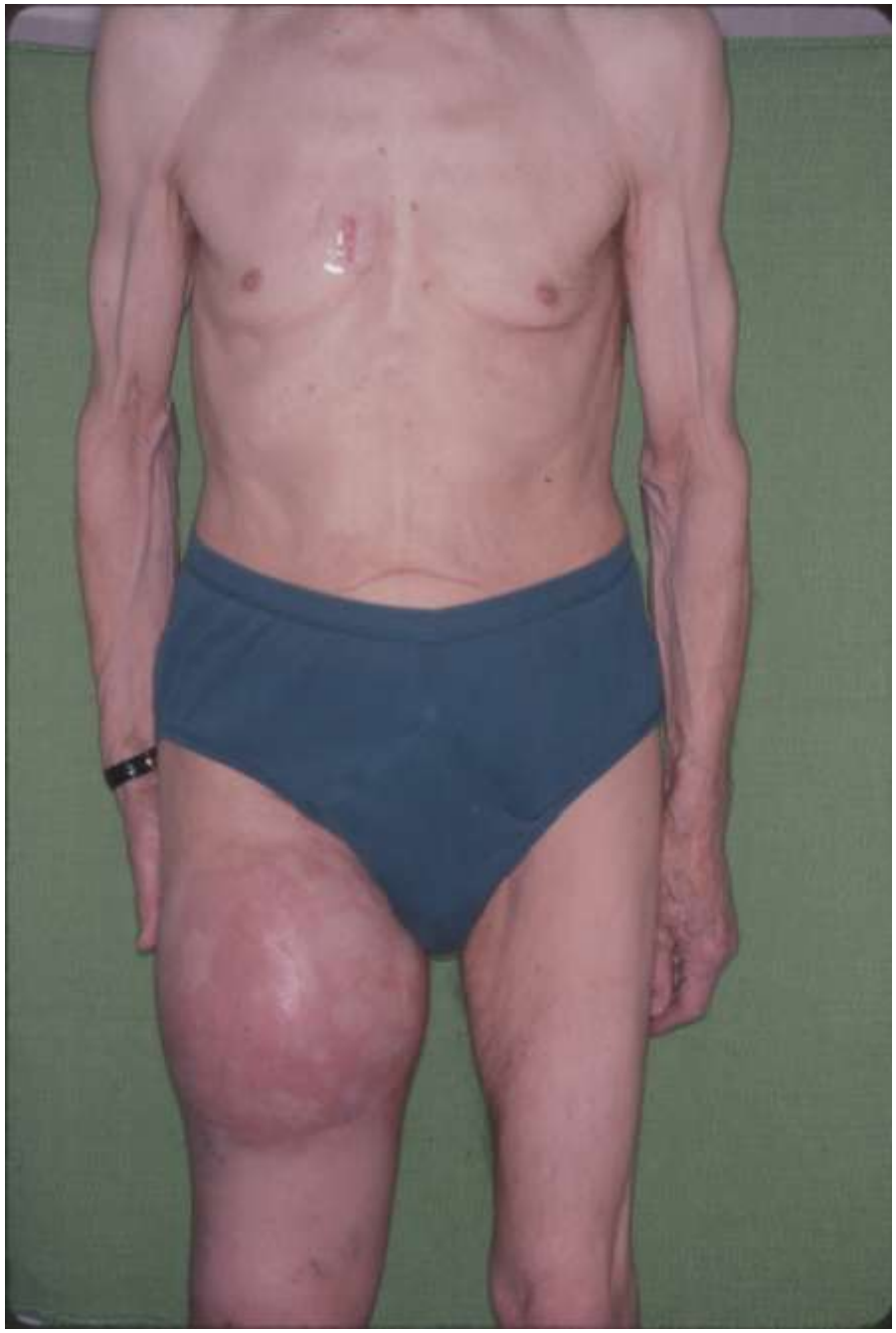
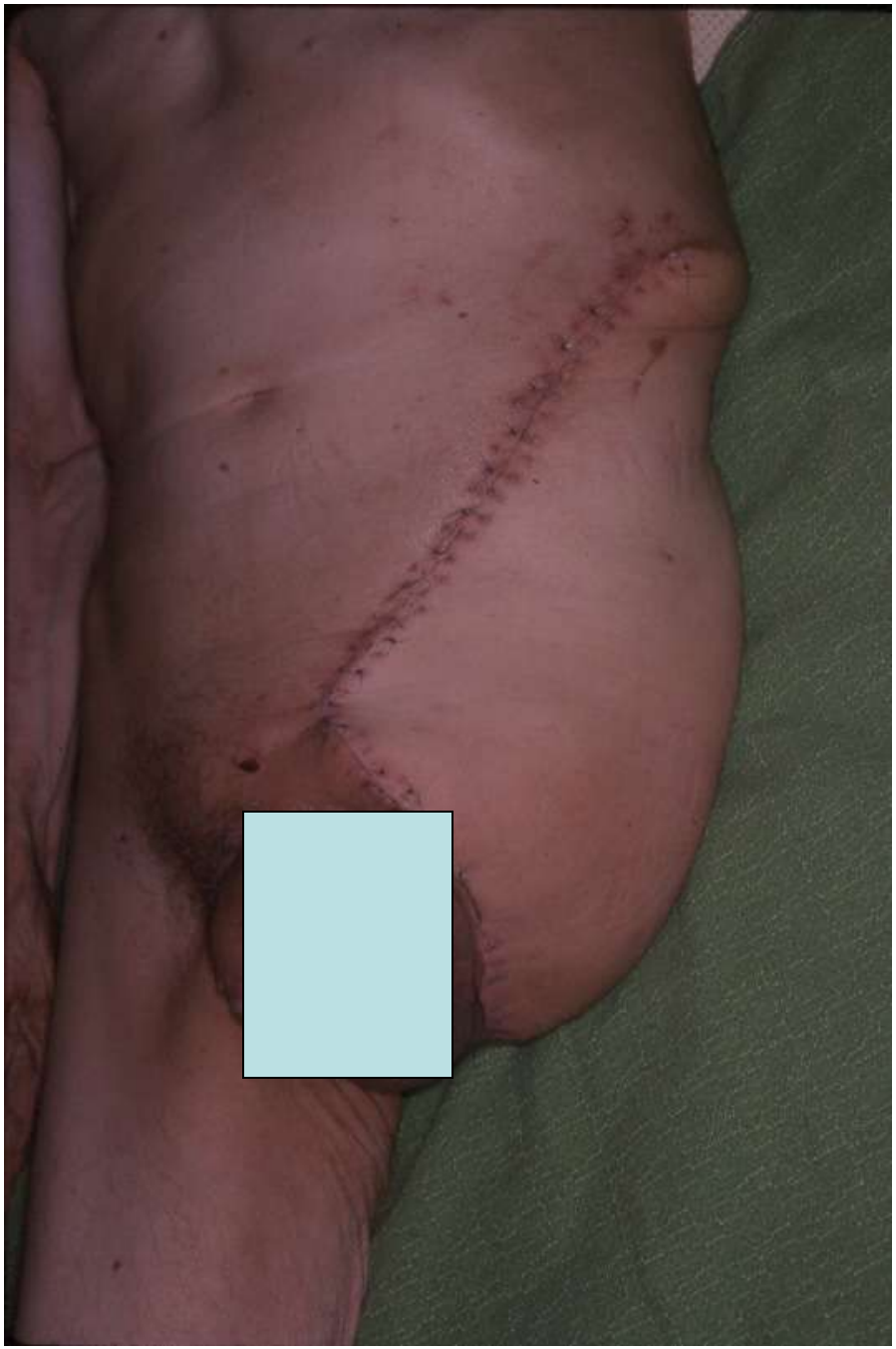

costovertebral area
cartilaginous
junction







Control of cancer pain

What evidence is there of the efficacy of radiotherapy in controlling cancer pain?

Numerous RCT's, SR's
SR: 50% additional pain relief (Cochrane 2000) + improved mobility+ minimal side effects
'all suitable patients should be referred for RT'

What evidence is there of the efficacy of vertebroplasty in controlling cancer pain?

A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures
August 06, 2009 |

Good evidence that it is <u>ineffective</u> in osteoporotic collapse *(RCT NEJM 2009, n=131, no sig benefit or difference @ 1 month)*

Anecdotal evidence for effectiveness in cancer collapse

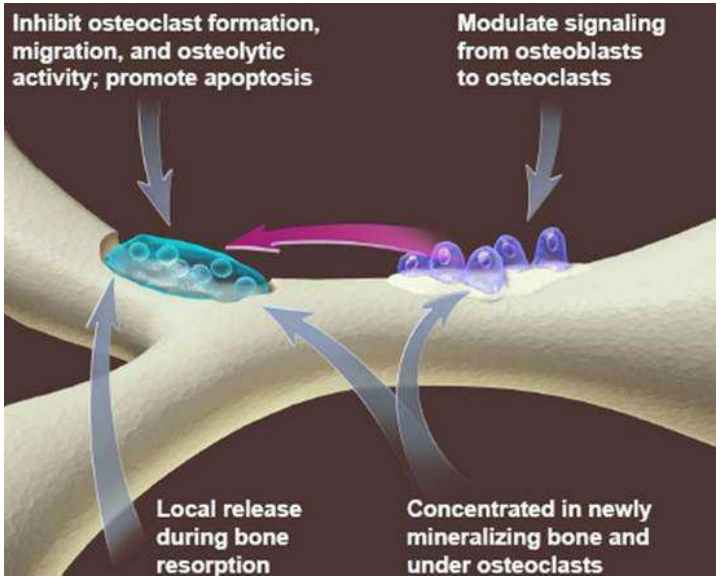
Bisphophonates

- effective for metastatic bone pain *(Cochrane 2006)*
- NB: renal toxicity, bone pain, osteoradionecrosis of jaw, hypocalcaemia
- use as part of multidisciplinary treatment plan

-***Research Questions:***

Which bisphophonate is best?
Optimum dose/route?
Efficacy compared with RT or analgesic drugs?
Efficacy in individual cancers

-AUDIT : proportion of patients with metastatic disease receiving bisphosphonates

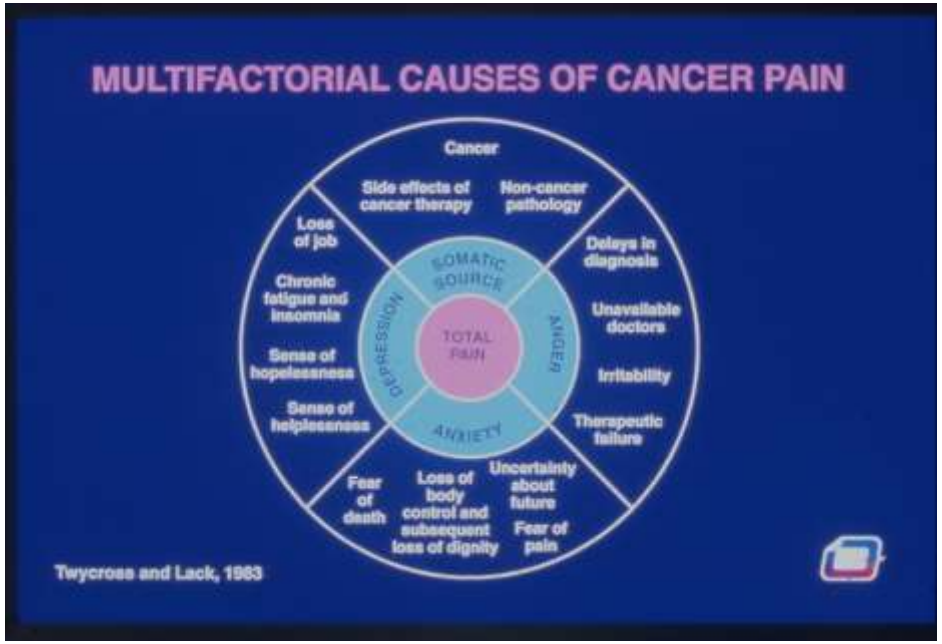


Bisphosphonates include:

pamidronate (Aredia®) and zoledronic acid (Zometa®) given by intravenous infusion, and alendronate (Fosamax®) and risedronate (Actonel®) given in tablet form.

Cancer pain treatment options

1. Physical
2. Drugs
3. Psychological
4. Complementary
5. Interventions



Psychological therapy

strong association between psych distress and cancer pain, **(SR, 31 studies , 2002)**

Is there any evidence supporting the use of cognitive behavioural therapy (CBT) rather than other psychotherapeutic approaches to reducing disability and distress in patients suffering cancer pain?

- **One meta analysis *(SR, Pain 1999, n=3,216 patients)* some benefit from CBT in cancer pain**

(NB strong evidence in non cancer pain)

- **CBT in breast cancer – some benefit *(SR, n=2,133 breast cancer patients, 2006)***
- **Poor evidence for impact of other therapies eg psychoanalysis *(SR, 2006)***
- **'CBT should be offered'**

Is there any evidence that would help identify <u>predictors of cancer pain</u> related distress and/or disability?

YES, an association with worse cancer pain - poor social support, catastrophising

NO association with cancer pain – pre morbid coping style
(SR, 2002)

Is there any evidence that treatment of anxiety or depression in cancer pain patients improves outcome?

Limited evidence

One study: 'treat depression and the pain improves'
(SR, BJC, 2006)

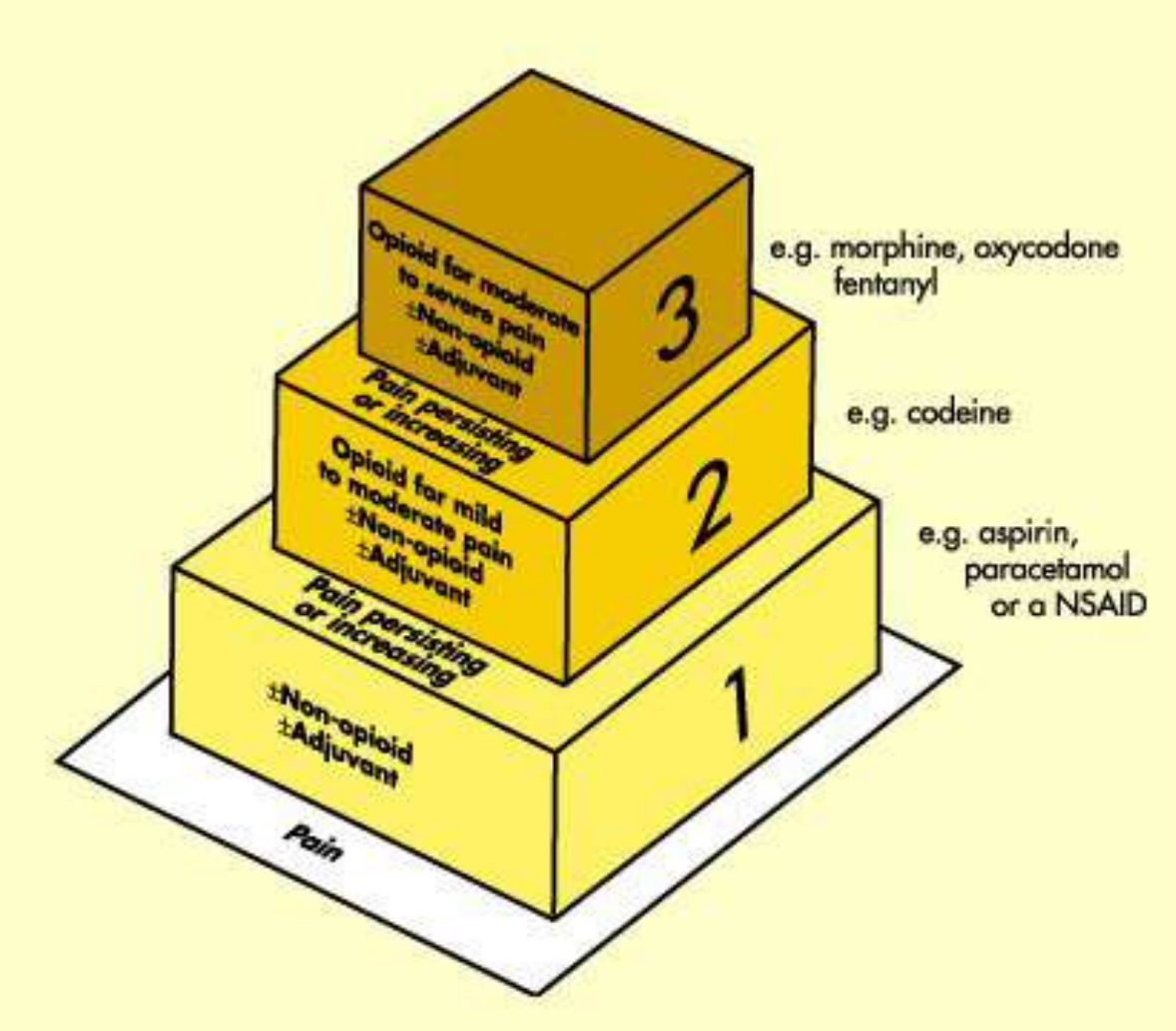
Is there any evidence supporting specific psychological factors as predictors of adherence to treatments for cancer pain?

Yes, strong belief in pain medicine = better adherence to analgesic regime *(JPSM, 2002)*

Is there any evidence that education of patients and/or health care professionals is effective in changing health beliefs in relation to cancer pain treatments?

Meta analysis showed that 'education of patients' is effective….similar to effect of paracetamol *(Bennett, SR n=3,501, Pain 2009)*

WHO ladder


Opioid for moderate to severe pain
±Non-opioid
±Adjuvant
3
e.g. morphine, oxycodone fentanyl
Pain persisting or increasing
Opioid for mild to moderate pain
±Non-opioid
±Adjuvant
2
e.g. codeine
Pain persisting or increasing
±Non-opioid
±Adjuvant
1
e.g. aspirin, paracetamol or a NSAID
Pain

Paracetamol & NSAID's

Paracetamol; additional benefit in patients on strong opioids

(RCT n=30, sig improvement in patients already on a strong opioid regime, 2004)

NSAID's: 'effective' ***(Cochrane 2006…but no evidence of hierarchy)***

'Use at all stages of WHO ladder'

NSAID's *(Drug & Therapeutics Bulletin, Jan 2005)*

- *'Unqualified assertions that COX 2 are a class safer than NSAID's are untenable'*
- *'COXIB's less dyspeptic symptoms, less endoscopically visible erosions & lower likelihood of upper gi bleeding'*
- *'However longer term outcome studies – no significant reduction in major ulcer complications'*
- *'Possible increase in serious CVS events'* (withdrawal of rofecoxib)
- *'Few, if any indications for a COXIB'*
- *'All NSAID's potentially dangerous' (especially in cancer)*

What evidence is there to identify the best gastroprotective drugs to be prescribed along with NSAIDs?

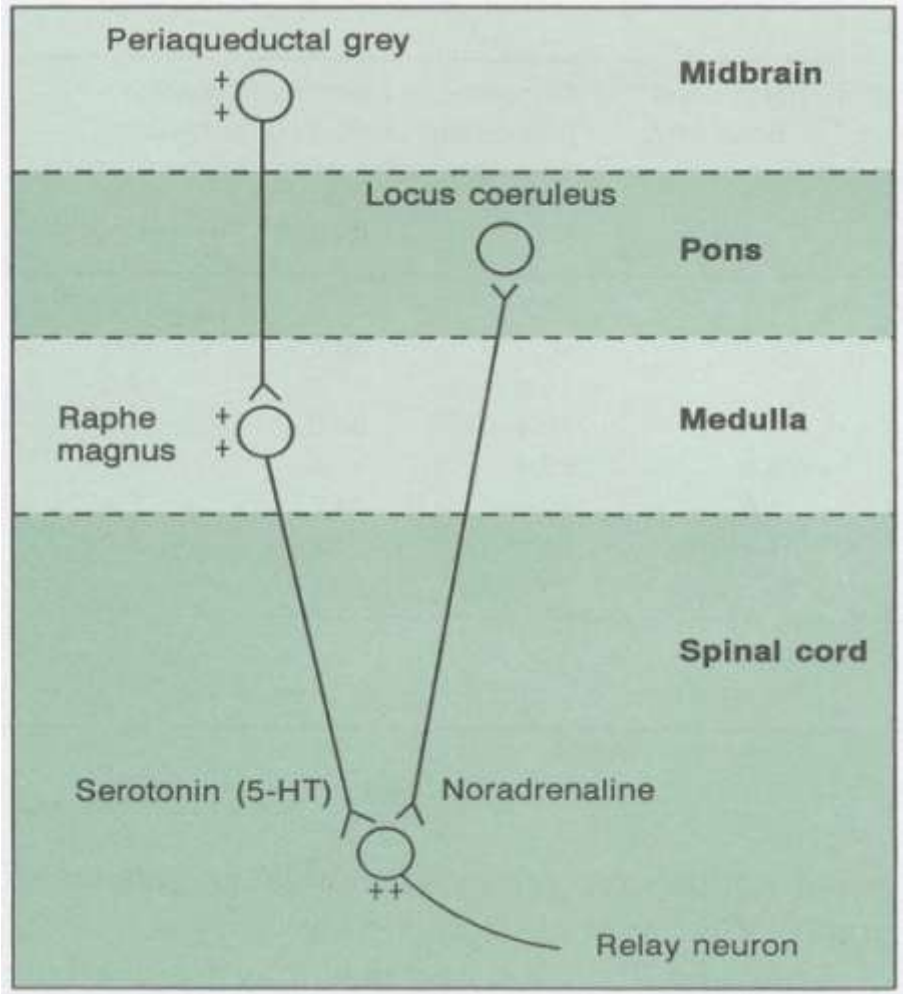
Ibuprofen
COX-2
(anecdotal reporting, 2007)

Misoprostol 800mcg/day
PPI's (lansoprazole 30mg/day)
Double dose H2 receptor antagonists (Ranitidine 300mg/day)

Antidepressants

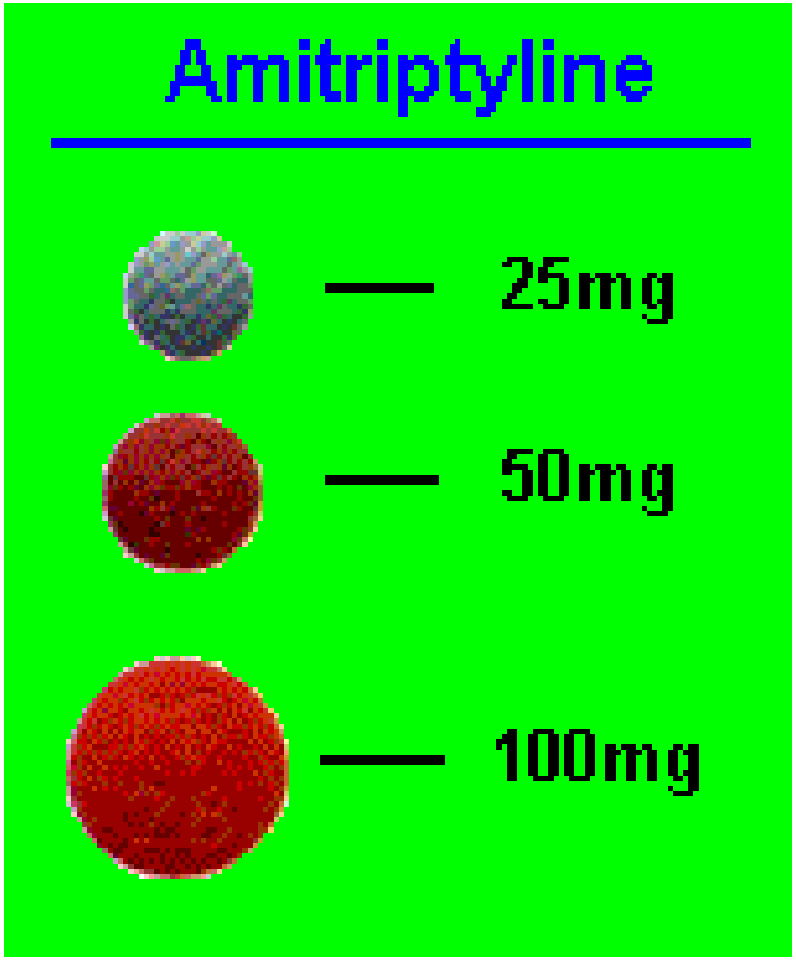
- **Unlicensed indication**
- **Analgesic properties**
- **Poorly understood**
- **Target dose;**

amitriptyline 50mg/day



Amitriptyline - evidence for efficacy

- 16 RCT's
- **NNT 3,** NNH 3
- 2 RCT's *ineffective* in HIV pain



Antidepressants

1. which drug is best ?

2. SSRI's (***fluoxetine, citalopram***) better than TCA's ? SNRI's (***venlafaxine***) ?

3. analgesia or mood alteration ?

4. comparison with anticonvulsants ?

5. dose range + titration ?

6. character of pain predictive of response ?

7. speed of onset 1 - 7 days

8. adverse effects problematical

Which antidepressants/ anticonvulsants have been shown to be effective in the treatment of cancer pain?

Antidepressants:

effective in neuropathic pain *(Cochrane 2007)*

2 RCT's in cancer-related neuropathic pain

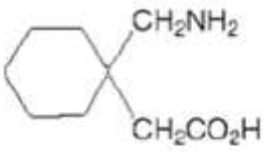
Insufficient evidence for SSRI's

Duloxetine : licensed in PDN, 60mg/day

Anticonvulsants

2 positive systematic reviews in neuropathic pain *(Cochrane 2006, 2007)*

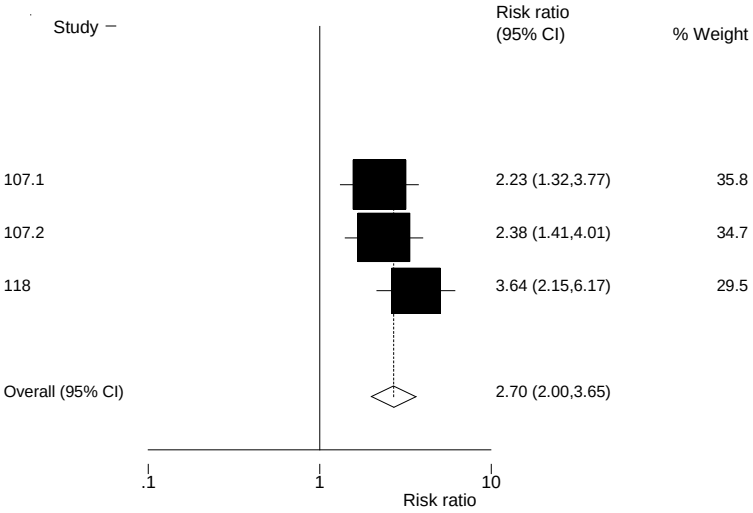
Gabapentin



- Licensed for all types of neuropathic pain
- Calcium channel blocker,increase GABA synthesis + reduce Glu
- 8 RCT's
- Significantly reduces pain
- **NNT 3.2**
- dizziness + somnolence + gi upset + weight gain

(Drug & Therapeutics Bulletin, 2000)

Starting dose	200-300mg per day
Escalation	100-300mg every 3 days
Target dose	900-1800mg/day
Max dose	1800mg/day (UK) 3600mg/day (US)



Pregabalin (Lyrica)

Indication	Peripheral neuropathic pain
Starting dose	75mg bd
Target dose	300mg – 600mg/day

Research Question:

Is pregabalin more effective than gabapentin in neuropathic pain?

Peri-operative Venlafaxine in the prevention of postmastectomy pain syndrome

Reuben, J Pain & Symp Manage, Feb 2004; 27;133-139

- 100 breast surgery patients

- **Venlafaxine 75mg**

for 2 weeks, starting night ***before*** surgery vs. **placebo**

- **Significant reduction in chronic pain @ 6 months in venlafaxine group**

Pain research fraud

- Fabricated 21 studies (over 3000 citations)
- Pleaded guilty
- Sentenced to 6 months prison (June 2010), fined $410,000

Neuropathic pain treatment

(Dworkin et al, 2003)

First line

- **Gabapentinoids**
- **Tricyclics**
- **Opioids**
- **Tramadol**
- **5% lidocaine patch**

& COMBINATIONS

Second line

- **Anticonvulsants**
- **SSRI's**
- **SNRI's**
- **Capsaicin**
- **Mexiletine**

Neuropathic pain treatment

(Dworkin et al, 2007)

First line

- Gabapentinoids
- Tricyclics
- 5% lidocaine patch

Second line

- Tramadol/ other opioids
- Capsaicin
- Mexiletine

Combine & individualise

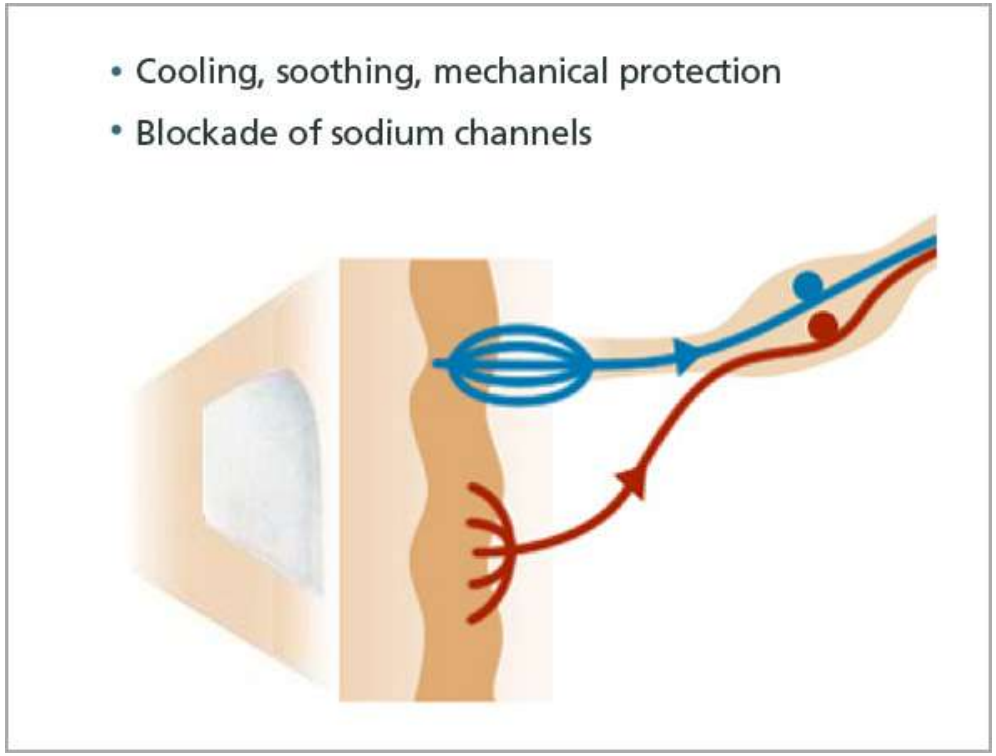
AUDIT: proportion receiving these drugs

Lidocaine plaster

- no evidence for effectiveness in cancer pain
- more effective than placebo in 2 RCT's in PHN

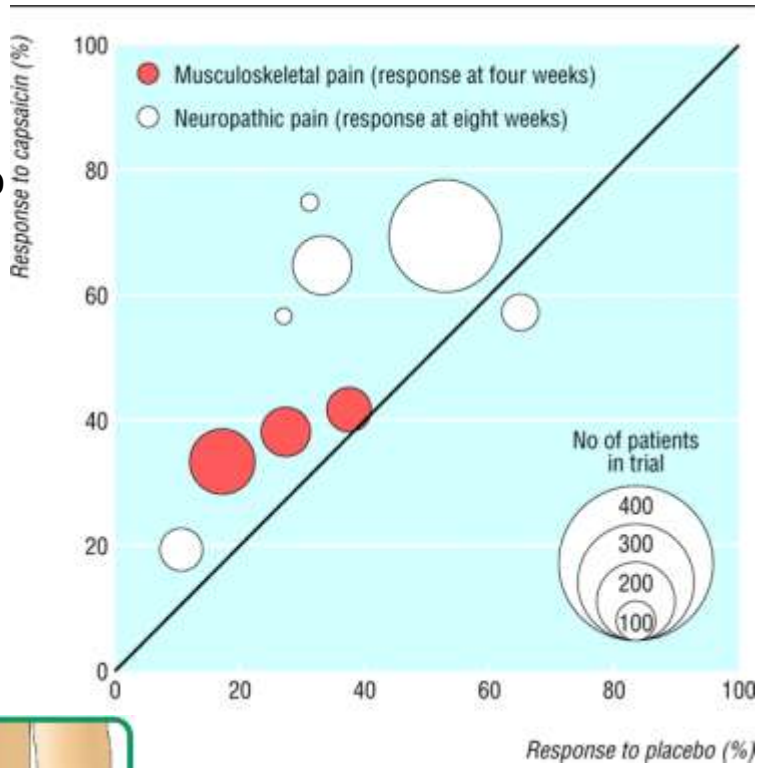
-? Better than anything else we already use?

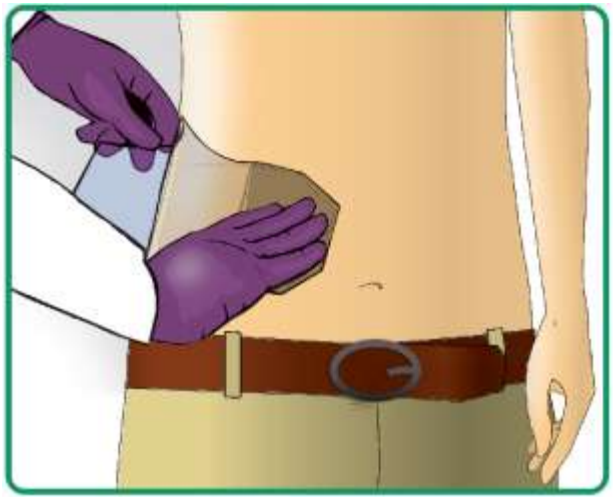
-? What about EMLA?

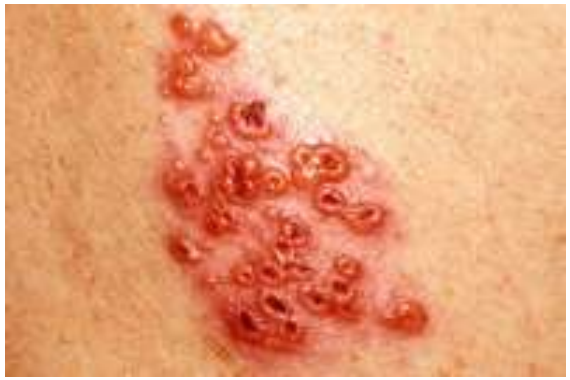


Capsaicin 0.075% cream

- licensed for PHN, diabetic neuropathy
- 3/5 RCT's (n=338) showed benefit over placebo in neuropathic and musculoskeletal pain
  (SR, BMJ, 2004)
- **NNT 5.8**
- **Qutenza 8% Capsaicin single shot (100x stronger)**







Ketamine

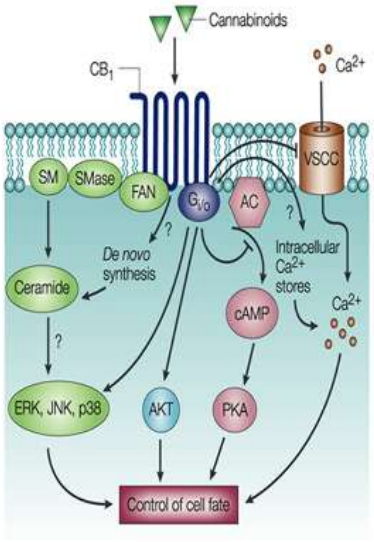
- **2 RCT's ; insufficient evidence**

- ***Cochrane review, 2006***

'useful in special situations'

<u>Research Question:</u> 'what is the role of ketamine as an adjuvant analgesic?'

Cannabinoids



Nature Reviews | Cancer

- <u>Not recommended</u> for the treatment of cancer pain
- Currently being researched
- THC available & licensed in USA
- Systematic review, n=128 cancer pain patients *(BMJ, 2001) 'as effective as codeine 60mg'*
- *2 RCT's in HIV (smoked) , MS (nasal spray) effective neuropathic pain*

Opioid responsiveness

- 1986 ‘*dull pain more responsive than sharp’*
- 1994 *‘a continuum of opioid responsiveness* + *dose-responsiveness’*
- 5 RCT’s since 1984
- 2 placebo-controlled RCT’s of Oxycodone, **NNT 2.5**
- ***Our guidelines***; use early, use in conjunction

Opioids & neuropathic pain; hierarchy

1. **Co-codamol / Tramadol**
2. **Morphine**
3. **Oxycodone**
4. **Fentanyl patch**
5. **Methadone**

(Buprenorphine patch- not recommended in cancer pain – some evidence for efficacy in osteoarthritic pain,)

WHO step 2

- **Codeine ceiling effect 240mg/day..therafter side effects only increase**
- **Co codamol 30/500 – better than paracetamol alone**
- **Tramadol vs Morphine (2001), comparable effect at equianalgesic doses (1:4)**
- **Overall – limited evidence to clearly define position in cancer pain**
- **Research question: benefit of omitting Step 2?**

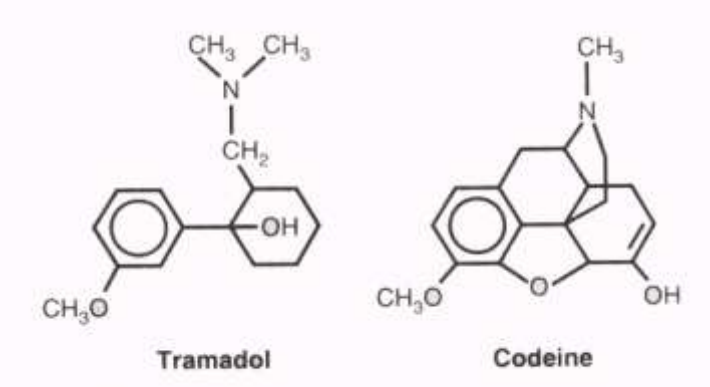


Fig. 1. Structural formulae of tramadol and codeine.

ULTRACET
(37.5 mg tramadol HCl
325 mg acetaminophen tablets)

Morphine

Starting dose	5-15mg/day
Target dose	After 1-2 weeks convert to slow release & PRN immediate release
Duration of adequate trial	4-6 weeks

Oxycodone

Indication	Moderate- severe pain neuropathic pain (RCT evidence)
Starting dose	5-10mg/4hrs

Oxycodone

– why choose oxycodone instead of morphine ?

- No clinical evidence (yet) of superiority over morphine in effect or side effects
- Switch *(oxycodone- cp450 system as opposed to glucuronidation)*
- Less first pass metabolism, greater oral bioavailability – more consistent clinical effect
- Less variability in plasma concentrations, more predictable & reliable pharmacokinetic profile
- Longer half-life than morphine, 3-5 hours after oral administration, administer every 6 hours

Strange facts about Oxycodone

- In clinical use since **1917**
- Used in the USA for

80 years as **Percocet** & **Percodan**

- In Finland,

main parenteral opioid for acute pain

- Not efficacious spinally

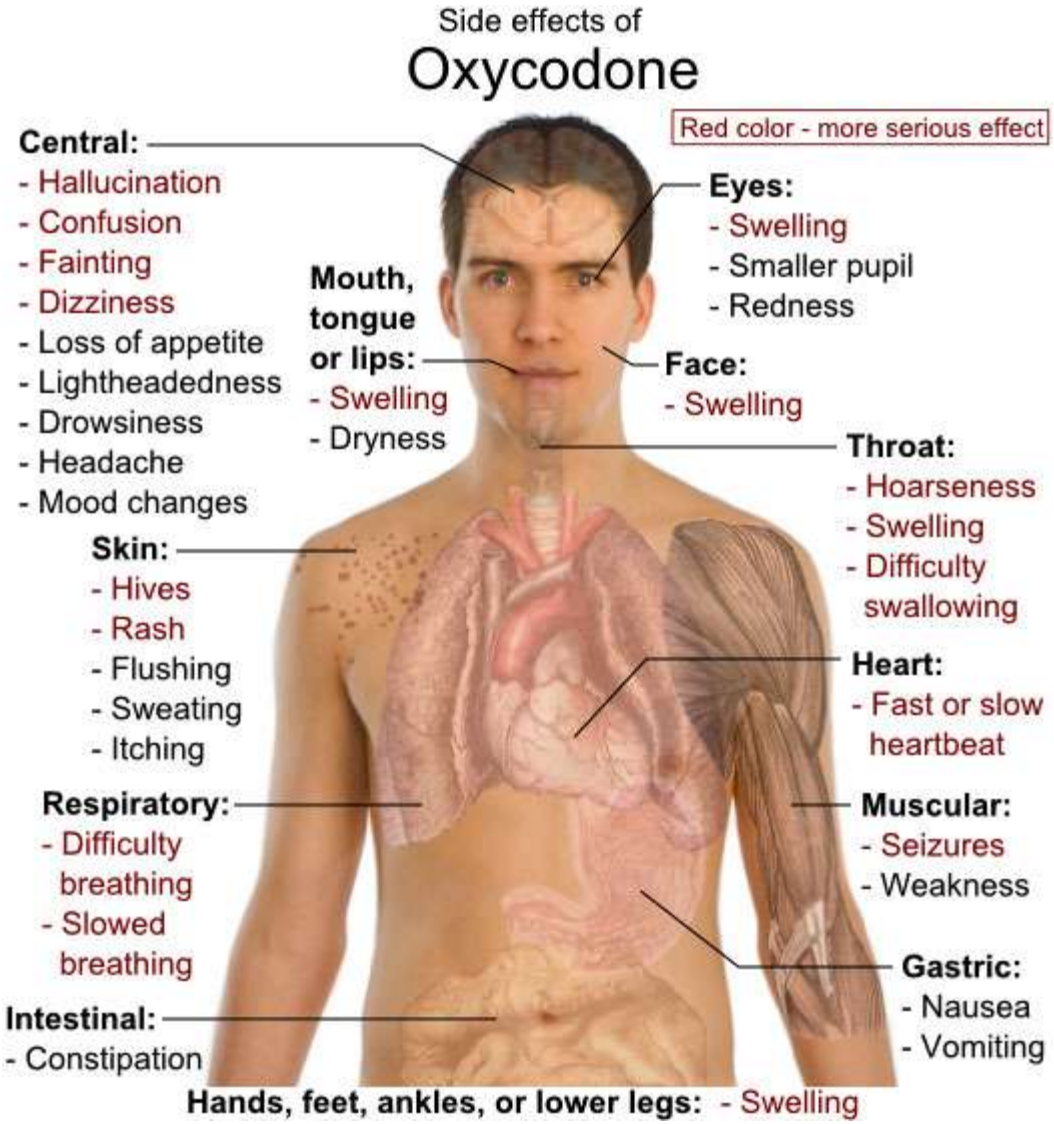
- 2009…Purdue

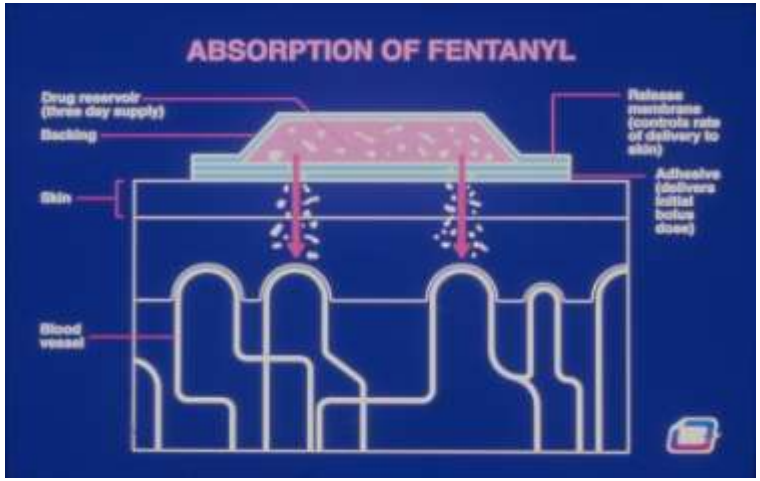
(CEO, top lawyer& 3 execs)
pleaded guilty to
'falsely marketing the drug and failure to warn of addiction'

- Fined $639m

- $10bn in US sales 2000-2010
- Company working on less

addictive preparation of Oxycontin





Fentanyl patches

'recommended as second line to oral strong opioids'

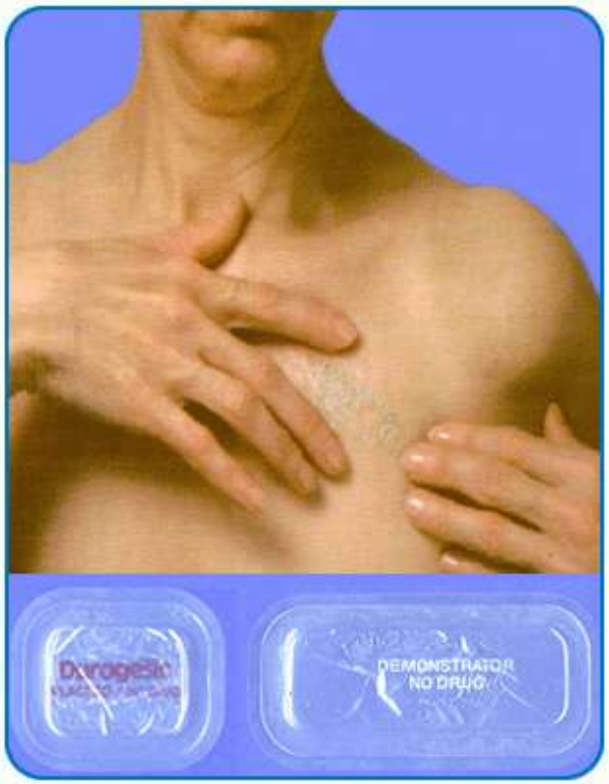
Useful for steady-state pain

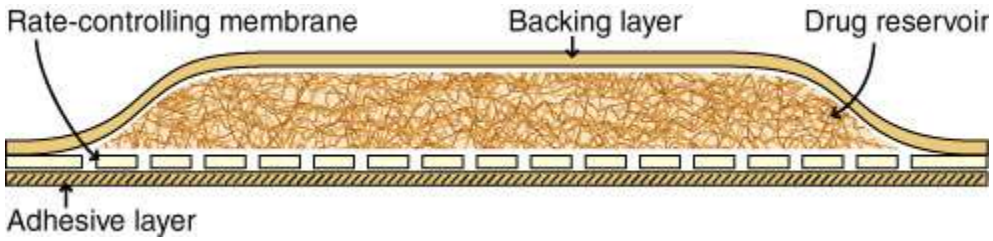
Head and neck cancer pain

Leave on during operations (personal opinion)

What evidence is there of equivalence in analgesic effect and pharmacokinetics between fentanyl gel filled patches and fentanyl matrix patches?

RCT showed similar effects





Opioid prescribing

When opioid doses are titrated upwards, is there evidence for the percentage increment which should be used? If so, does the percentage increment vary at different dose ranges, or with different opioids?

Start with oral morphine 5-10mg
Caution with adding up all breakthrough doses especially in patients with 'incident' pain

Opioid prescribing – conversion ratios

What is the evidence for conversion ratios between different opioids?

Some good evidence for commonly used drugs

What is the evidence for the current conversion ratios used when converting from one route of opioid administration to another?

Individual drugs (good for oxycodone)

What is the evidence that supports the current practice of reducing the dose of the new opioid by one third when converting from one opioid to another?

Anecdotal – equianalgesic dose ratio's can vary considerably

oral morphine to oral oxycodone	**Divide by 2**
oral morphine to subcutaneous morphine	**Divide by 2**
oral morphine to subcutaneous diamorphine	**Divide by 3**
oral oxycodone to subcutaneous morphine	**No change**
oral oxycodone to subcutaneous oxycodone	**Divide by 2**
oral oxycodone to subcutaneous diamorphine	**Divide by 1.5**

Opioid switching

What evidence is there that opioid switching can improve pain control/reduce side effects?

No strong evidence…yet

Research question: what is the value of opioid switching?

Clinical practice

1. **Document reasons for switch**
2. **Manage side effects with other drugs**
3. **Consider other drugs/treatments**
4. **Some symptoms resolve within a few days**
5. **SR *(Quigley, Cochrane 2004, Mercadente 2006)* showed 'poor prescribing practices, other causes of toxicity, switching route as well as drug'**

Breakthrough pain

What is the optimum choice/dose/timing/route of administration of short acting opioid to provide effective analgesia for incident pain

Anecdotal- 1/6th of total daily dose

OTFC – should be titrated independently of background pain

Which is better…individual titration of breakthrough pain or fixed dose prescribing?

Which is the best choice of opioid used for breakthrough pain (ie if morphine is used for maintenance analgesia, should it be morphine for breakthrough analgesia or another opioid)?

Limited evidence – use the drug that best suits the patient e.g. OTFC for fast acting pain control

AUDIT: proportion prescibed breakthrough meds

Treatment of opioid induced side effects

What is the evidence supporting the recommendation of different antiemetics in the control of opioid induced nausea and vomiting?

Not tested
Trial and error
Patients should have access to prophylactic antiemetic

What is the evidence supporting the recommendation of different laxatives in the control of opioid induced constipation?

Not tested
Trial and error
Prescribe routinely

Is there any evidence that the route or schedule of administration of opioids influences the efficacy of treatment?

Low quality evidence
Use oral route
S/c equally effective = i.v.
Consider topical
Stable pain…use MR

Combination therapy;

Morphine, Gabapentin or their combination for neuropathic pain

‘Gabapentin & morphine combined achieved better analgesia at lower doses of each drug than either as a single agent’

Gilron, N Engl J Med 2005;352:1324-34

Practicalities of prescribing

- Have **several drugs** in your armamentarium
- **Start low, go slow**
- Use **adequate doses** according to tolerability
- **Combine** drugs early
- Check **compliance**, offer advice, correct misconceptions
- **Liaise with GP**, detailed recommendations
- **Discuss goal** of treatment prior to treatment

The New England Journal *of* Medicine
August 19, 2010

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Conclusions

Among patients with metastatic non–small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end of life but longer survival.

Other therapies; neurosurgery

- **Neuroablative**

DREZ-lesions

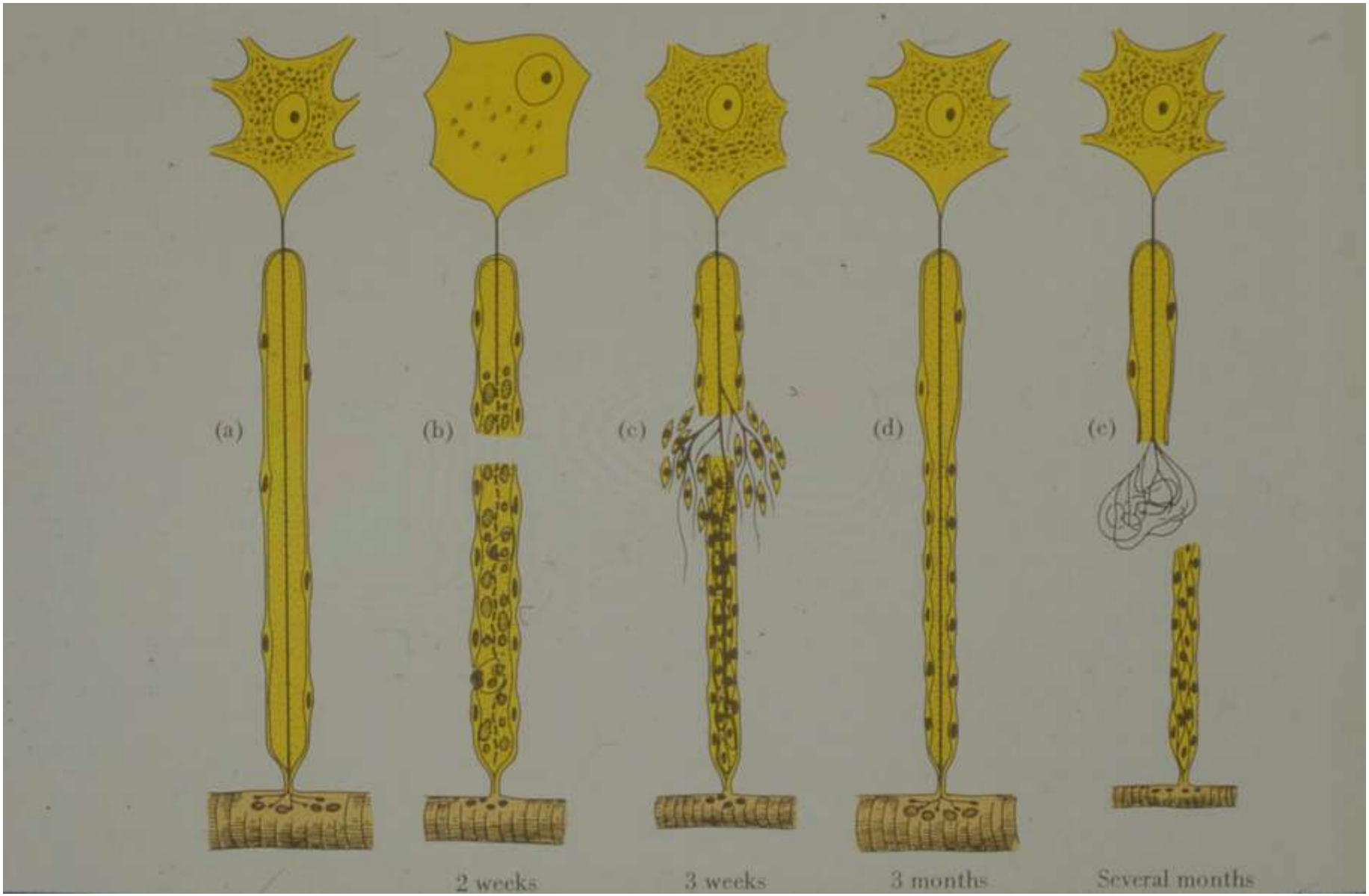
Neurolytic

- **Modulative**

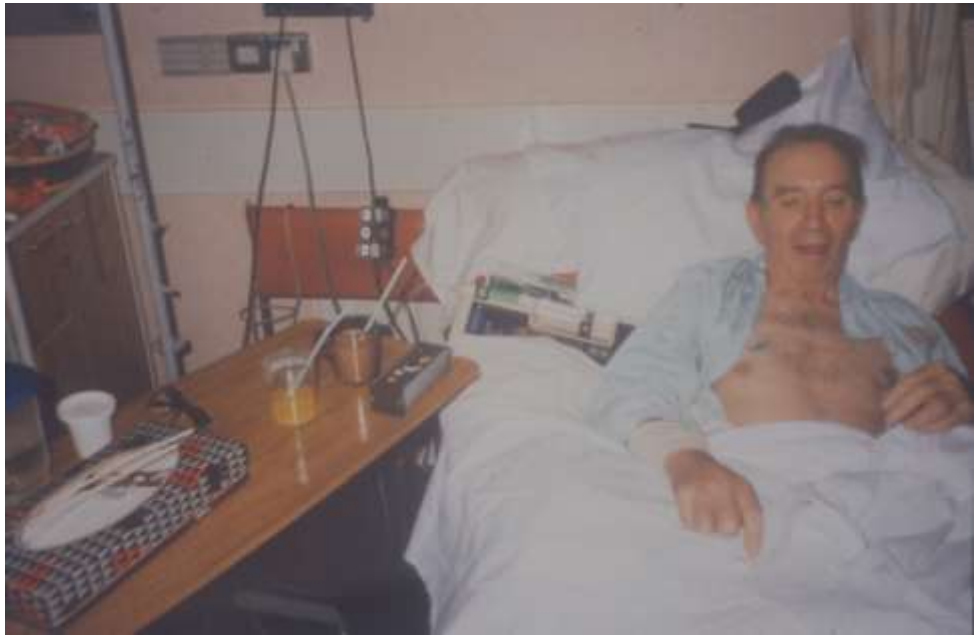
TENS

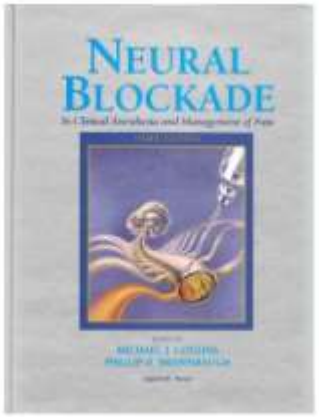
dorsal column stimulator

intrathecal pumps


(a)
(b)
(c)
(d)
(e)
2 weeks
3 weeks
3 months
Several months

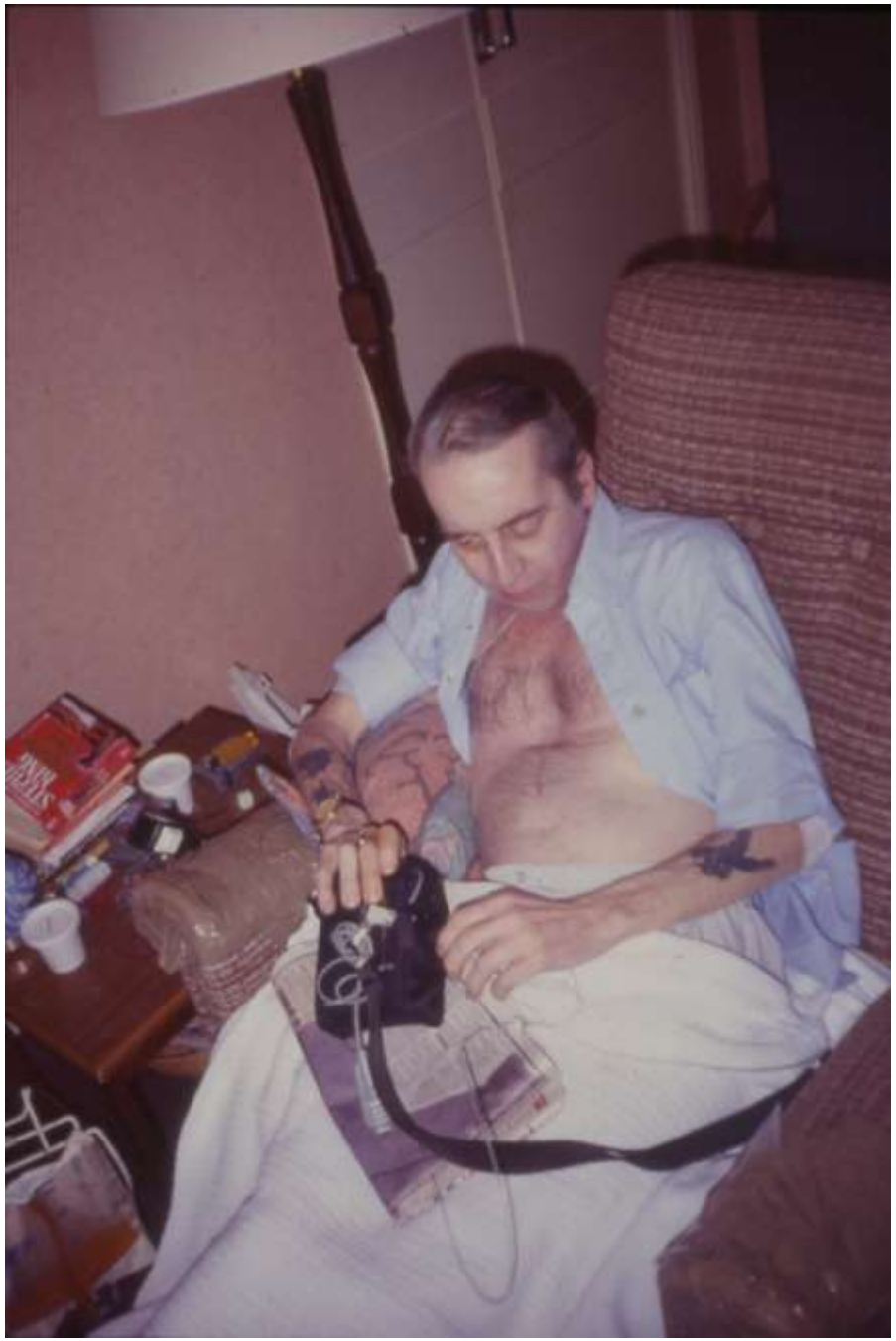
Neuraxial drug delivery

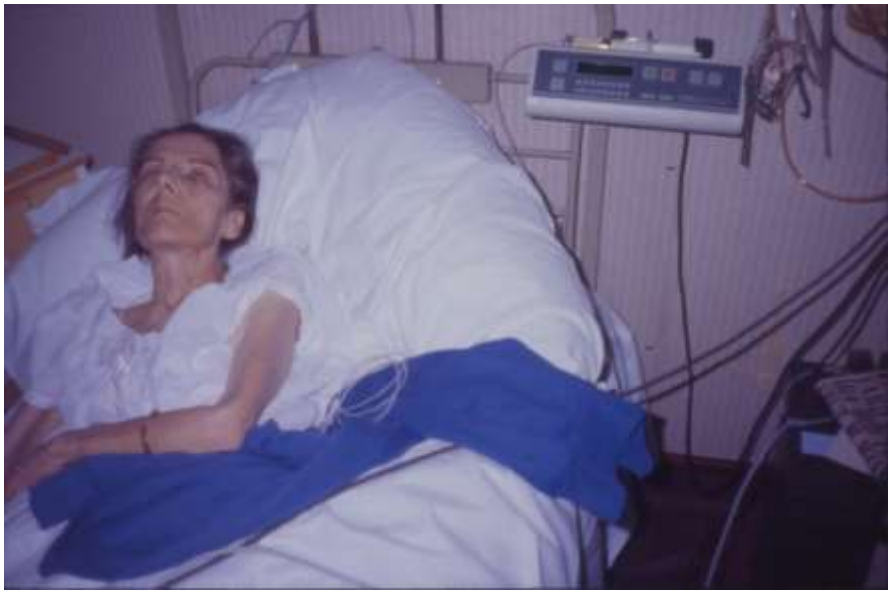


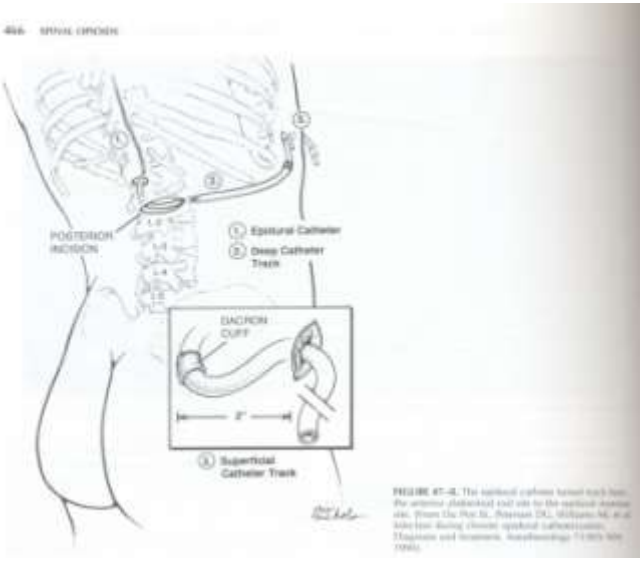


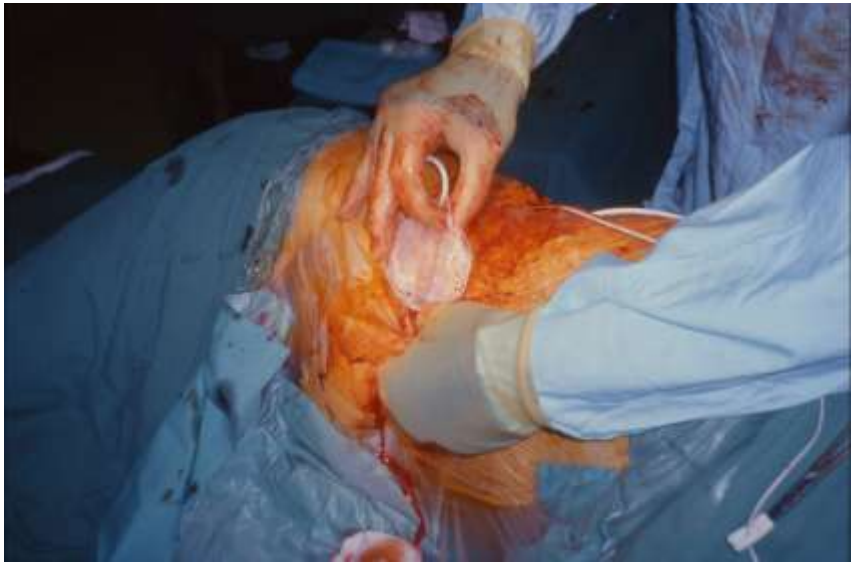
- *'Selective spinal analgesia' 1979*
- Pumps, 1-5
- Morphine, bupivacaine,clonidine ziconotide
- Epidural vs. intrathecal
- Follow-up, efficacy, adverse effects

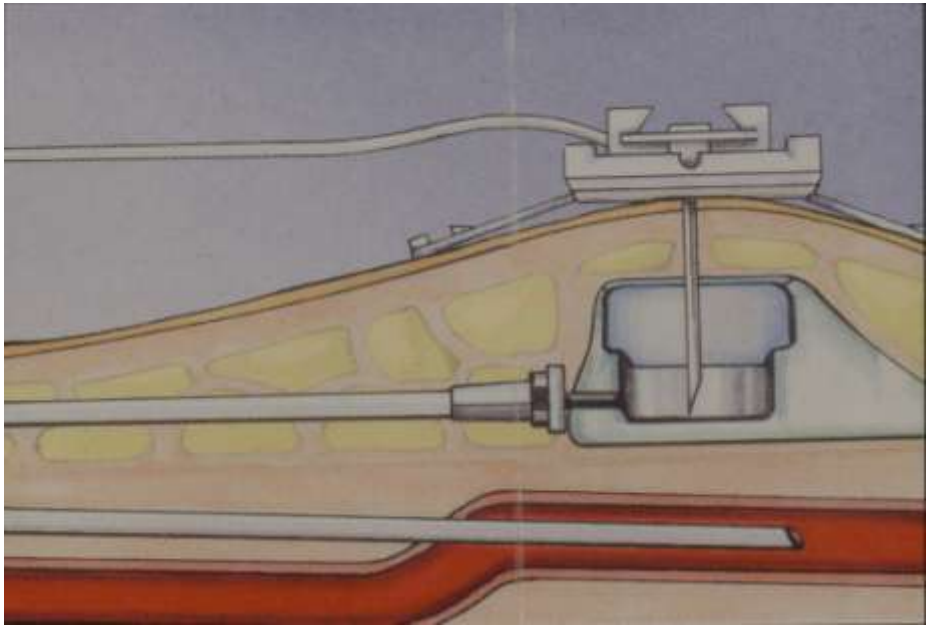
Oral	Parenteral	Epidural	Intrathecal
300mg =	100mg =	10mg =	1mg

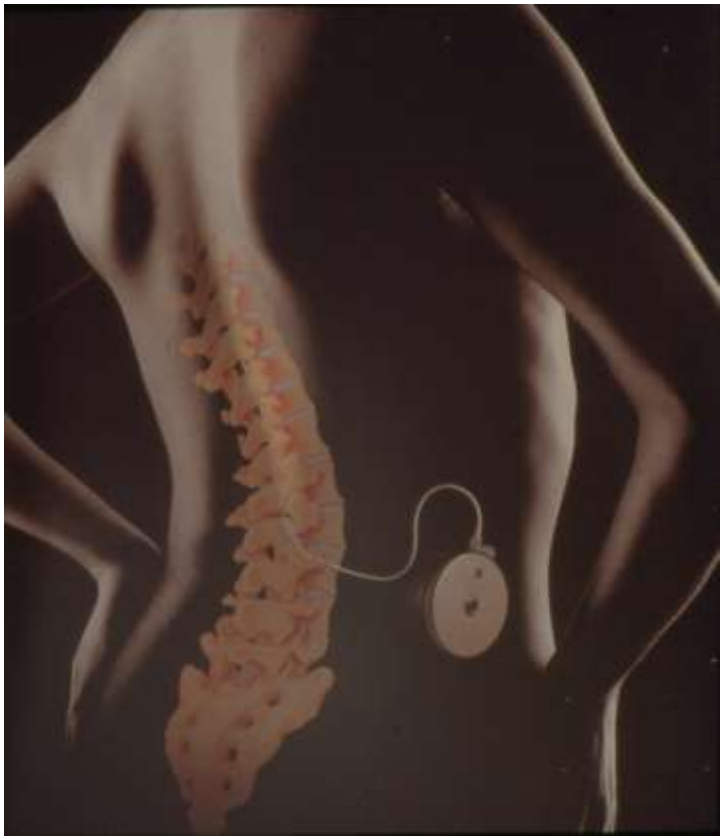


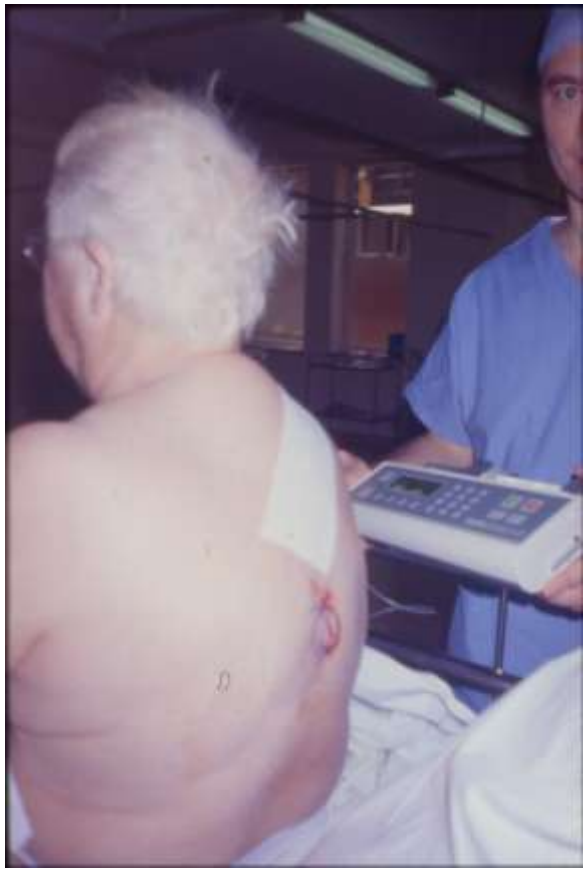


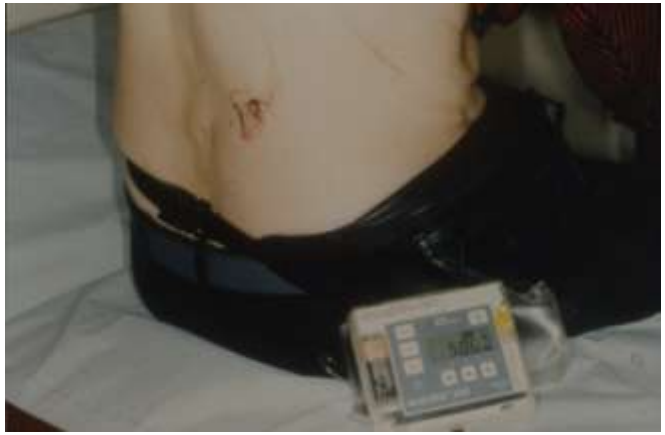

POSTERIOR INCISION
1 Epidural Catheter
2 Deep Catheter Track
DACRON CUFF
3 Superficial Catheter Track











Characteristics of patients who might benefit from Intrathecal Drug Delivery

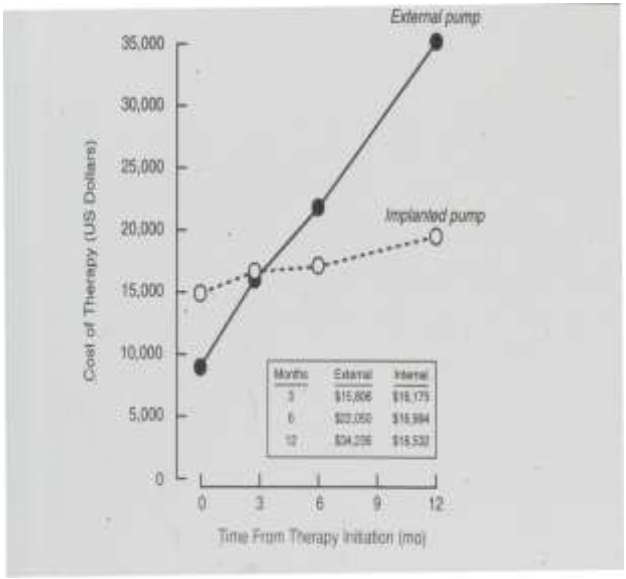
1. Pain refractory to oral treatments
2. Inability to tolerate adequate oral medications

3. Presence of visceral tumours that result in pain, anorexia, gut dysmotility
4. Severe neuropathic pain (plexopathies)
5. Acute unstable pathologic fractures
6. Complex regional pain syndromes secondary to surgery, chemotherapy, or radiation treatment

Drug delivery systems

1. Disposable short-term, tunnelled intrathecal catheter

- Can be implanted on ward, hospice, palliative care unit
- Minimal cost, quick, minimal discomfort
- Useful for life expectancy < 3 months
- After this, requires constant home-health monitoring which is expensive



2. **Long term (>3 months) implantable infusion pump and catheter system with programmable functions**

Smith TJ et al J. Clinical Oncology, 2002

Medical management & Intrathecal opioids

Medical management

- ‘Better pain control’
- ‘Less toxicity’
- ‘Improved survival’

….than with medical management alone

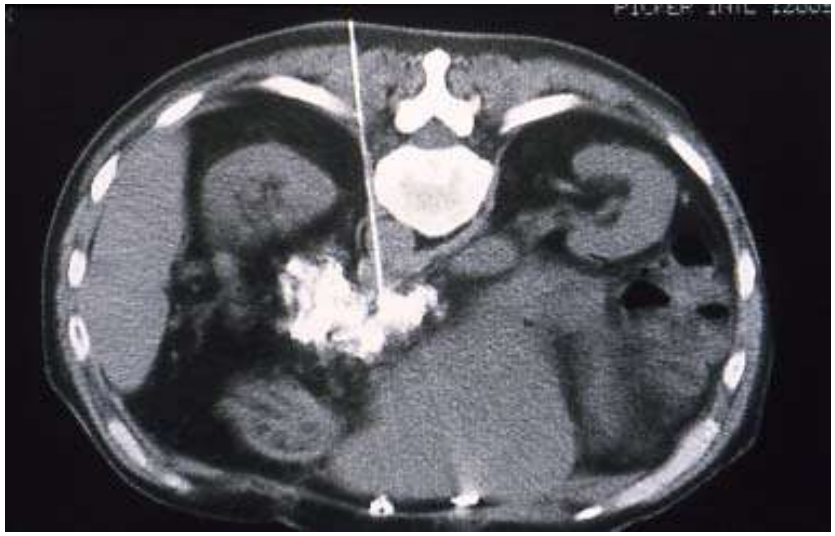
Is there any evidence for the effectiveness of anaesthetic interventions for control of cancer pain?

Some RCT evidence for coeliac block (2 RCT's, 2 Cohort studies, analgesic effect but no reduction in opioid dosage)

Weaker evidence for Neuraxial (one positive RCT)

Multimodal analgesia for breast cancer patients (Fassoulaki 2006, Ion, 2006)

Such techniques should be considered



NON-PHARMACOLOGICAL TREATMENTS

What evidence is there of efficacy for complementary therapies in the treatment of cancer pain?

In general: positive patient experience, short term effect

Massage/aromatherapy: no evidence of long term benefit (Cochrane Review 2004)

Music: RCT (2006) effective in non cancer pain, no evidence in cancer

Acupuncture: review of 7 RCT's – not effective in cancer pain *(Ernst 2007)*

TENS/TSE: not effective *(RCT, Robb 2007)*

Hypnotherapy: effective for oral mucositis

Reiki, Reflexology: poor evidence

Conclusion

- Recognise the problem of cancer pain
- Utilise WHO ladder
- Work with palliative care/oncology

Recommended

Scottish Intercollegiate Guidelines Network 2008

'Control of pain in adults with cancer'

www.sign.ac.uk/pdf/SIGN106.pdf