# Declarations

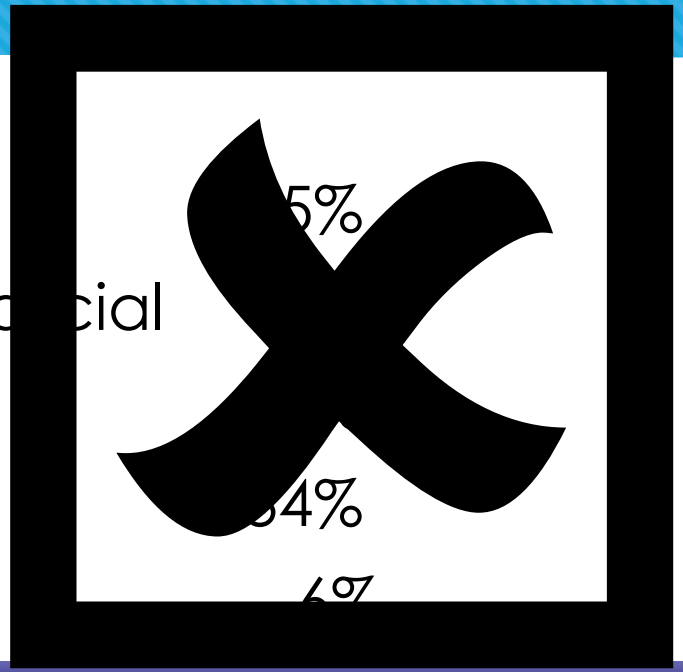
I have conducted research and consultancy for, and received educational support from –

- AstraZeneca
- Grunenthal
- Menarini
- Mundipharma
- Pfizer

*All patients and carers have given consent for their pictures*

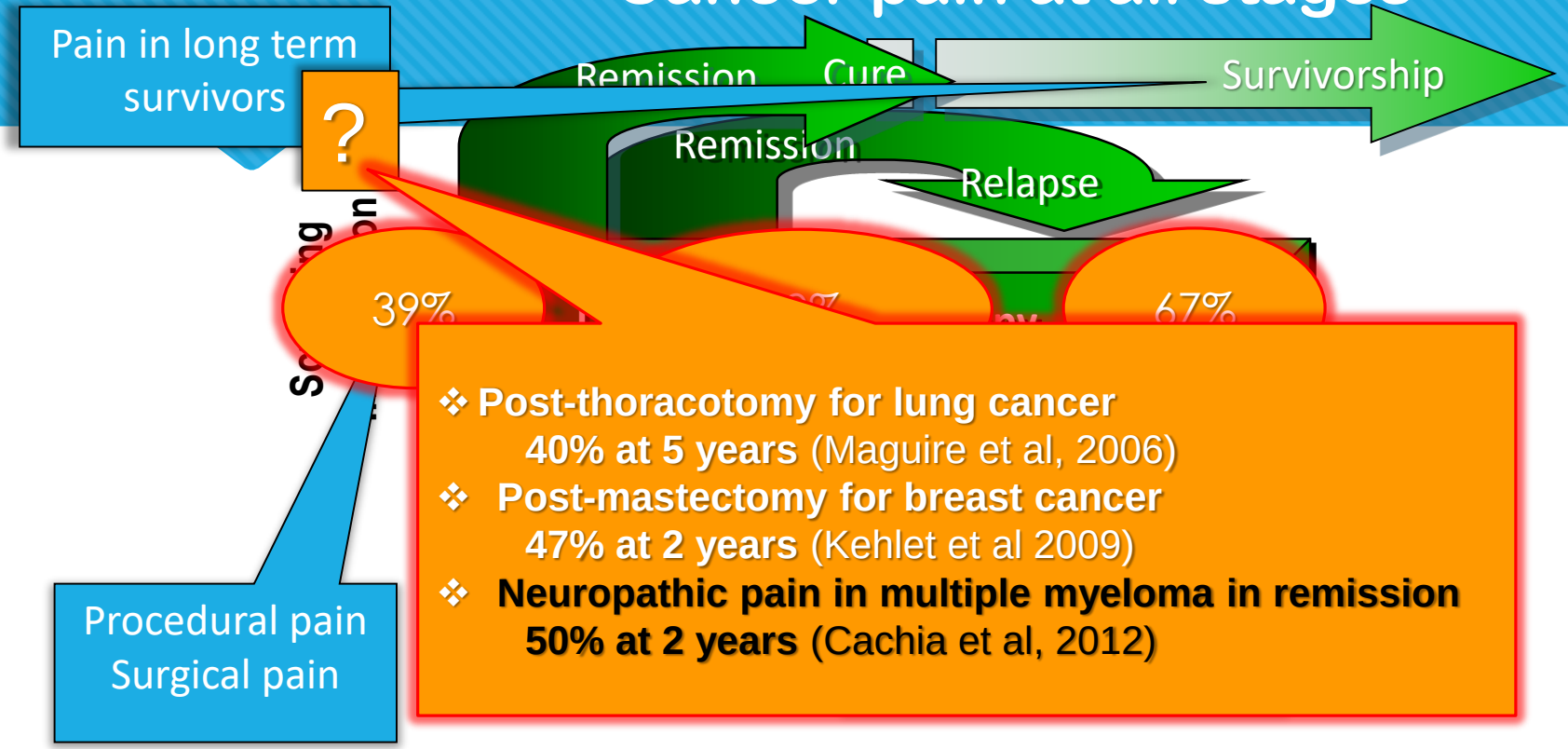
# Causes of pain in cancer patients

- Somatic
  - Bone
  - Soft tissue/myofc cial
- Visceral
- Neuropathic
- Unknown



Latest research using animal models shows that the conventional distinctions between somatic, neuropathic, bone etc pains – at cellular and molecular levels - are more complex

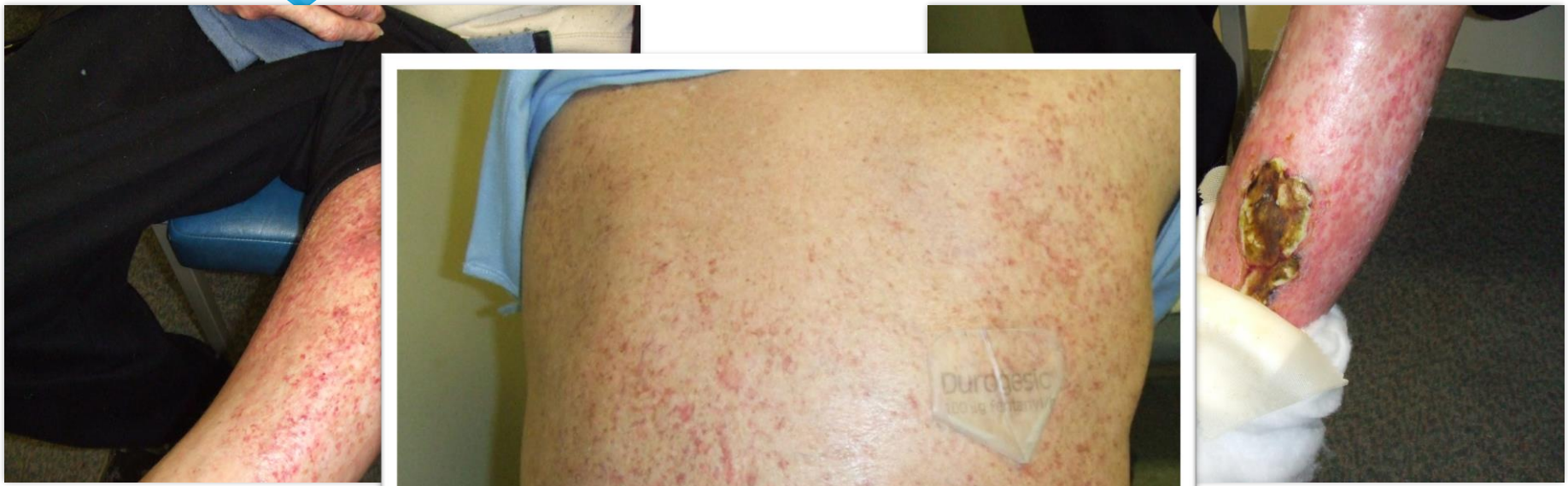
# Sheffield model of supportive care
# Cancer pain at all stages



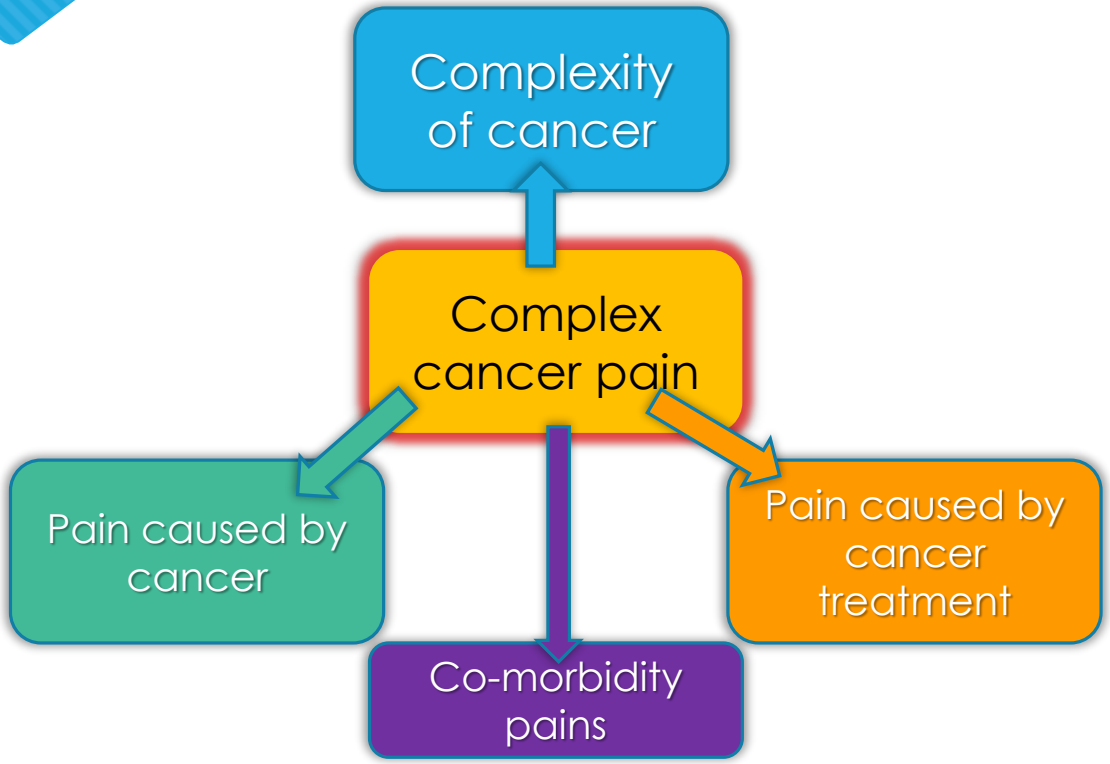

*adapted from*: Ahmedzai, Walsh *Seminars in Oncol* 2000

van den Beuken-van Everdingen et al, *J Pain Symptom Manage* 2016

# Painful cutaneous graft-versus-host disease in patient ‘cured’ of myeloma



# Cancer pain is much more complex than we thought!



REVIEW

***e Palliative Care***

Ahmedzai 2017

CURRENT OPINION

**Per**

**Table 1.** Main types of tr
cancer survivors

| System |
| --- |
| Surgery |
| Chemotherapy (including ors and |
| Radiation |
| Haematopoietic stem cell cluding s-host |

SURGERY

CHEMO, HORMONES

RADIATION

STEM CELL TRANSPLANT

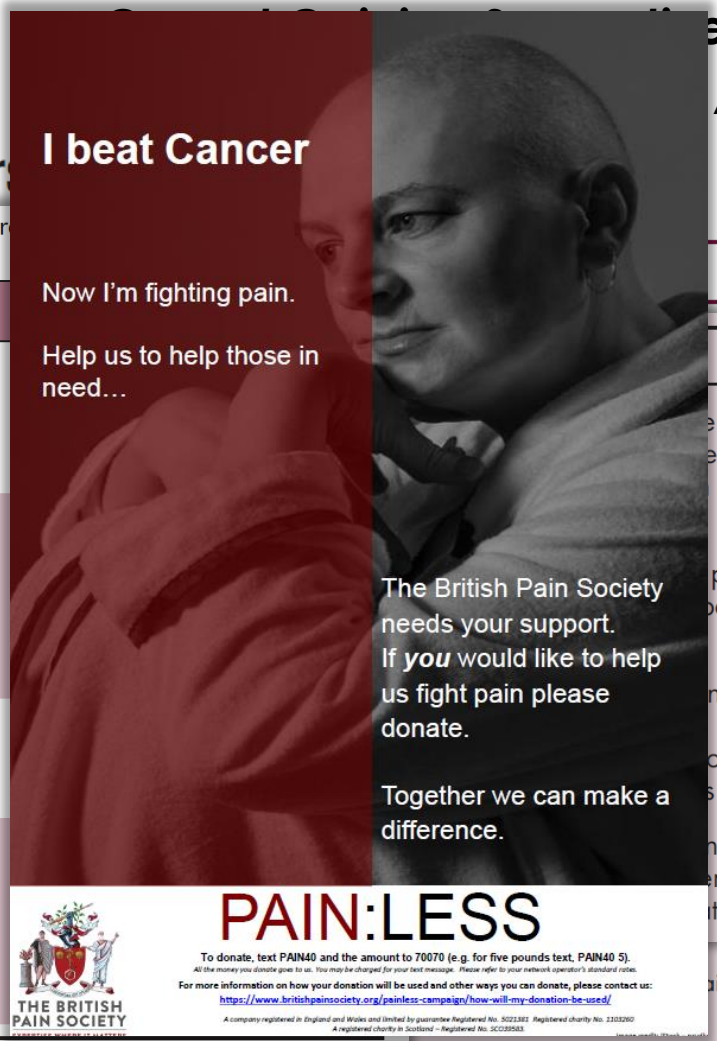
e surviving cancer, or living with
ease, can arise from the
anticancer treatments, or

psychological mechanisms of
etuation of persistent pain are

ncer survivors needs a holistic
medication (especially opioids)
on education, empowerment
s of self-management.

ncer survivors grows, clinicians
em will need to adapt and learn
tients with persistent pain.

ain prediction, persistent



# consequences after
# atment (salvage ASCT)

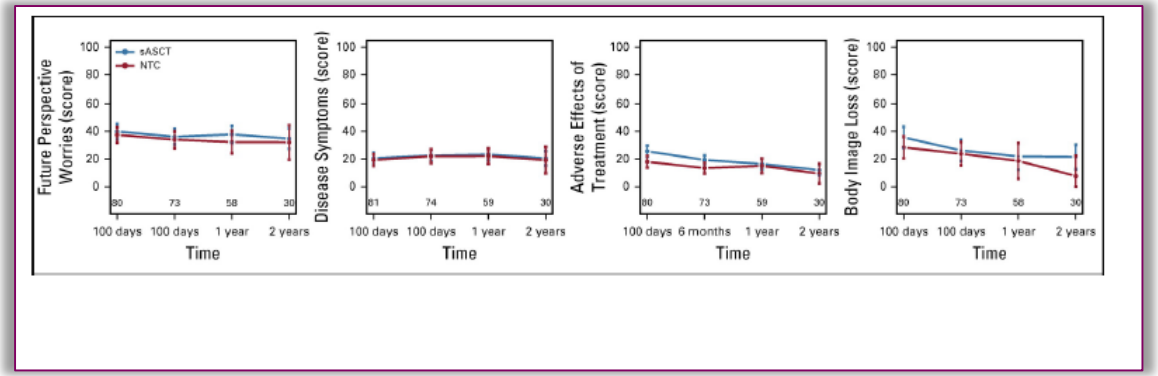
*J Clin Oncol* 2019

**Patient-Reported Outcome Results From the Open-Label, Randomized Phase III Myeloma X Trial Evaluating Salvage Autologous Stem-Cell Transplantation in Relapsed Multiple Myeloma**

Sam H. Ahmedzai, MBChB[1]; John A. Snowden, MD[2]; Andrew John Ashcroft, PhD[3]; David Allan Cairns, PhD[4]; Cathy Williams, MD[5]; Anna Hockaday[4]; Jamie D. Cavenagh, MD[6]; Debo Ademokun, MBChB[7]; Eleni Tholouli, PhD[8]; David Allotey, MBChB[9]; Vijay Dhanapal, MBChB[10]; Matthew Jenner, MBBS[11]; Kwee Yong, PhD[12]; Jim Cavet, PhD[13]; Hannah Hunter, MD[14]; Jennifer M. Bird, MD[15]; Guy Pratt, PhD[16]; Christopher Parrish, PhD[4]; Julia M. Brown, MSc[4]; Treen C.M. Morris, MD[17]; and Gordon Cook, PhD[4] on behalf of the National Cancer Research Institute Haemato-Oncology Clinical Studies Group

*t Oncol* 2014) – second (salvage)
multiple myeloma improves survival

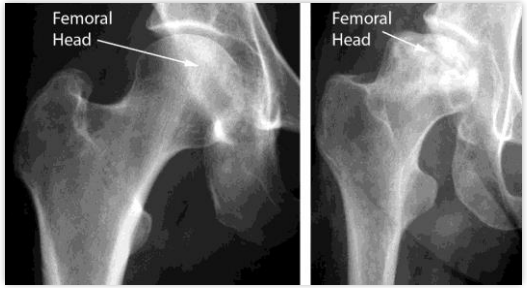
- from Myeloma X now published
- Pain and QoL *initially worse after salvage transplant – up to 2 years* – then better outcomes compared to non-transplant treatment
- *Patients who had lower adverse effects after transplant had survival advantage*

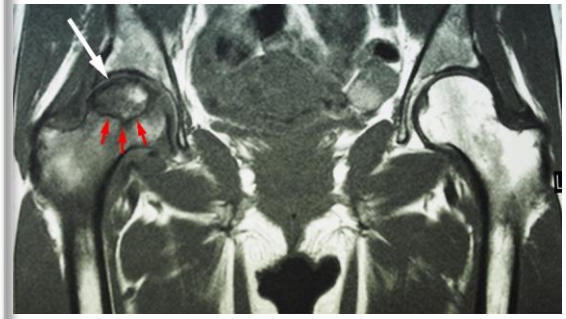


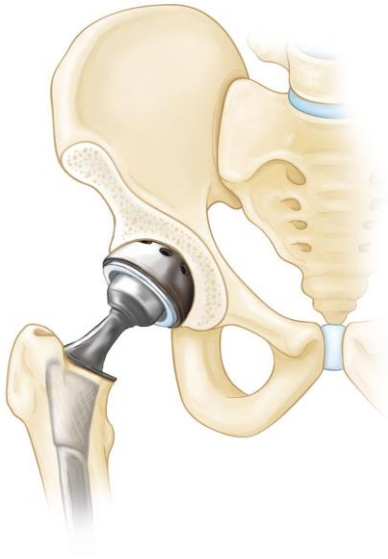
# Late effects after intensive treatment with steroids

## Avascular osteonecrosis of bones and joints

*NB: More commonly seen in children / TYA*





Clinical Advances in Myeloma 2020

# Complex pain in myeloma patients

**Sam H Ahmedzai FRCP FFPM**

Emeritus Professor, University of Sheffield

NIHR: National Specialty Lead for Supportive Care

NCRI: Chair of Supportive & Palliative Care Clinical Studies Group

*Email:* s.ahmedzai@sheffield.ac.uk

*twitter:* @samhja

# Pain management in long-term cancer survivors

Cancer survivors are trying to return to normal daily life

- Prefer not to keep coming back to hospital
- Prefer not to be 'drugged up', suffer longterm side-effects - especially constipation, sedation
- Want to carry on driving
- Want to return to work and hobbies

**Solution is multimodal analgesia with minimal opioids, access to interventional techniques and focus on exercise and self-management approaches**

# Balanced multimodal analgesia in myeloma patients – *Sheffield approach*

| | Younger | Older | Survivors |
|---|---|---|---|
| **Opioids** | **++** | **+** | **(+)** |
| **Pregabalin** | **+++** | **+** | **+** |
| **Duloxetine** | **++** | **++** | **+** |
| **Clonazepam** (night-time only) | **++** | **+** | **(+)** |
| **Ketamine *(short burst only)*** | **+++** | **++** | **-** |
| **Exercise and diet** | **+++** | **+++** | **+++++** |

When opioids get to morphine equivalent dose of 120mg/day in younger or 60mg/day in elderly patients -> refer to specialist! (*Snowden, Ahmedzai et a*l BSH 2011)

# Neuropathic pain in myeloma patients

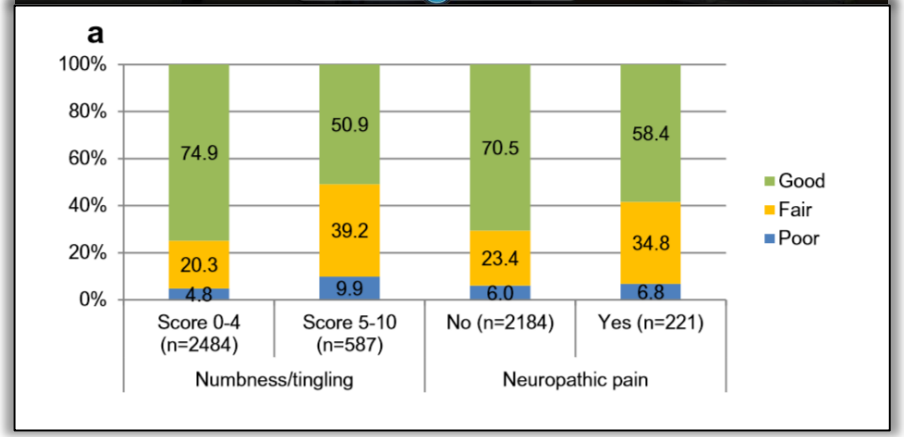
- First – look for **co-morbidities**! (pre-existing, eg diabetes - or arising from post-treatment metabolic dysfunctions)
- Common drug causes – **bortezomib, thalidomide**
- Worse pain & greater impact on functioning and quality of life
- Impairment of balance, leading to falls
- Chemo-related neuropathic pain – risk of reduced doses or early cessation of treatment

# Chemotherapy-induced neuropathic pain

*"I get sharp electric shocks that shoot up my legs"*

*"When I walk it feels as I have sharp stones in my shoes"*

*"My feet feel like they're burning / blocks of ice"*



Pergamon

PII: S0306-4522(97)00147-4

*Neuroscience* Vol. 81, No. 1, pp. 255–262, 1

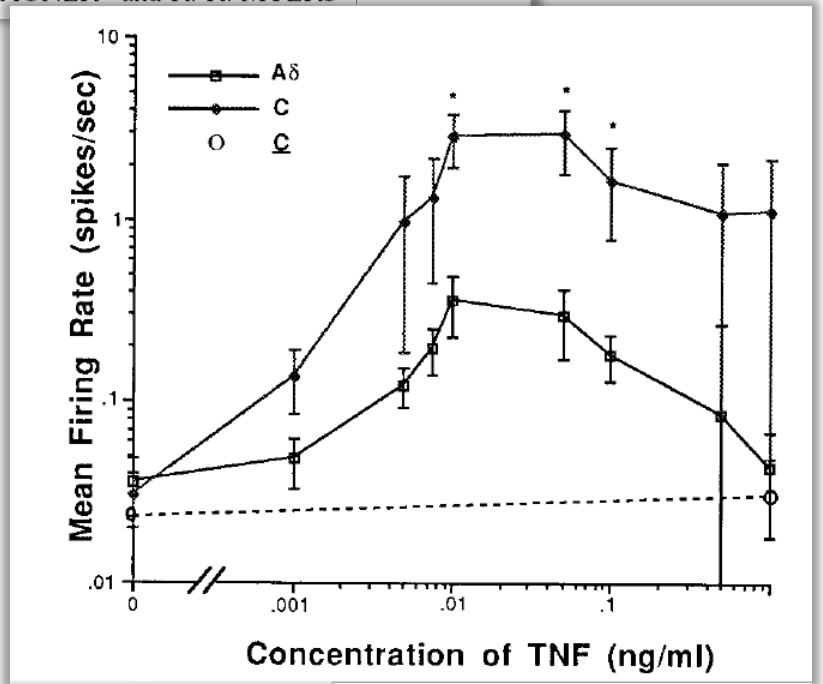
0306–4522/97 $17.00+0

*Neurosci* 1997

# TUMOUR NECROSIS FACTOR-α INDUCES ECTOPIC ACTIVITY IN NOCICEPTIVE PRIMARY AFFERENT FIBRES

L. S. SORKIN,*‡ W.-H. XIAO,* R. WAGNER* and R. R. MYERS*†

- Known for long time that inflammatory molecules – eg TNF1alpha, IL-6 - sensitise neurones, increase pain sensitivity



# Cancer pain experience in myeloma patients is related to inflammatory mediators *(Boland et al, 2013)*

Living With Advanced But Stable Multiple Myeloma: A Study of the Symptom Burden and Cumulative Effects of Disease and Intensive (Hematopoietic Stem Cell Transplant Based) Treatment on Health-Related Quality of Life

Elaine Boland, MD, MRCP, Christine Eiser, PhD, Yousef Ezaydi, MRCP, Diana M. Greenfield, PhD, Sam H. Ahmedzai, FRCP, and John A. Snowden, MD
*Academic Unit of Supportive Care (E.B., S.H.A.) and; Academic Unit of Psychology (C.E.), University of Sheffield; Department of Haematology (Y.E., J.A.S.), Sheffield Teaching Hospital NHS Foundation Trust; Weston Park Hospital (D.M.G.), Sheffield Teaching Hospital NHS Foundation Trust; and Late Effects Group Sheffield (D.M.G., J.A.S.), Sheffield, United Kingdom*

*JPSM* 2013

**Chronic inflammatory mediators – especially IL-6 – are important factors in pain, depression and appetite suppression**

*Table 2*
**Quality of Life From the EORTC QLQ-C30**

| Components | Median (IQR) | Mean (SD) |
|---|---|---|
| Functional scales | | |
| Physical functioning | 60 (41.7–80.0) | 60.6 (25.4) |
| Role functioning | 67 (33.0–79.0) | 55.2 (31.2) |
| Emotional functioning | 71 (44.0–92.0) | 68.8 (23.9) |
| Cognitive functioning | 83 (50.0–95.7) | 71.8 (25.9) |
| Social functioning | 50 (33.0–67.0) | 46.9 (28.3) |
| QoL/global health status | | |
| Appetite loss | 33 (0–33.0) | 27.0 (31.0) |
| Dyspnea | 33 (0–67.0) | 33.3 (30.6) |
| Nausea and vomiting | 0 (0–17.0) | 11.1 (17.3) |
| Constipation | 0 (0–33) | 14.4 (24.2) |
| Diarrhea | 0 (0–25) | 10.4 (19.7) |

| Components | IL-6 (*P*-value; *r*) | TNF-α (*P*-value; *r*) |
|---|---|---|
| Functional scales | | |
| Physical functioning | *0.03*; *−0.38* | 0.62; −0.09 |
| Role functioning | 0.07; −0.33 | 0.63; 0.09 |
| Emotional functioning | 0.85; 0.03 | 0.93; −0.02 |
| Cognitive functioning | 0.61; −0.09 | 0.39; 0.16 |
| Social functioning | 0.81; −0.04 | 0.22; 0.22 |
| QoL/global health status | | |
| QoL/global health status | 0.23; −0.22 | 0.63; −0.09 |
| Symptom scales/items | | |
| Pain | *0.02*; *0.41* | 0.84; 0.04 |
| Fatigue | 0.37; 0.16 | 0.89; 0.25 |
| Insomnia | *0.02*; *0.40* | 0.47; 0.13 |
| Appetite loss | *0.02*; *0.41* | 0.09; 0.30 |
| Dyspnea | 0.20; 0.23 | 0.66; 0.08 |
| Nausea and vomiting | 0.28; 0.20 | 0.31; 0.18 |
| Constipation | 0.57; 0.34 | 0.16; 0.26 |
| Diarrhea | 0.37; −0.16 | 0.51; −0.12 |

*Table 5*
**Correlations of Serum Cytokines With BPI-SF Components**

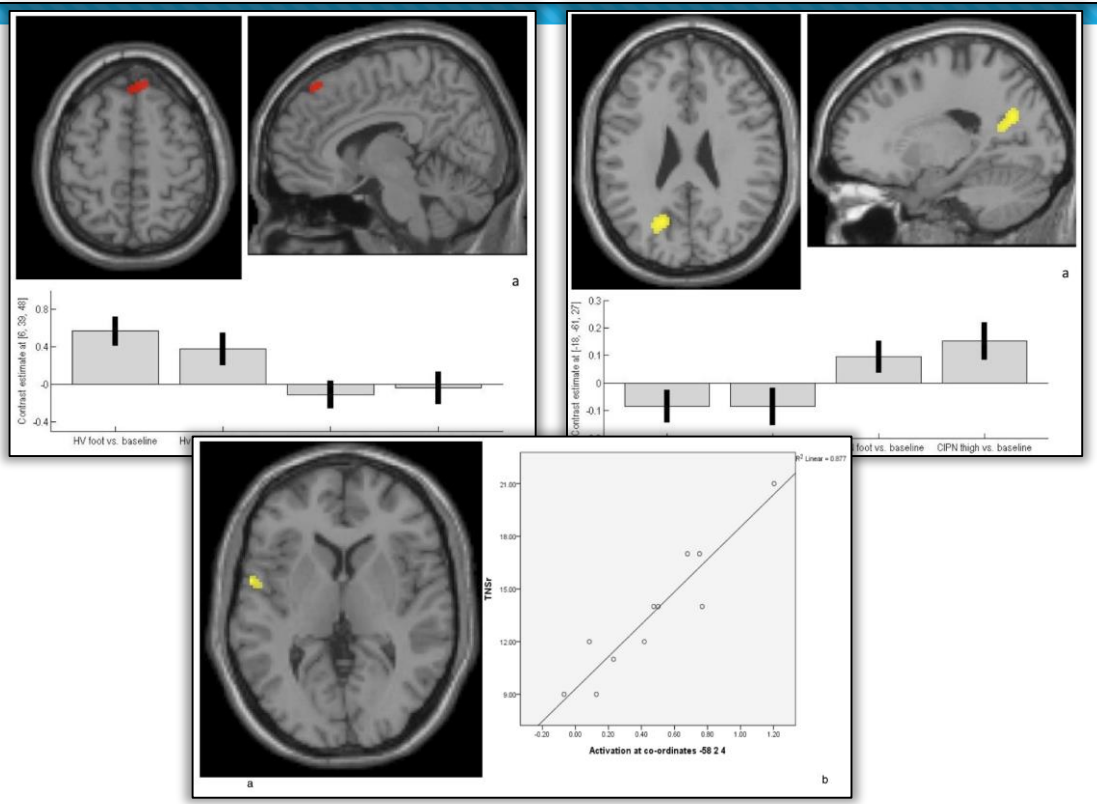
| BPI-SF | IL-6 (*P*-value; *r*) | TNF-α (*P*-value; *r*) |
|---|---|---|
| Average pain | *0.03*; *0.38* | 0.15; 0.27 |
| Pain interference | *0.003*; *0.52* | 0.46; 0.14 |

# Central Pain Processing in Chronic Chemotherapy-Induced Peripheral Neuropathy: A Functional Magnetic Resonance Imaging Study

*PLOS* 2014

Elaine G. Boland[1,2*], Dinesh Selvarajah[3], Mike Hunter[4], Yousef Ezaydi[5], Solomon Tesfaye[3], Sam H. Ahmedzai[2], John A. Snowden[5], Iain D. Wilkinson[1]

**Boland et al, 2014**




In patients with CIPN after multiple myeloma treatment –

Unusual pattern of brain activity:

- Activation of precuneus area
- Hypoactivation of anterior cingulate gyrus

# Management of neuropathic pain in cancer patients

- Very little high quality evidence for specific treatment approaches
- Only **Duloxetine has good evidence in RCT and meta-analysis** for CIPN
- Best policy – multimodal analgesia with minimal opioids, adrenergic drugs, topical treatments
- Sheffield regime – topical Capsaicin or Menthol cream
- Future – NGF antibody (Tanezumab)?

# Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial

*JAMA* 2013

**Ellen M. Lavoie Smith, PhD**,
Department of Nursing, University of Michigan, Ann Arbor, Michigan

## Duloxetine for chemo-induced neuropathy

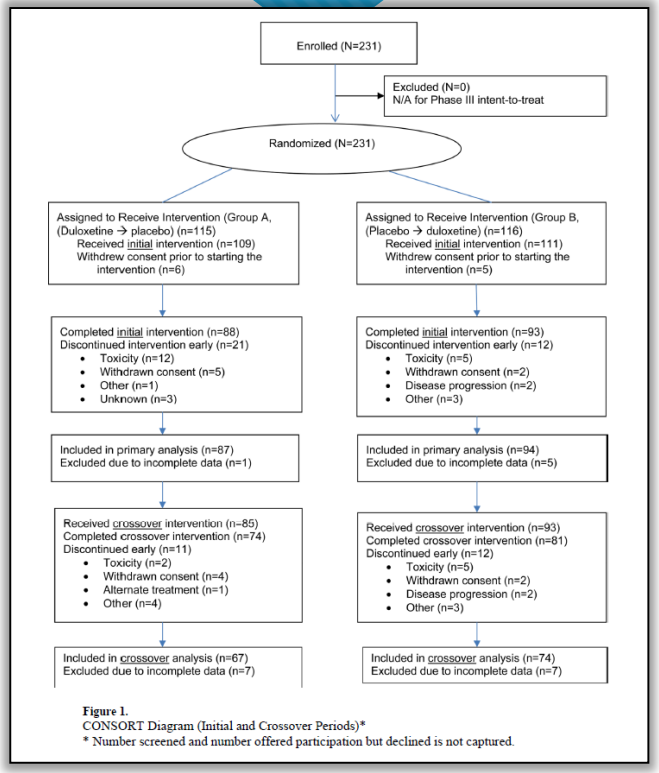
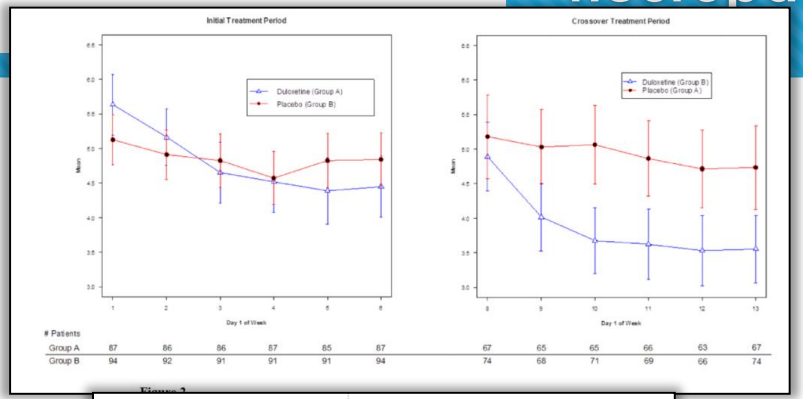
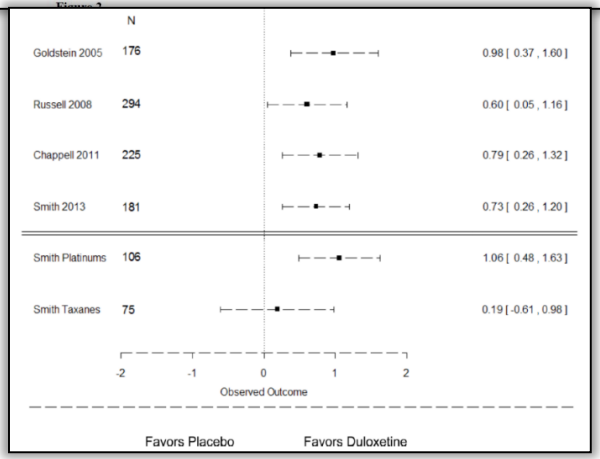
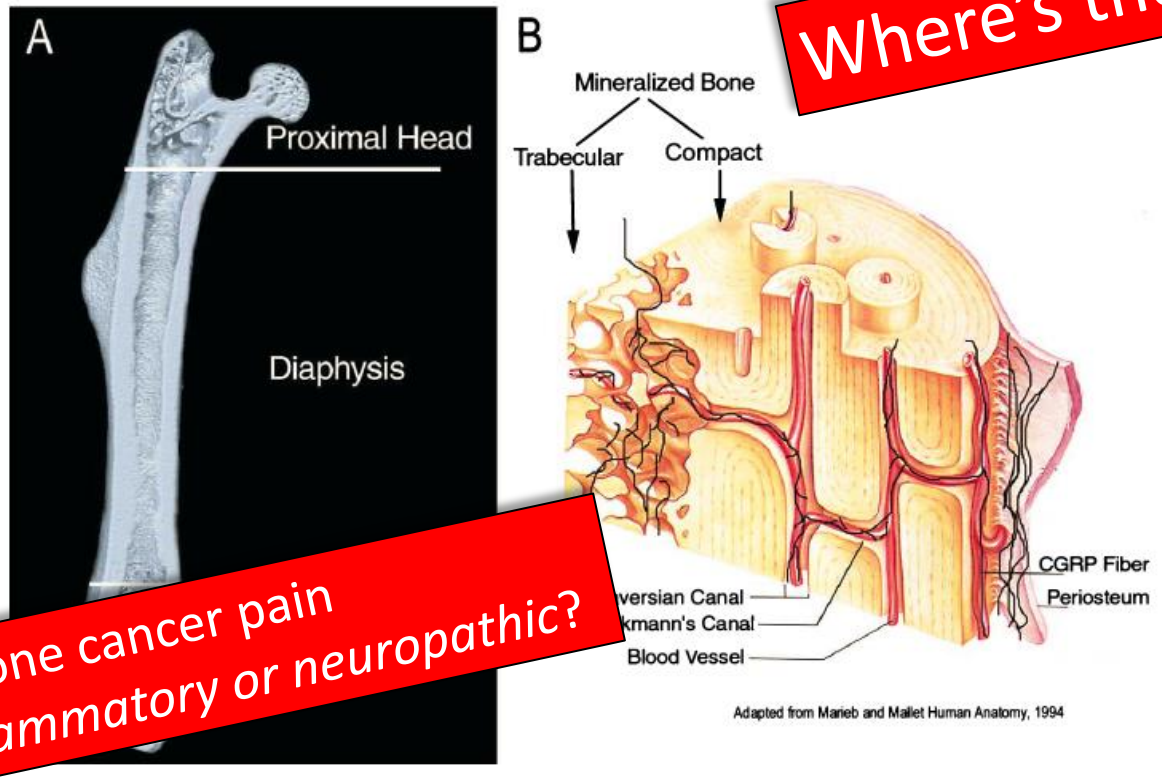



**Figure 1.**
CONSORT Diagram (Initial and Crossover Periods)*
* Number screened and number offered participation but declined is not captured.



# Origin of bone cancer pain




Where's the pain?

Is bone cancer pain *inflammatory or neuropathic?*

Mach DB *et al*. *Neuroscience* 2002; **113**: 155-66

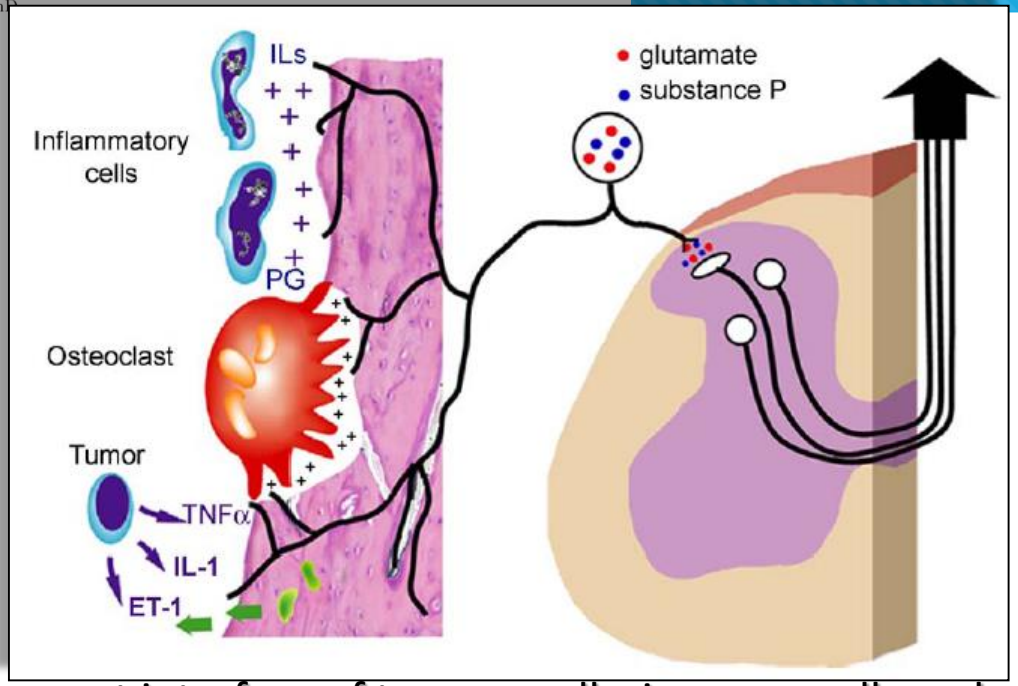
Luger NM *et al. J Pain Symptom Manage* 2005

*Proceedings of the Symposium "Updates of the Clinical Pharmacology of Opioids with Special Attention to Long-Acting Drugs"*

# Bone Cancer Pain: From Model to Mechanism to Therapy

Nancy M. Luger, BA, David B. Mach, BS, Molly A. Sevcik, BA, and Patrick W. Mantyh, BS, JD, PhD

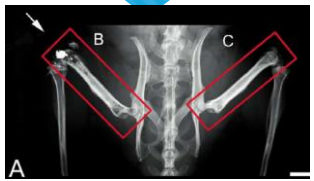
Cancer bone is a combination of inflammatory and neuropathic mechanisms

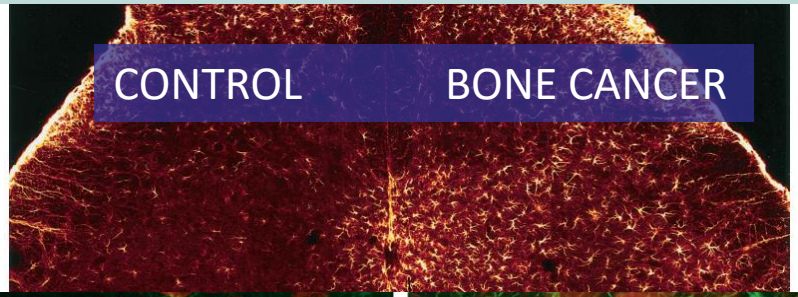


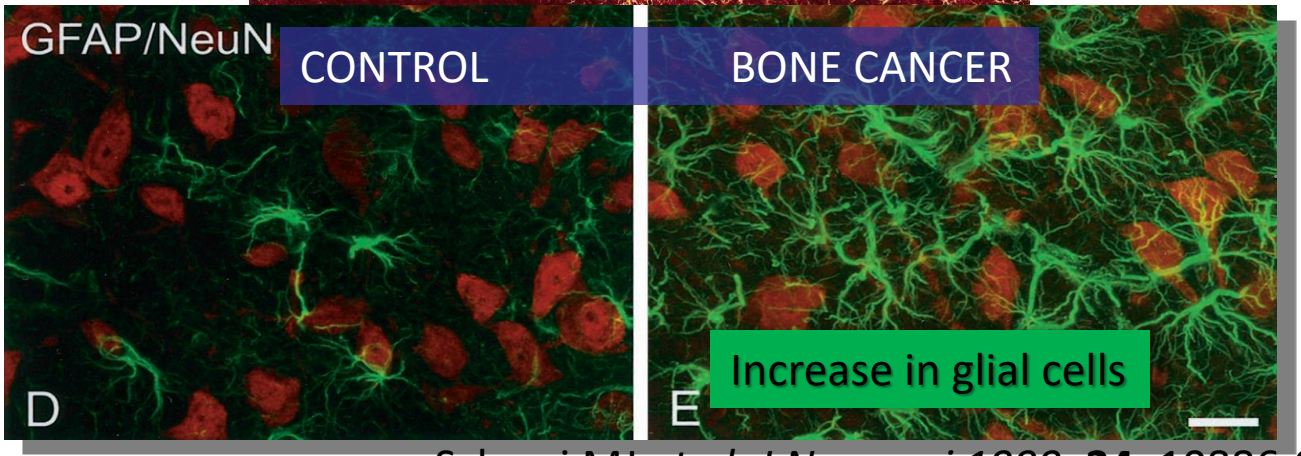

Cell damage at interface of tumour cells, immune cells and osteoclasts causes neuronal activation, induces neuropathic changes

# Malignant bone disease and neuroplastic changes → spinal sensitisation

Cross-section of dorsal horn of spinal cord (mouse)

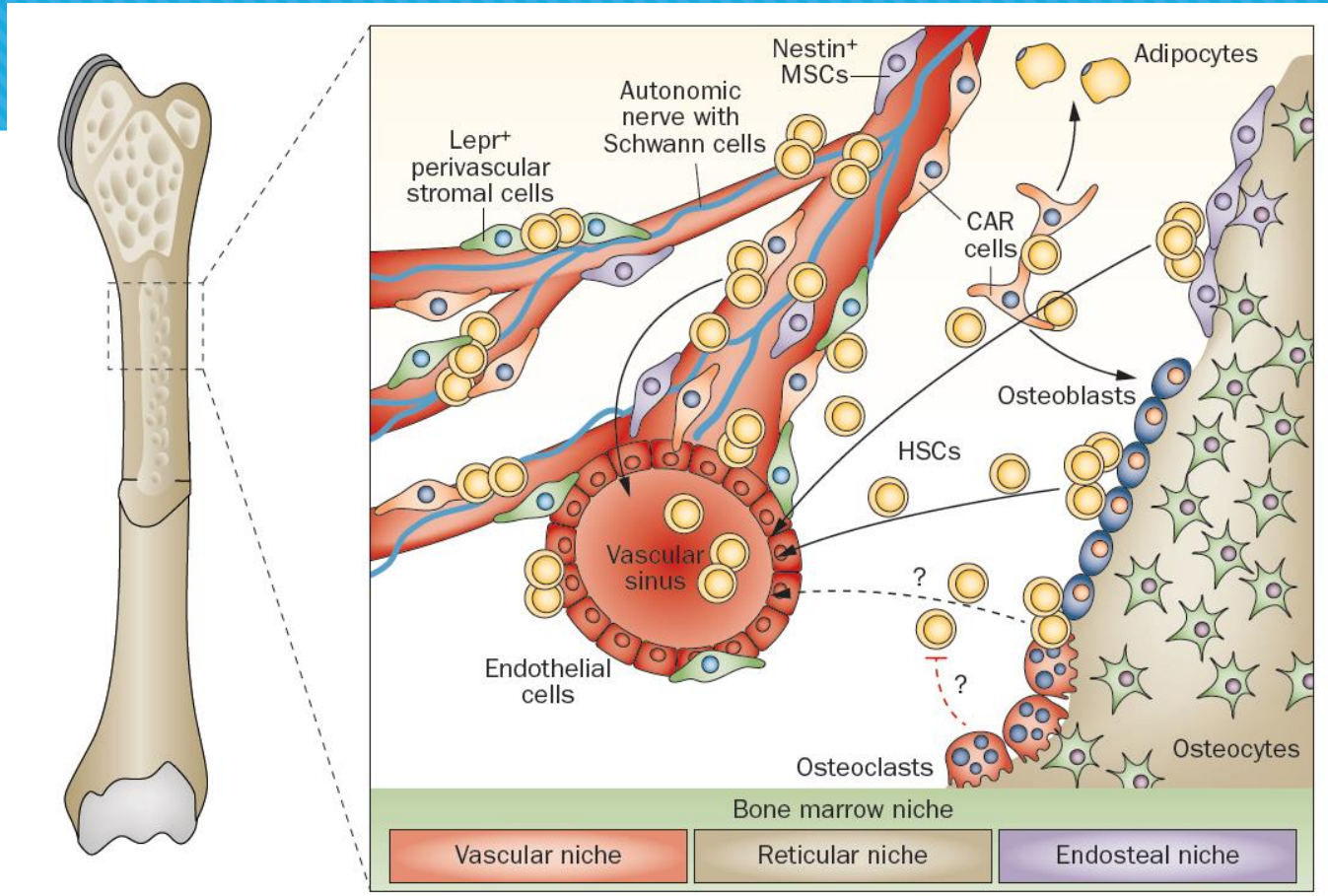



Schwei MJ *et al. J Neurosci 1999*; **24**: 10886-97

# Neuro-vascular infrastructure of bone



# Pathological Sprouting of Adult Nociceptors in Chronic Prostate Cancer-Induced Bone Pain

J NeuroSci 2010

Juan M. Jimenez-Andrade,[1] Aaron P. Bloom,[1] James I. Stake,[1] William G. Mantyh,[1] Reid N. Taylor,[1] Katie T. Freeman,[3] Joseph R. Ghilardi,[3] Michael A. Kuskowski,[4] and Patrick W. Mantyh[1,2,3]

Bone cancer implantation leads to increased and branching CGRP sensory neurones (yellow/red) in bone marrow

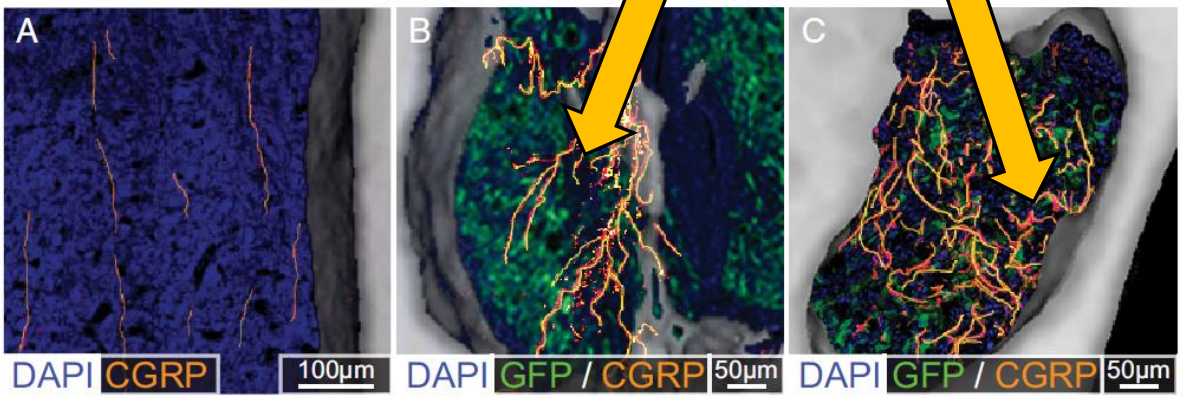



**Figure 3.** Prostate cancer cells induce sprouting of sensory nerve fibers. ***A–C***, High-power μCT cross sections of bone (100 μm thick) overlaid with confocal images (20 μm thick) of a sham femur (***A***) and tumor-bearing femur from mice killed at early (***B***) and more advanced stages of the disease (***C***). In these images the DAPI stained nuclei appear blue, the GFP-expressing prostate cancer cells appear green and the $CGRP^+$ sensory nerve fibers appear yellow/red. Note that in the sham mice, $CGRP^+$ nerve fibers that are present in the marrow space appear as single nerve fibers with a highly linear morphology. As $GFP^+$ prostate tumor cells proliferate and form tumor colonies (***B***, ***C***), the $CGRP^+$ sensory nerve fibers undergo marked sprouting which produces highly branched sensory nerve fibers (***B***) and a high density of sensory nerve fibers (***C***) that is never observed in the normal marrow (***A***).

**BLOCKADE OF NERVE SPROUTING AND NEUROMA FORMATION MARKEDLY ATTENUATES THE DEVELOPMENT OF LATE STAGE CANCER PAIN**

W. G. MANTYH,[a1] J. M. JIMENEZ-ANDRADE,[a1] J. I. STAKE,[a1] A. P. BLOOM,[a] M. J. KACZMARSKA,[a] R. N. TAYLOR,[a] K. T. FREEMAN,[b] J. R. GHILARDI,[b] M. A. KUSKOWSKI[c] AND P. W. MANTYH[a,b,d*]

Neuroscience 2010

**Sarcoma** in bone (green) causes proliferation of CGRP neurones (yellow) in highly disorganised pattern


New sprouting neurones express abnormal Na channels – spontaneous firing

**BLOCKADE OF NERVE SPROUTING AND NEUROMA FORMATION MARKEDLY ATTENUATES THE DEVELOPMENT OF LATE STAGE CANCER PAIN**

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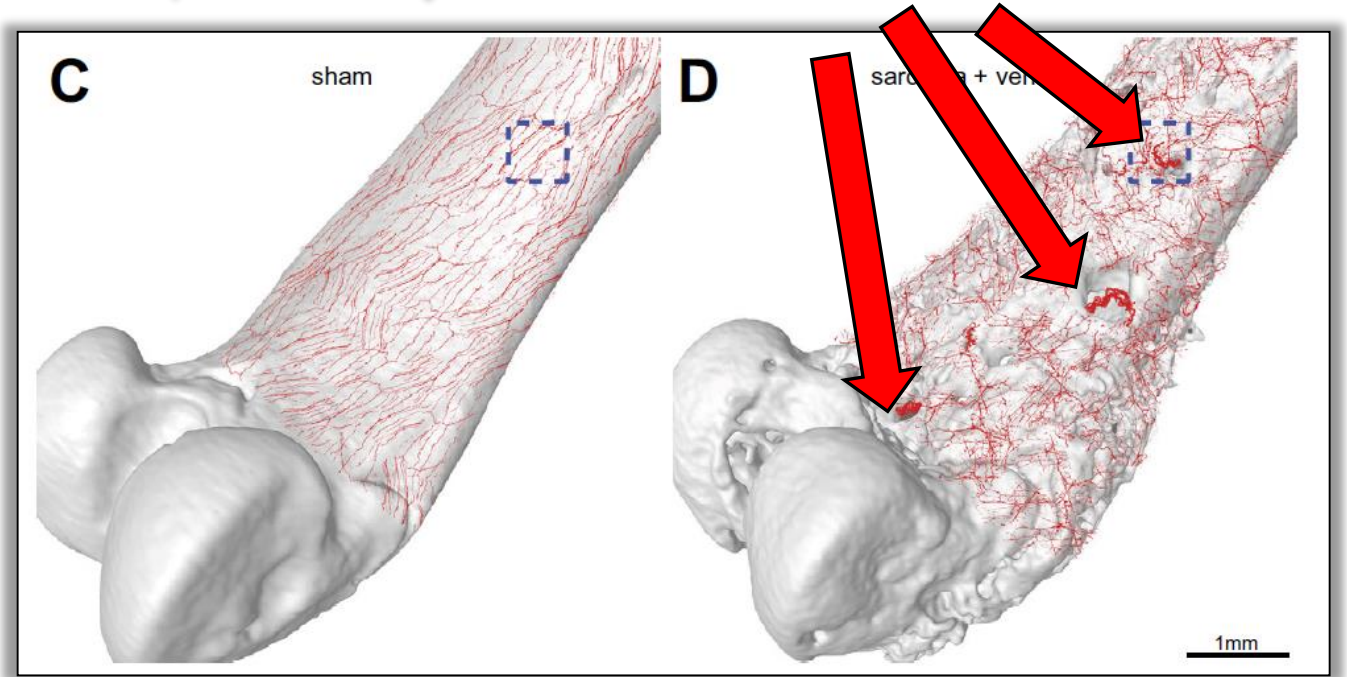
Neuroscience 2010

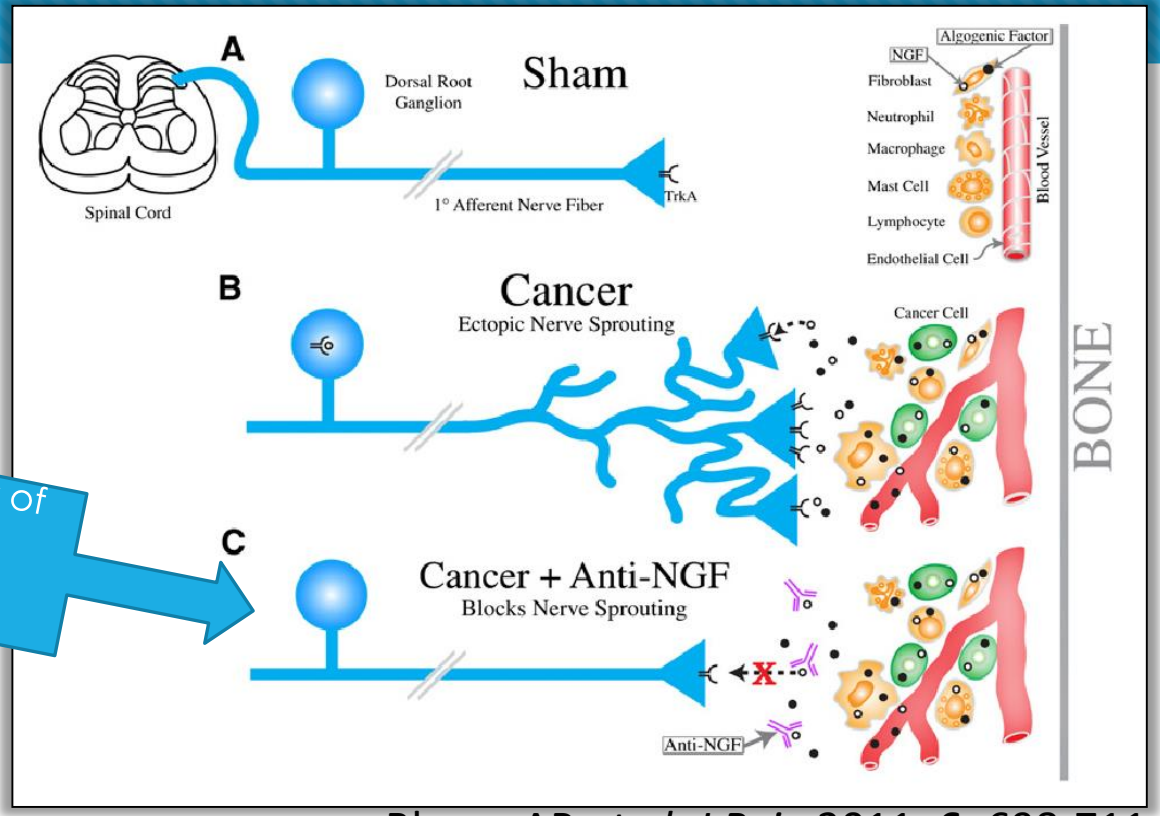
Cancer in bone marrow later induces increased neurone expression in **periosteum** with **neuroma** formation



Breast Cancer-Induced Bone Remodeling, Skeletal Pain, and Sprouting of Sensory Nerve Fibers

Aaron P. Bloom,* Juan M. Jimenez-Andrade,* Reid N. Taylor,* Gabriela Castañeda-Corral,*,† Magdalena J. Kaczmarska,* Katie T. Freeman,‡ Kathleen A. Coughlin,‡ Joseph R. Ghilardi,‡ Michael A. Kuskowski,§ and Patrick W. Mantyh*,‡,¶

# Blocking neuropathic damage




Clinical trials of anti-NGF antibody Tanezumab

Bloom AP *et al. J Pain* 2011; **6**: 698-711

# Is morphine still the 'gold' standard for cancer-related pain?

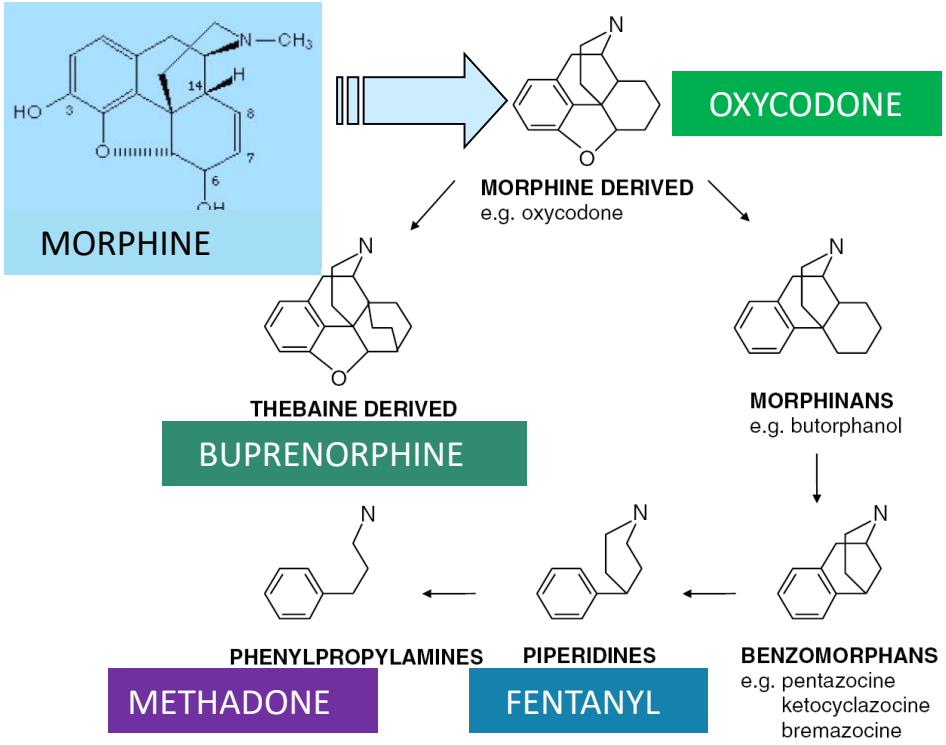
What makes the 'ideal' opioid for use in end of life care?

- **Reliable efficacy** – bioavailability and pharmacodynamics
- **Minimal side-effects** – minor and serious
- **Safe metabolism and elimination**
- **Range of routes** of administration and available formulations

*Morphine fails on all these criteria!*

# Therapeutic opioids are not all the same – *development of improved synthetic opioids*

Corbett et al, *Brit J Pharmacol* 2006



# Why do opioids cause so many adverse effects?

- Central nervous system
- Peripheral nervous system
- Gastrointestinal system
- Cardiovascular system
- Respiratory system
- Renal system
- Immune system
- Endocrine system
- Skin…

*Opioid receptors are found throughout the human body so -*

***Opioid 'adverse effects' are actually just 'opioid effects'***

# Opioid 'adverse effects'

**Commonly recognised**

- Constipation
- Dry mouth
- Nausea & vomiting
- Drowsiness
- Cognitive impairment & hallucinations
- Itching
- Urinary retention
- Respiratory depression

**Less well recognised**

- Endocrine suppression (testosterone, ACTH)
- Immunosuppression
- Opioid-induced hyperalgesia

# Analgesic side-effects adversely affect QoL

**Side effects of analgesia may significantly reduce quality of life in symptomatic multiple myeloma: a cross-sectional prevalence study**

*Supp Care Cancer* 2014

Sarah Sloot · Jason Boland · John A. Snowden · Yousef Ezaydi · Andrea Foster · Alison Gethin · Tracy Green · Louise Chopra · Stans Verhagen · Kris Vissers · Yvonne Engels · Sam H. Ahmedzai

| Side effects | Pain medication *n* value | Unknown cause *n* value | *Cumulative n* value |
|---|---|---|---|
| Constipation | 10 | 7 | *17* |
| Tiredness/fatigue | 8 | 4 | *12* |
| Dizziness | 8 | 1 | *9* |
| Drowsiness | 5 | 4 | *9* |
| Hallucinations | 4 | 1 | *5* |
| Nausea | 1 | 4 | *5* |
| Increased sweating | 0 | 5 | *5* |
| Feeling sad, depressed | 3 | 1 | *4* |
| Jerky movements | 2 | 2 | *4* |
| Dry mouth | 1 | 3 | |
| Vomiting | 2 | 1 | |
| Loss of interest in sex | 1 | 2 | |
| Problems passing urine | 0 | 3 | |
| Itching | 1 | 1 | |
| ONJ | 1 | 0 | |
| Flatulence | 1 | 0 | |
| Withdrawal | 1 | 0 | |
| Hot flushes | 1 | 0 | |
| Flu symptoms | 1 | 0 | |
| Swelling | 1 | 0 | |
| Indigestion/heartburn | 0 | 1 | |
| Itching | 0 | 1 | *1* |
| Skin rash | 0 | 1 | *1* |
| Total | 52 | 42 | *94* |

| Severity of side effects | Pain medication *n* value | Unk… |
|---|---|---|
| Mild | 9 | |
| Moderate | 18 | |
| Severe | | |
| Total | | |

…h-related quality …
…) ('Overall quality of …
for Research and Treatment of Cancer (EOR…
from 0–100

WITH analgesic side-effects

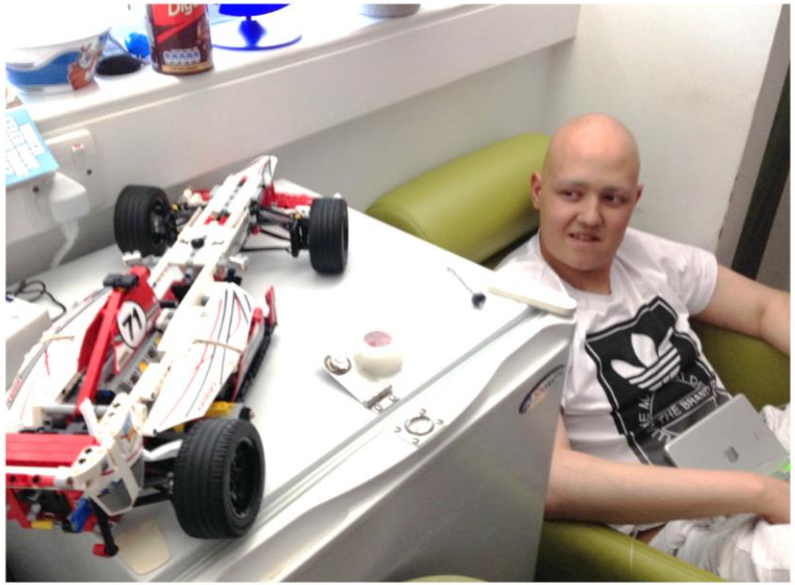
WITHOUT anlagesic side-effects

| HRQoL scores (95% CI)[2] |
|---|
| 48.3 (38.7–57.9) |
| 62.6 (53.5–71.7) |

# Morphine *versus* oxycodone

| | Morphine | Oxycodone |
|---|---|---|
| Oral bioavailability | 16-68% | 60-87% |
| Toxicity in renal failure | +++ | + |
| CNS adverse effects | +++ | + |
| Histamine adverse effects | ++ | (+) |

# Oxycodone: a ‘strong opioid’ with reduced CNS side-effects



**“The data suggest that oxycodone offers similar levels of pain relief** and overall adverse events to other strong opioids including morphine.

The RR for **hallucinations was significantly lower after treatment with CR oxycodone** compared to CR morphine (RR 0.52, 95% CI 0.28 to 0.97).”

(Review)

Schmidt-Hansen M, Bennett MI, Arnold S, Bromham N, Hilgart JS. Oxycodone for cancer-related pain. *Cochrane Database of Systematic Reviews* 2017, Issue 8. Art. No.: CD003870.

# Buprenorphine – a complex strong opioid

Multiple activities at opioid receptors

- 'Partial' agonist at mu (*but acts as full agonist in clinical doses*)
- Antagonist at kappa
- Agonist at ORL-1

This combination leads to

- Improved side-effect profile
- Anti-hyperalgesic effect

Largely misunderstood and ignored because of poor understanding of action

# Buprenorphine – unique safety feature

British Journal of Anaesthesia 96 (5): 627–32 (2006)
doi:10.1093/bja/ael051 Advance Access publication March 17, 2006
BJA

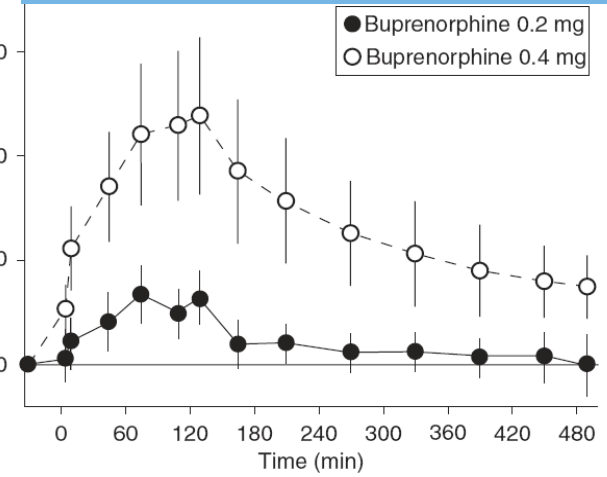
## Buprenorphine induces ceiling in respiratory depression but not in analgesia

A. Dahan[1]*, A. Yassen[2], R. Romberg[1], E. Sarton[1], L. Teppema[1], E. Olofsen[1] and M. Danhof[2]

[1]Department of Anesthesiology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands. [2]Leiden/Amsterdam Center for Drug Research, Division of Pharmacology, Gorlaeus Laboratory, Leiden, The Netherlands

*Corresponding author: Anesthesia and Pain Research Unit, Department of Anesthesiology, Leiden University Medical Center (LUMC, P5-Q), PO Box 9600, 2300 RC Leiden, The Netherlands. E-mail: a.dahan@lumc.nl

## No ceiling to analgesic effect




Influence of i.v. buprenorphine, 0.2 and 0.4 mg (per 70 kg), on olerance in healthy volunteers. Values are the increase in currents ieve pain tolerance relative to baseline pain tolerance currents ). A significant increase in analgesia is observed going from norphine 0.2 to 0.4 mg.

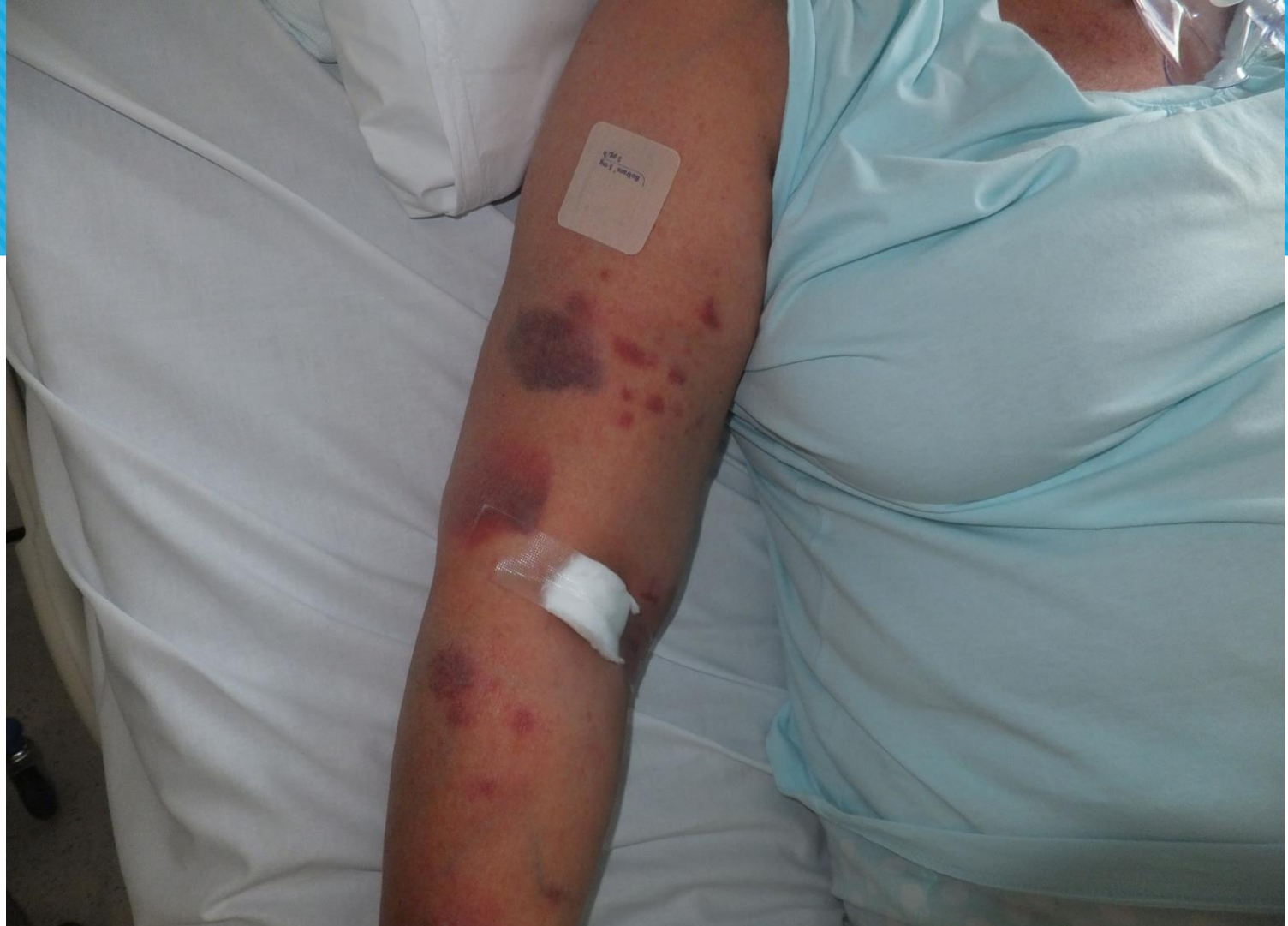
# Buprenorphine:
# No dose adjustment needed for -

Elderly Patients

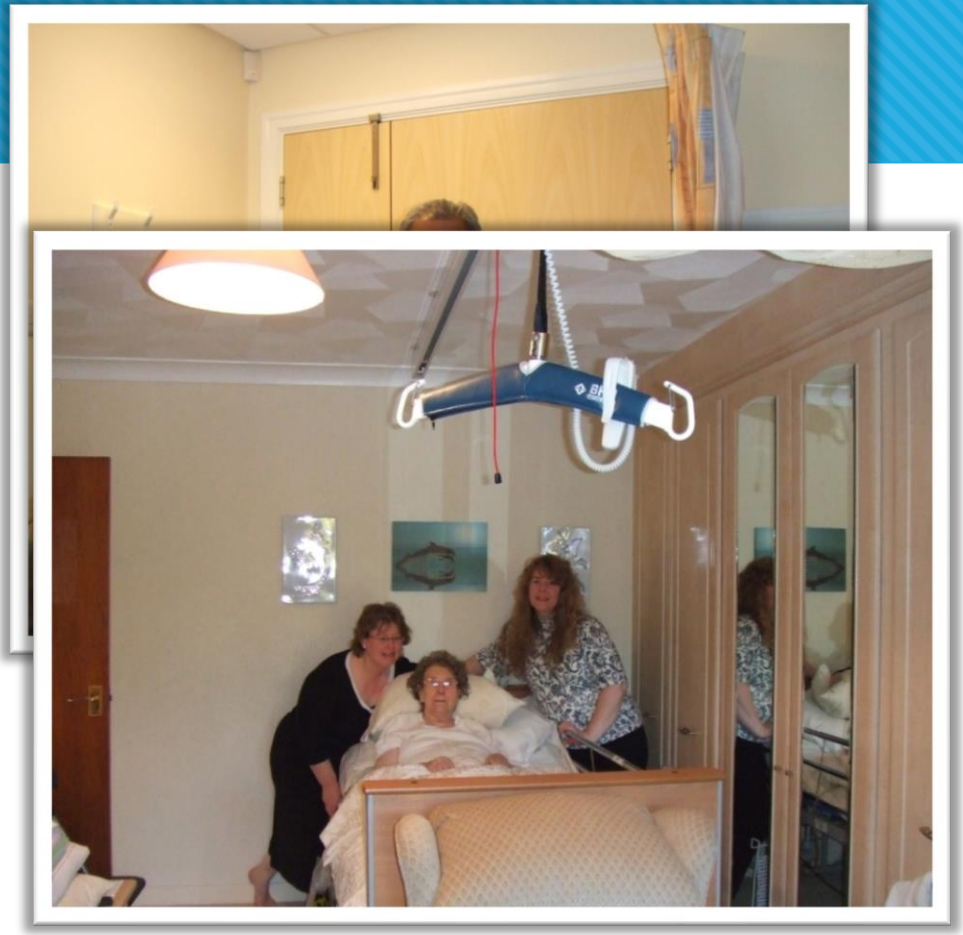
Renal Impairment

**1. Sovenor** Buprenorphine Patch Prescribing Information 2017. **2.** Kress HG. *Eur J Pain 2009;13:219-230.*


Hill-Rom



# SR, 75 years, myeloma survivor




Multiple vertebral fractures over 2 years – **surgical stabilisation**

Nearly killed by opioid overuse – switched from fentanyl to **buprenorphine**

**Implanted intrathecal management of pain** from vertebral fractures – 15 months survival

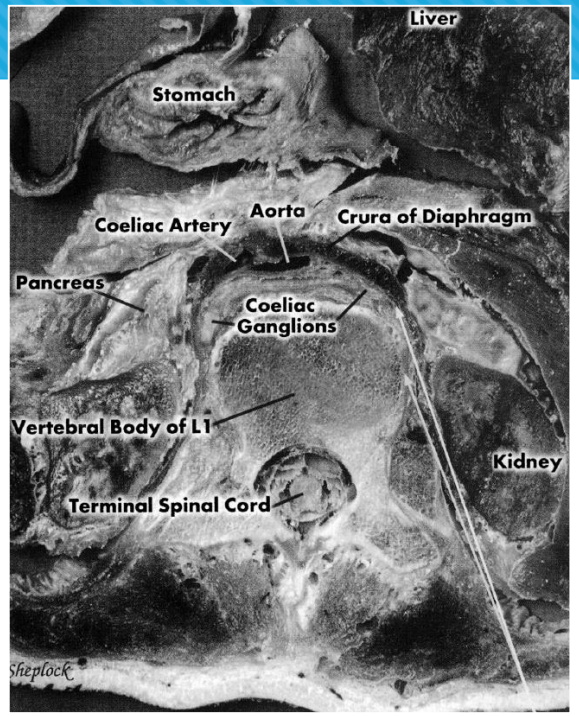
Daughter taught to give sc ketamine prn

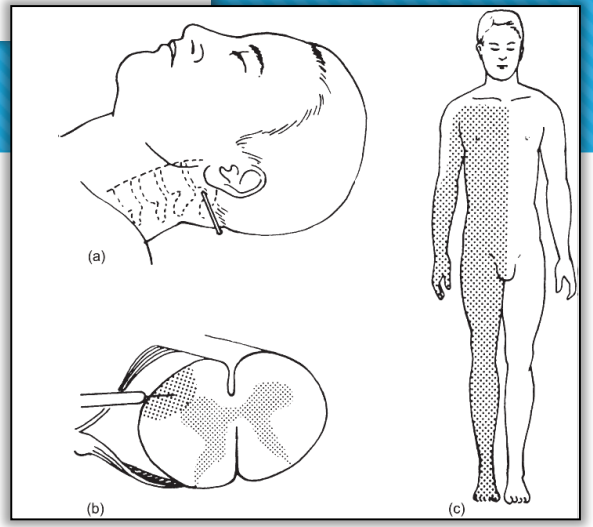
*Importance of family support for care at home*

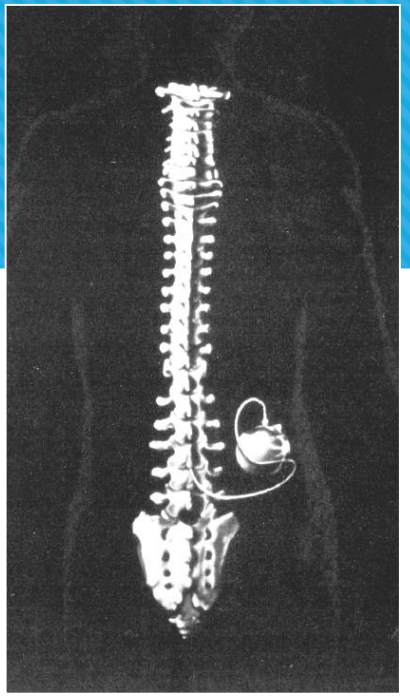
## Acute and chronic pain management in palliative care

Best Practice & Research Clinical Obstetrics & Gynaecology
Vol. 15, No. 2, pp. 203–234, 2001

Vitaly Gordin MD



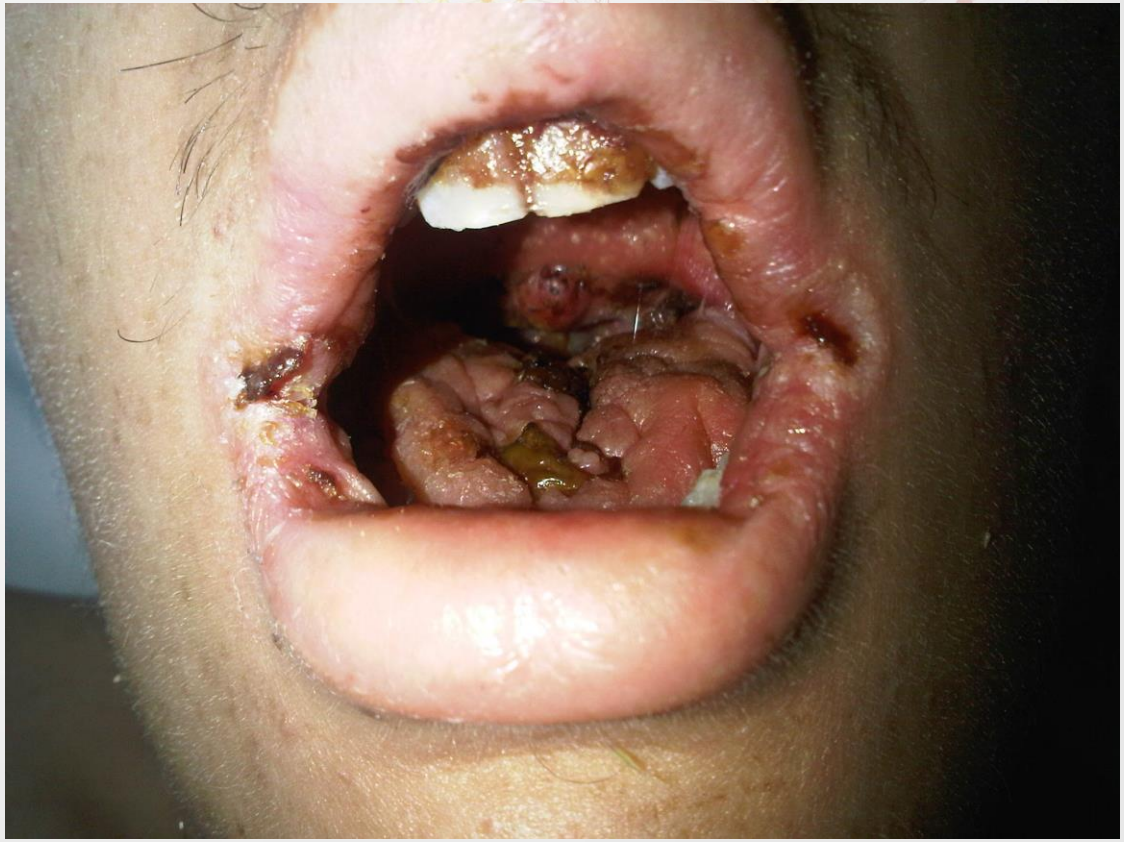



The rise of ‘palliative care’ coincided with decrease in use of targeted neurolytic blocks and spinal delivery of drugs for persistent cancer-related pain

# Management of oropharyngeal mucositis in SCT

Main principles

- Topical anaesthesia
- Systemic analgesia
- Nutritional support
- Mucosal protection
- (Prevention)



# Symptom management of oropharyngeal mucositis

- Patients often need background pain control for pre-existing bony and neuropathic pathology
  - Preference for oral, transdermal, nasal routes
  - Potential myelosuppression from gabapentin – use Pregabalin
  - Avoidance of subcutaneous injections or infusions
- Topical treatments for pain
  - Benzydamine (Difflam)
  - Local anaesthetics
  - (Gelclair, Mugard)

# Symptom management of oropharyngeal mucositis – Sheffield SOP

- Rapid assessment and treatment
  - Patients seen <1 working day, and out of hours
- Evidence-based symptom management
  - Use of newer opioids and delivery systems
    - Transdermal opioids – esp buprenorphine
    - Nasal fentanyl (Pecfent™) for rapid analgesia
  - Topical sodium channel blockers ('local anaesthetics')
    - Oxetacaine
    - Lidocaine
- Holistic overview – nutritional support

***NB: Above medications are unlicensed for this purpose***

# Do cannabis-based medicines have a role in pain management?

NICE NG144 guidance was published on 11 November 2019. The main recommendations with respect to pain were:

***1.2 Chronic pain***

*1.2.1* ***Do not offer*** *the following to manage chronic pain in adults:*

- *nabilone*
- *dronabinol*
- *THC (delta-9-tetrahydrocannabinol)*
- *a combination of cannabidiol (CBD) with THC.*

*1.2.2* ***Do not offer CBD to manage chronic pain in adults unless as part of a clinical trial.***

# Conclusion:
# Model for holistic pain management

**Comprehensive, multimodal, evidence-based approach**

- **Targeting the underlying disease** process
  - Cancer, inflammatory, neuropathic, degenerative
- **Pharmacological**
  - Targeting all available molecular mechanisms
- **Surgical, interventional techniques**
  - Local nerve blockade, kyphoplasty, longterm spinal drug delivery
- Biopsychosocial
  - **Psychological, exercise, nursing & AHP care**