Living with and beyond cancer – *the challenges of managing pain in an ageing population*

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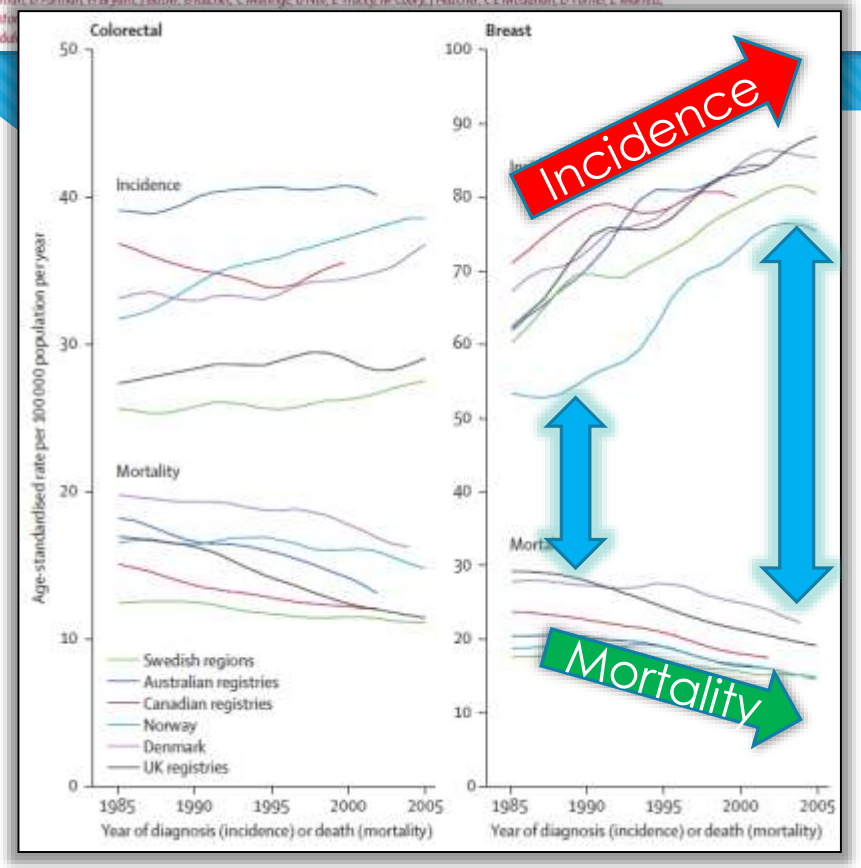
GOOD NEWS! Rise of cancer survivorship

Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data

Lancet 2011



Increasing cancer incidence
+ decreasing mortality
= more survivors
Now – 2.5m in UK

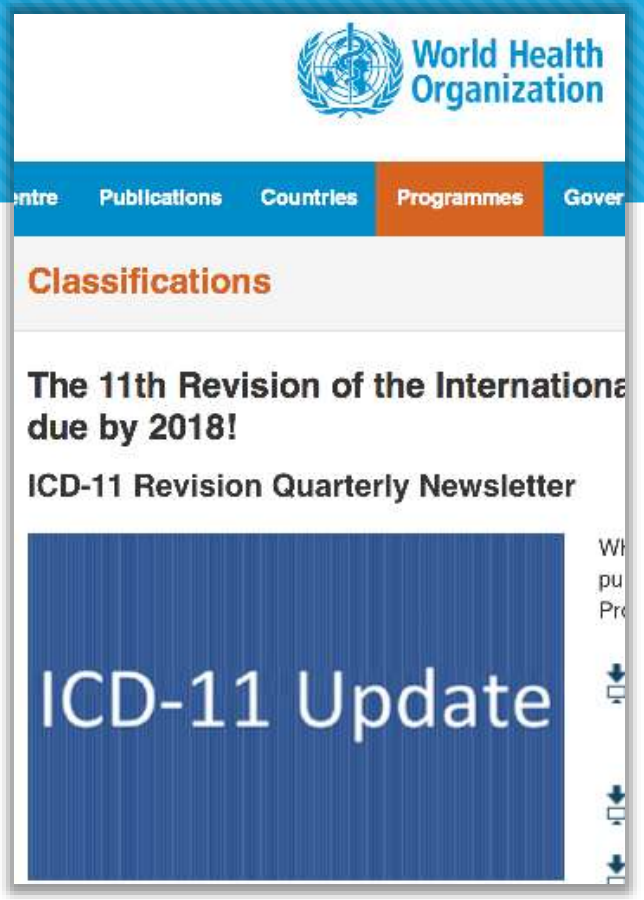
Adverse events of targeted therapies

Jean A. Klastersky — *Curr Opin Oncol* 2014

BAD NEWS:
Cancer treatments cause pain!

Table 1. Main adverse reactions – % all severity grades and ( ) grades at least 3 and 4

	Systemic manifestations			Renovascular			Skin and mucosa			Gastrointestinal symptoms			
Targeted therapy	Fatigue/ asthenia	Arthralgia/ myalgia	Headache	Hypertension	Proteinuria	↑ Creatinine	Rash and similar	Hand and foot syndrome	Stomatitis/ mucositis	Anorexia	Nausea/ dyspepsia	Vomiting	Diarrhea
Bevacizumab	20 (4)		22 (3)	36 (8)	5 (0)		10 (3)	(3)			6 (0)		5 (2)
Sorafenib	28 (4)	15 (3)	7 (0)	30 (12)	8 (1)		31 (4)	51 (17)	12 (1)	26 (2)	19 (1)	13 (0)	52 (8)
Axitinib	37 (10)	19 (2)	11 (1)	42 (17)	13 (3)		13 (1)	28 (6)	15 (1)	31 (4)	30 (2)	18 (1)	13 (1)
Sunitinib	63 (19)	28 (2)	22 (1)	41 (15)	14 (4)	46 (1)	23 (1)	50 (11)	27 (1)	37 (3)	46 (2)	27 (3)	57 (8)
Pazopanib	55 (11)	30 (3)	23 (3)	46 (16)	18 (4)	32 (1)	18 (1)	29 (6)	14 (1)	37 (1)	45 (2)	28 (2)	63 (9)
Aflibercept	67 (7)	32 (1)	42 (7)	51 (13)	48 (11)					21 (0)	12 (0)	2 (0)	11 (0)
Tivozanib	29 (3)			45 (11)	64 (3)	70 (1)							33 (2)
Cabozantinib	63 (16)			22 (12)				30 (8)	19 (1)	54 (6)	49 (5)	28 (4)	51 (3)
Regorafenib	28 (4)			30 (1)				40 (19)	36 (2)	26 (2)			32 (8)
Vandetanib	24 (6)		26 (0)	32 (9)			45 (4)		56 (8)	26 (1)	29 (1)	14 (1)	30 (2)
Cetuximab	9 (0)	(7)	(7)				18 (12)	7 (0)	6 (0)	5 (0)	6 (0)	6 (0)	30 (0)
Panitumumab	24 (4)						64 (5)	20 (1)		22 (3)	22 (1)	18 (2)	21 (1)
Trastuzumab		(8)	(4)	14 (1)									(6)
Pertuzumab	12 (1)		5 (0)				19 (0)			2 (0)	19 (0)	7 (1)	24 (7)
Lapatinib	19 (0)		9 (0)				29 ()		2 (0)	10 (1)	28 (0)	18 (0)	48 (7)
Gefitinib	30 (6)						62 (32)	4 (4)	3 (1)	8 (3)	7 (1)		36 (15)
Erlotinib	60 (30)						94 (65)	11 (9)	17 (3)	37 (11)	14 (7)		17 (14)
Crizotinib	27 (2)						9 (0)	8 (0)			55 (1)	47 (1)	60 (0)
Olaparib	48 (6)	12 (0)	18 (0)							18 (0)	68 (2)	31 (2)	23 (2)
Imatinib	35 (1)						31 (0)			32 (0)	28 (1)	16 (3)	31 (4)
Vemurafenib	11 (2)		4 (1)				10 (8)				7 (1)	3 (1)	5 (1)
Vismodegib	36 (4)	68 (4)								23 (3)	29 (11)		22 (1)
Everolimus	33 (3)	20 (2)	19 (1)				36 (1)		56 (8)	29 (1)	29 (1)	14 (1)	30 (2)
Ipilimumab		37 (0)					25 (1)						36 (4)
Lambrolizumab	30 (1)	19 (0)	14 (0)			2 (1)	21 (2)			4 (1)			



ICD-11 – recognition of chronic pain

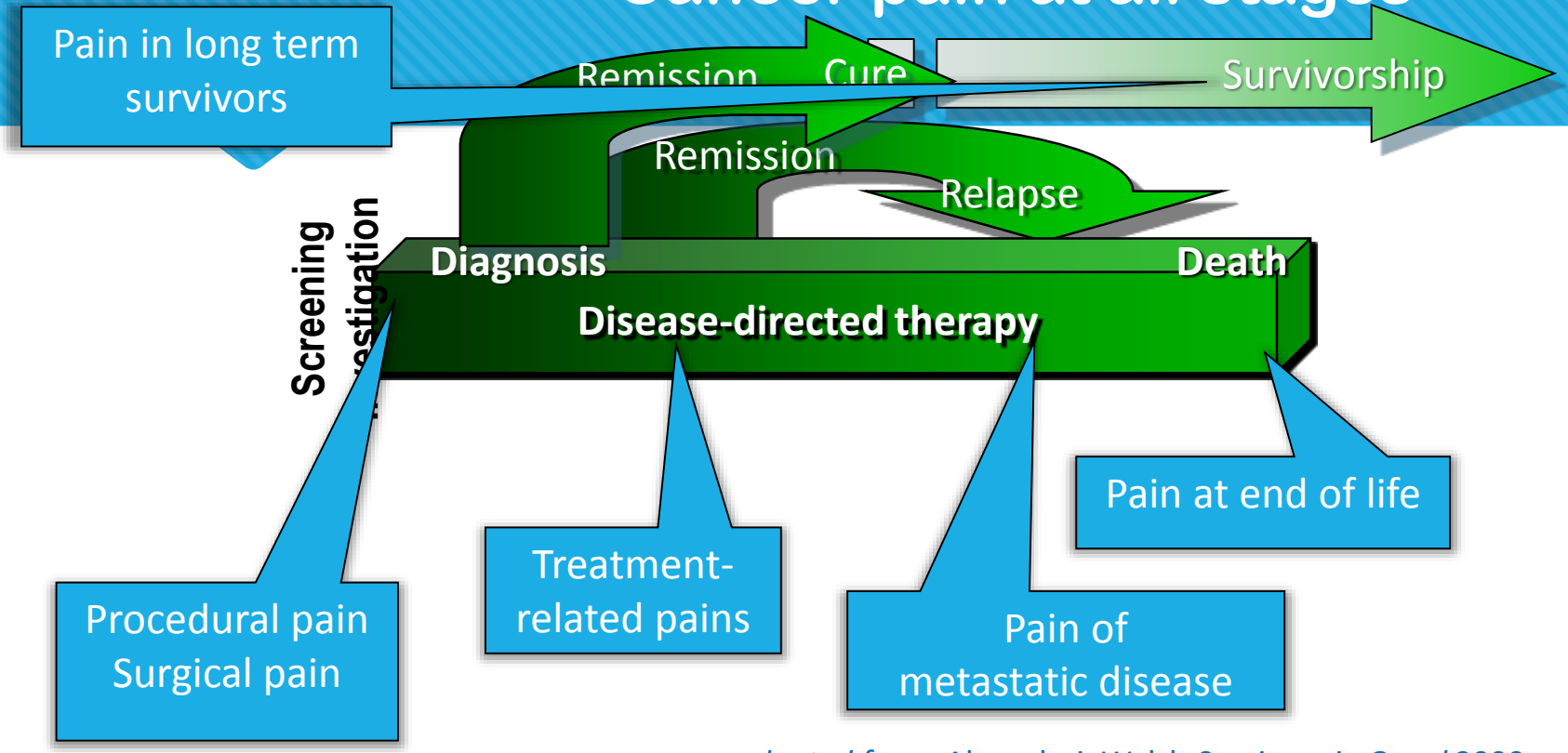
(persistent or recurrent pain lasting longer than 3 months)

1. Chronic primary pain
2. **Chronic cancer pain**
3. Chronic postsurgical and posttraumatic pain
4. Chronic neuropathic pain
5. Chronic headache and orofacial pain
6. Chronic visceral pain
7. Chronic musculoskeletal pain

Cancer-related pains

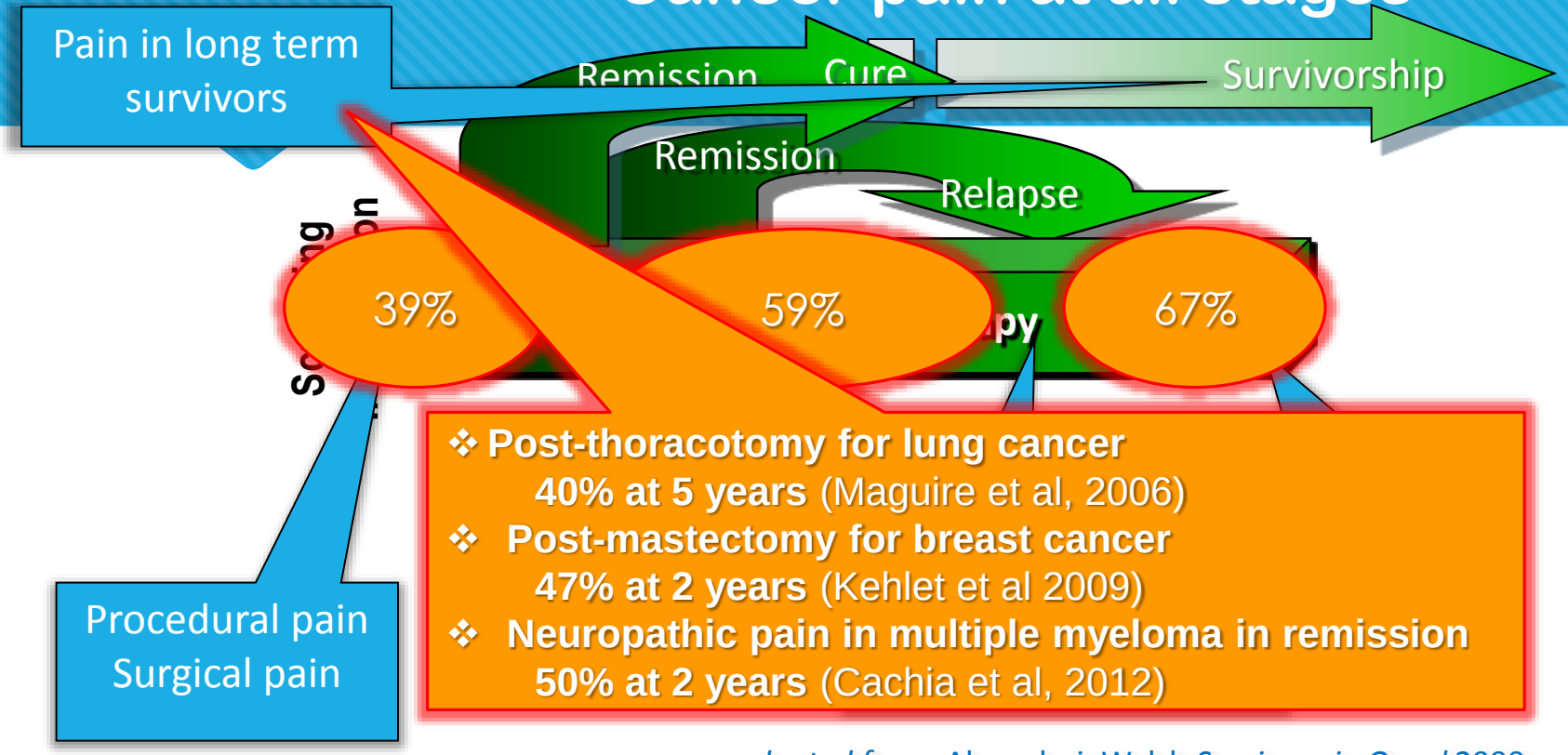
- **Acute pains** related to cancer biopsy, surgical procedures
  - May lead to chronic pain
- Pain arising from **direct effect of primary cancer** on local site – bone, soft tissue, nerves
- Pain arising from **persistent, progressive, metastatic** cancer
- Pain **related to cancer treatments** at all stages

Sheffield model of supportive care
Cancer pain at all stages



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

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


I beat Cancer
Now I'm fighting pain.
Help us to help those in need…
The British Pain Society needs your support.
If *you* would like to help us fight pain please donate.
Together we can make a difference.
PAIN:LESS
To donate, text PAIN40 and the amount to 70070 (e.g. for five pounds text, PAIN40 5).
THE BRITISH PAIN SOCIETY

REVIEW

Current Opinion Supportive Palliative Care

Boland, Ahmedzai 2017

CURRENT OPINION

Persistent pain in cancer survivors

...am H. Ahmedzai[b]

Table 1. Main types of treatment-related persistent pain in cancer survivors

System	Example of pain syndromes
Surgery	Lymphoedema Breast implants/reconstruction Phantom limb Postmastectomy Postthoracotomy
Chemotherapy (including ...tors and	Arthralgia/myalgia Bisphosphonate-related osteonecrosis of jaw Chemotherapy-induced peripheral neuropathy Osteonecrosis Osteoporosis
Radiation	Cystitis Enteritis/proctitis Fistula formation Plexopathies
Haematopoietic stem cell ...cluding ...-host	Arthralgia/myalgia Corneal ulcerations Fibrosis/scleroderma Mucous membrane inflammation, strictures Peripheral neuropathy Osteonecrosis of joints

SURGERY

CHEMO, HORMONES

RADIATION

STEM CELL TRANSPLANT

KEY POINTS

- Persistent pain in people surviving cancer, or living with cancer as a chronic disease, can arise from the malignant process, from anticancer treatments, or from comorbidities.
- Molecular, genetic and psychological mechanisms of the generation and perpetuation of persistent pain are being identified.
- Pain management in cancer survivors needs a holistic approach, with minimal medication (especially opioids) and increased reliance on education, empowerment and psychological forms of self-management.
- As the population of cancer survivors grows, clinicians and the healthcare system will need to adapt and learn new ways to support patients with persistent pain.

...opathy, pain management, pain prediction, persistent

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"

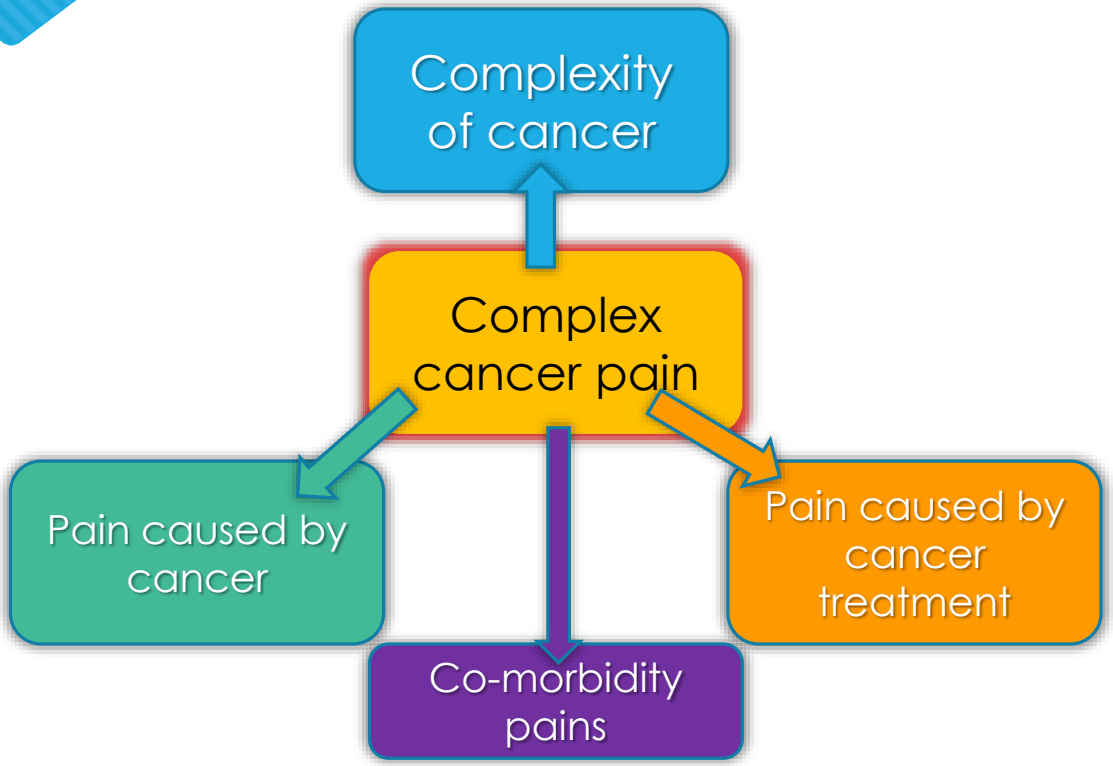
Only evidence-based treatment for CIPN is Duloxetine (Smith et al, JAMA 2013)
Important role for topical creams – Capsaicin and Menthol

Pain management in long-term cancer survivors

Cancer survivors are trying to return to normal daily life

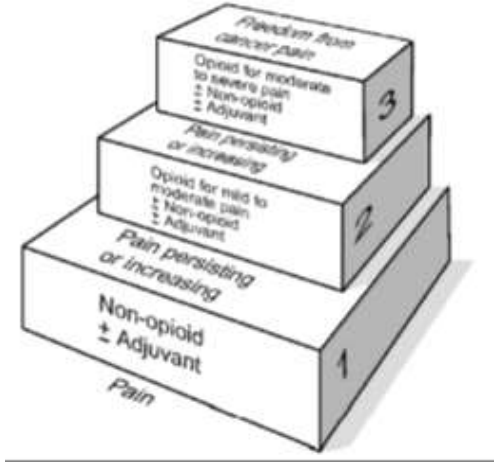
- Prefer not to keep coming back to hospital
- Prefer not to be ‘drugged up’, suffer longterm side-effects - especially constipation, sedation
- Want to carry on driving
- Want to return to work and hobbies

Cancer pain is much more complex than we thought!

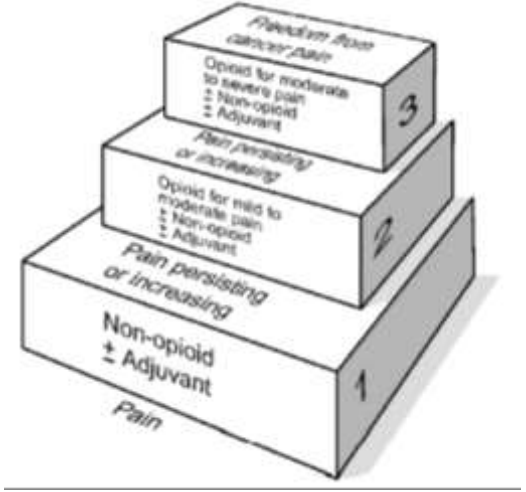


Cancer pain treatment guidelines – *should they remain the same forever?*

WHO 3-step ladder (1986)

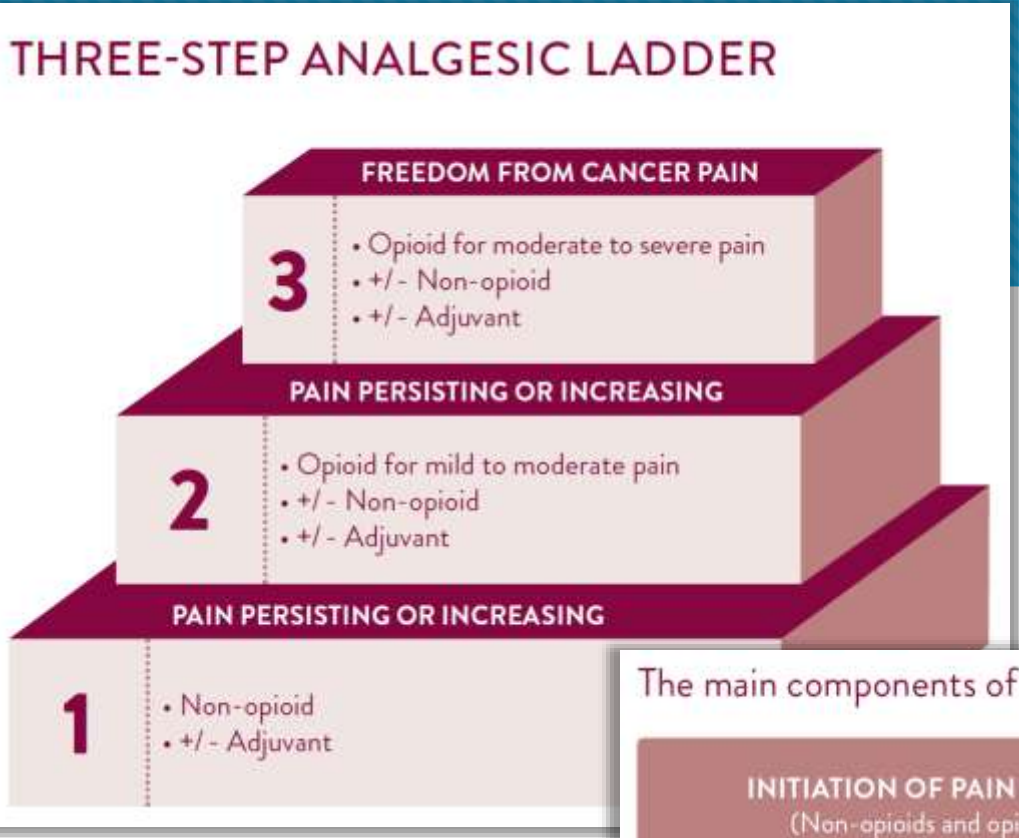


Scottish guidelines (2008)



Cancer pain relief. Geneva: World Health Organisation. 1986.
SIGN. 106 A National Clinical Guideline – Control of pain in adults with cancer. 2008.

WHO 'update' 2019



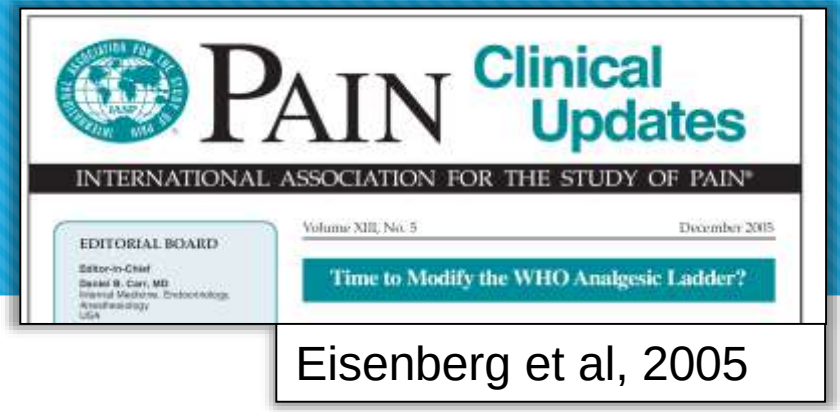
In 1986 WHO wanted a 'simple' approach to cancer pain

HL Mencken

"For every difficult problem, there is an easy answer –

short, simple – and wrong."

Can we start cancer patients straight onto 'strong' opioids?


PAIN Clinical Updates

INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN®

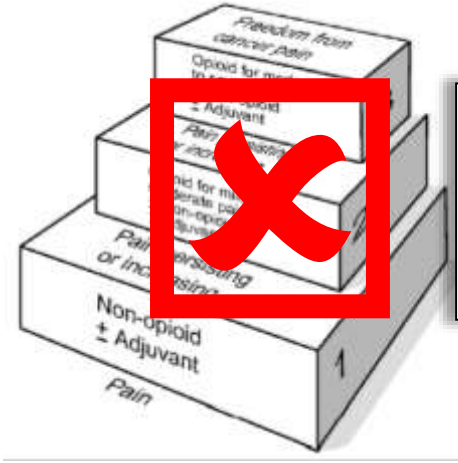
EDITORIAL BOARD

Volume XIII, No. 5 December 2005

Time to Modify the WHO Analgesic Ladder?

Eisenberg et al, 2005

WHO 3-step ladder (1986)



Patients who were started on "strong" opioids had significantly better pain relief than those who were treated according to the WHO guidelines.

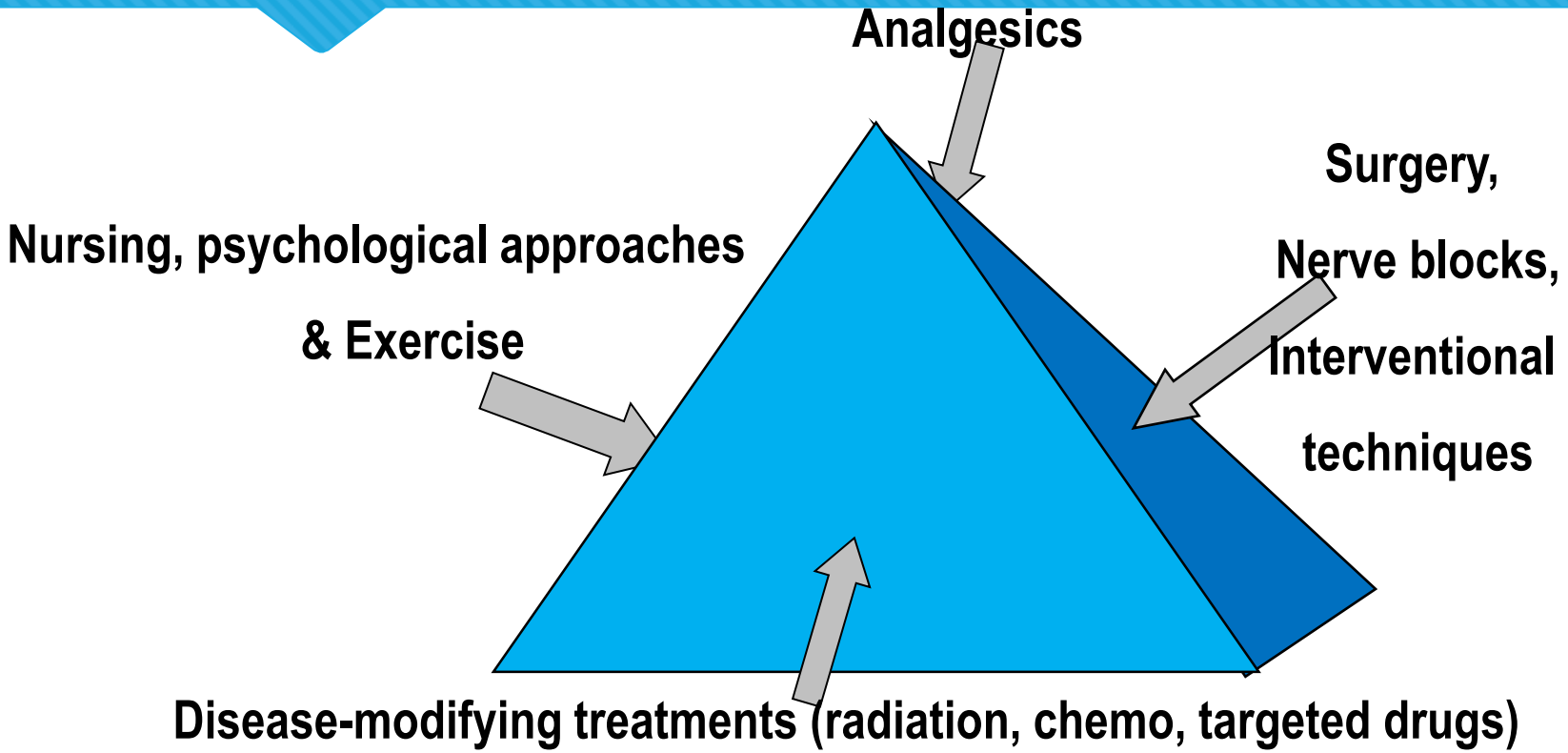
What we've learnt about using opioids from treating cancer-related pain

- **Opioids: medications of choice for moderate-severe cancer pain**
  - - in combination with non-opioid pharmacotherapies with non-pharmacological therapies as appropriate
- **Comprehensive patient assessment** – before and during Rx
- **Document treatment plan** and outcomes
- **Cautious titration**: balance between efficacy and tolerability
  - Monitor response to therapy, including analgesia, adverse effects, and the development of aberrant behaviours

21st century Pyramid model

Modern multimodal approach to pain in cancer patients

based on: Ahmedzai & Lübbe, *Lancet* 2001



Standards for the management of cancer-related pain across Europe—A position paper from the EFIC Task Force on Cancer Pain

Eur J Pain, 2019

Michael I. Bennett[1*] | Elon Eisenberg[2*] | Sam H. Ahmedzai[3] | Arun Bhaskar[4] | Tony O'Brien[5,6,7] | Sebastiano Mercadante[8] | Nevenka Krčevski Škvarč[9] | Kris Vissers[10] | Stefan Wirz[11] | Chris Wells[12] | Bart Morlion[13]

Standards for European cancer pain management

Standard 1. **Patients with a history of cancer should be routinely screened for pain at every engagement** with a healthcare professional. [GRADE 1B]

Standard 2. Patients **identified with cancer-related pain should receive a pain assessment when seen by a healthcare professional**, which at a minimum classifies the cause of pain based on proposed ICD-11 taxonomy and establishes the intensity and impact on quality of life of any pain that they report. [GRADE 1B]

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10 standards for European cancer pain management

Standard 4.

Patients should receive **tailored multimodal treatment** which reduces the pain and its impact on daily living and that may include a **combination of medicines, nonpharmacological treatments, oncological interventions, physical rehabilitation and psychosocial or spiritual support**.

[GRADE 1A]

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
Mild	9
Moderate	18
Severe	
Total	

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)

for Research and Treatment of Cancer (EO
from 0–100

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

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'

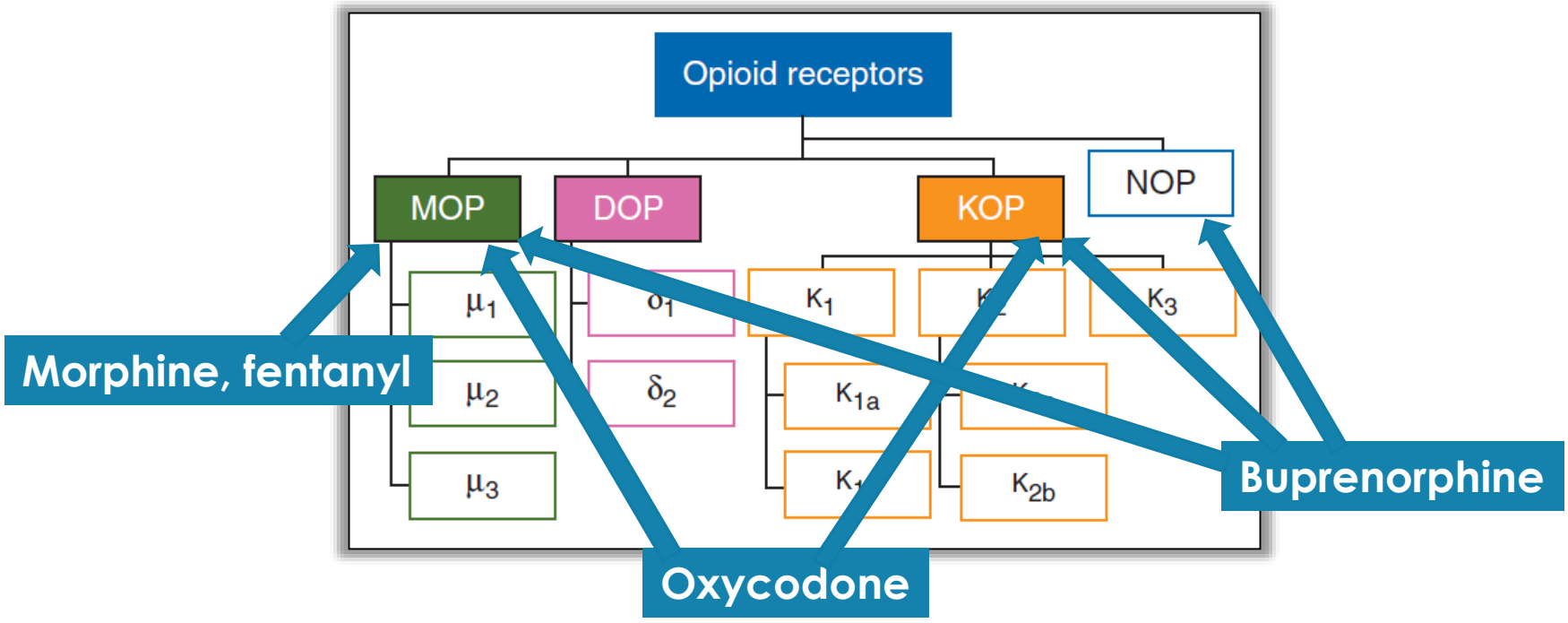
Is morphine still the 'gold' standard for cancer-related pain?

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**
- **Wide range of routes** of administration and available formulations

Morphine fails on all these criteria!

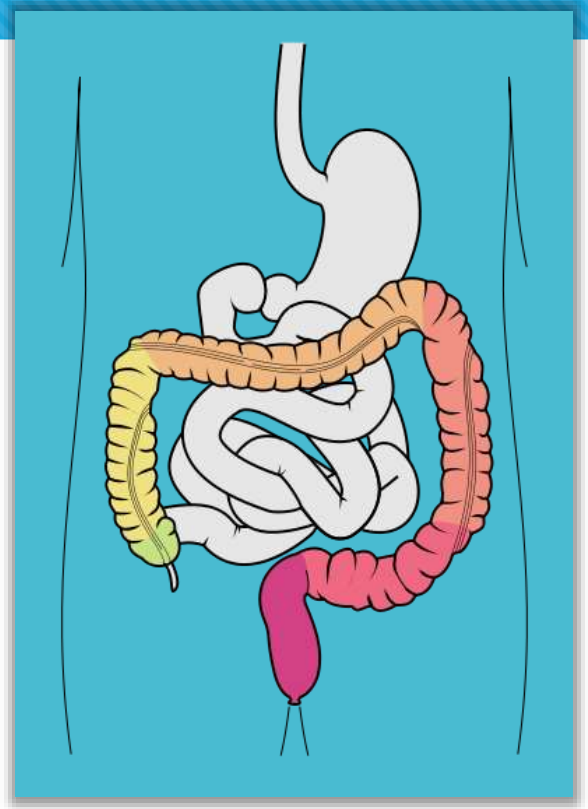
Opioid receptors and subtypes



Commonest adverse effect: Opioid-Induced Constipation (OIC)

- Opioids:
  - suppress forward peristalsis
  - raise sphincter tone
  - increase fluid absorption
  - reduce intestinal secretions

- Largely mediated by peripheral mu (μ)-opioid receptors:
  - on myenteric and submucosal neurons in the gut



Targeted treatment of opioid-induced constipation

- Oral laxatives and rectal measures are not based on good evidence

  ➔ *They can only **palliate symptoms***

- New **targeted approach** is to antagonise peripheral gastrointestinal opioid receptors (**PAMORAs**) whilst allowing CNS penetration of opioids for analgesia

  ➔ ***Blocks mechanism of OIC***

  - *Oxycodone + Naloxone PR oral combination*
  - *Methylnaltrexone – subcutaneous injection*
  - *Naloxegol – oral*
  - *Naltemidine - oral*

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).”

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.

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Morphine *versus* oxycodone

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

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

Buprenorphine – unique safety feature is relative lack of respiratory depression

Ceiling to respiratory depression

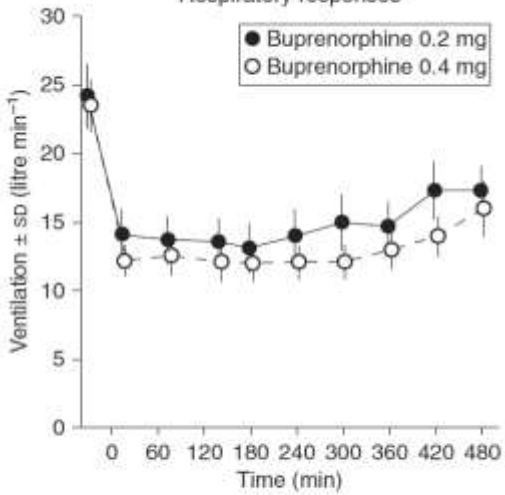


Fig 1 Influence of i.v. buprenorphine, 0.2 and 0.4 mg (per 70 kg), on inspired minute ventilation at a fixed end-tidal P_{CO_2} of 7 kPa in healthy volunteers. The influence of the two buprenorphine doses is similar with respect to peak respiratory depression and duration of effect.

No ceiling to analgesic effect

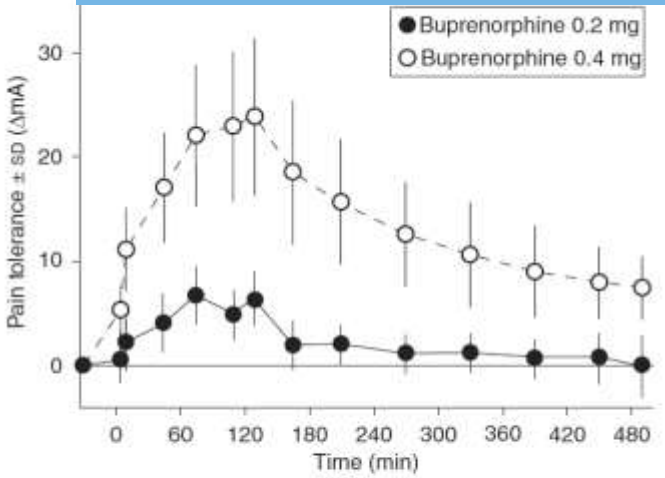


Fig 2 Influence of i.v. buprenorphine, 0.2 and 0.4 mg (per 70 kg), on pain tolerance in healthy volunteers. Values are the increase in currents to achieve pain tolerance relative to baseline pain tolerance currents (ΔmA). A significant increase in analgesia is observed going from buprenorphine 0.2 to 0.4 mg.

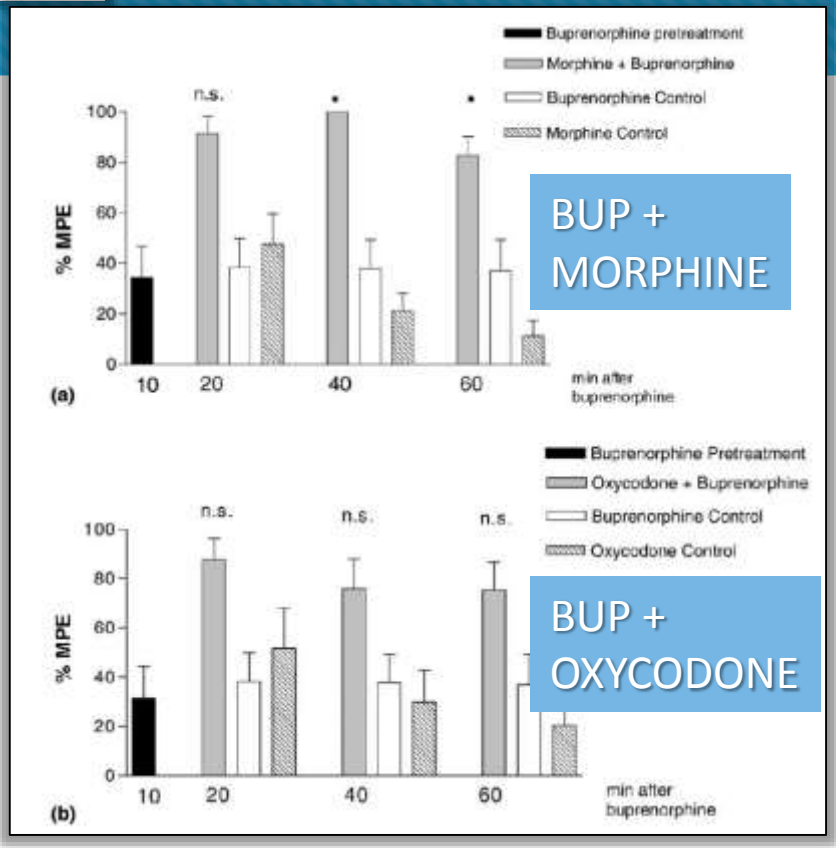
Eur J Pain 2005

Interaction of μ-opioid receptor agonists and antagonists with the analgesic effect of buprenorphine in mice

Babette Kögel, Thomas Christoph, Wolfgang Straßburger, Elmar Friderichs *

Buprenorphine can be combined with other mu-opioid analgesics

- Mouse studies – combinations of buprenorphine with morphine, oxycodone or fentanyl
- Additive or synergistic effects of combinations of buprenorphine + any other opioid
- Effect reduced by naloxone, showing acute analgesic action mediated by MOP

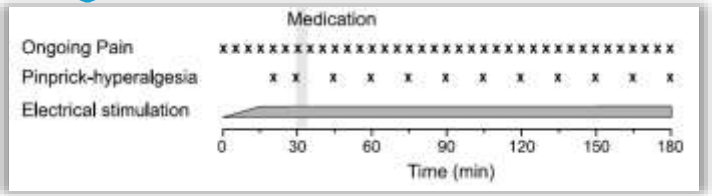


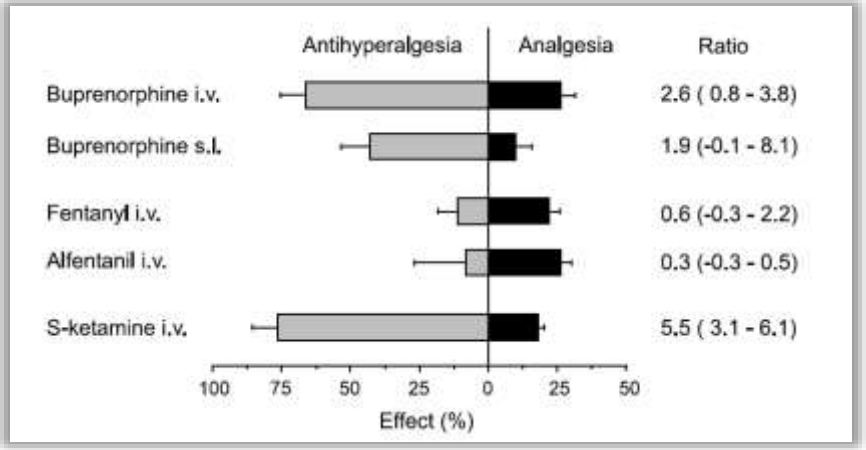
Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model

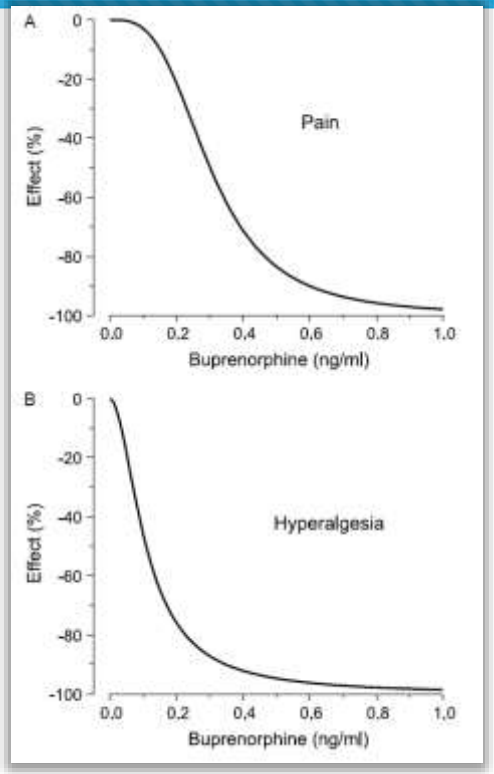
Wolfgang Koppert[a,*], Harald Ihmsen[a], Nicole Körber[a], Andreas Wehrfritz[a], Reinhard Sittl[a], Martin Schmelz[b], Jürgen Schüttler[a]

Pain 2005

Buprenorphine is anti-hyperalgesic







Buprenorphine:
No dose adjustment needed for -

Elderly Patients

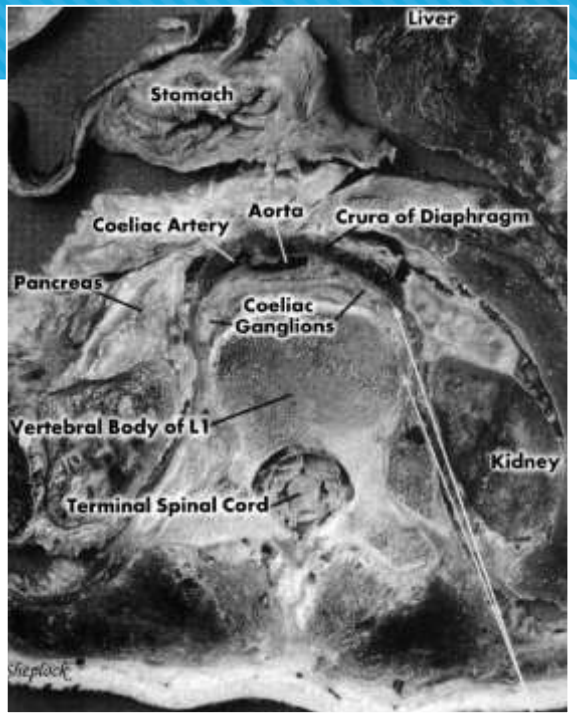
Renal Impairment

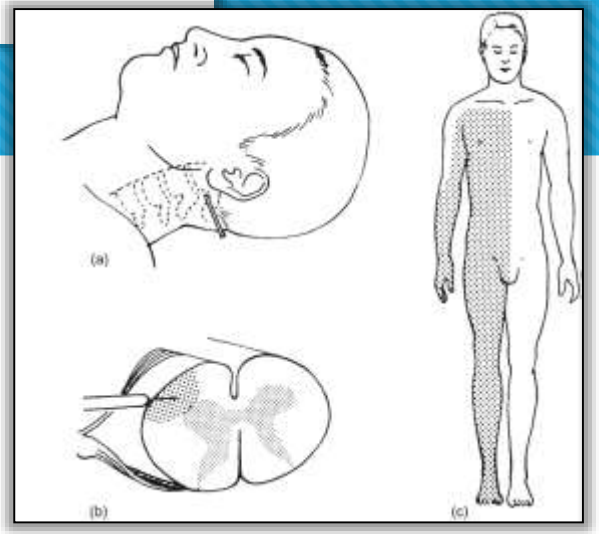
1. Sovenor Buprenorphine Patch Prescribing Information 2017. **2.** Kress HG. *Eur J Pain 2009;13:219-230.*

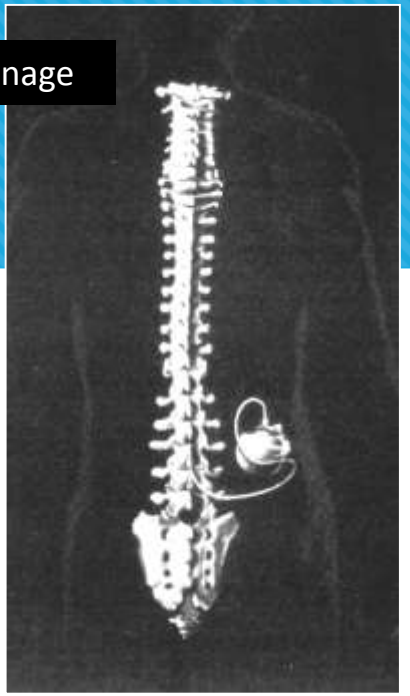
Acute and chronic pain management in palliative

Vitaly Gordin MD

Sacral nerve infiltration from recurrent cervical cancer starting in teenage







"The role of interventional pain management, including spinal analgesia and neurolytic blocks, was significantly suppressed"

(Burton, Hamid. *Expert Rev Anticancer Ther* 2007)

Can J Anesth/J Can Anesth
https://doi.org/10.1007/s12630-019-01482-w

REVIEW ARTICLE/BRIEF REVIEW

Interventional anesthesia and palliative care collaboration to manage cancer pain: a narrative review

Compte rendu narratif d'une collaboration entre les services d'anesthésie interventionnelle et de soins palliatifs pour prendre en charge la douleur cancéreuse

Jenny Lau, MD · David Flamer, MD · Patricia Murphy-Kane, RN, BA, BScN

Interventional techniques and spinal opioid delivery

Peripheral nervous system interventional analgesic procedures

- Peripheral nerves: somatic pain
- Sympathetic nerves: visceral pain
- Celiac plexus and thoracic splanchnic nerve blocks
- Superior hypogastric plexus
- Ganglion impar

Neuraxial analgesia infusions

- Percutaneous short-term catheter (epidural or intrathecal) connected to an external pump—*recommended for patients near the end of their life*:
- Subcutaneous intrathecal catheter and injection port connected to an external pump—*recommended for patients with a life expectancy of one to six months*:
- Subcutaneous intrathecal catheter with a fully implanted programmable infusion pump (also known as an ''intrathecal drug delivery system'' [IDDS])—*recommended for patients with a life expectancy of > six months:*

SR, 75 years, myeloma survivor

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

Nearly died from 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

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.***

Pain at the end of life

- Patients should be fully involved in decision-making and receive individualised care (NICE NG31, 2015)
- Not all patients need to die with a syringe driver!
- Home may be preferred place of death – *if there is good family support*
- Pain management at end of life is often worse at home than in hospice or hospital

Conclusion:
Pain management – Solutions for the 21st century

- Attention to **cancer-related pain at all stages** – after surgery, chemotherapy, survivors, end of life
- **Optimise post-operative pain management –** taper early and discharge with only short-term supply
- **Supportive and palliative care** have potentially major role in survivors as well as end of life
- **Holistic biopsychosocial approach** – take into account **age, family situation, comorbidities, organ function, polypharmacy**
- **Multimodal analgesia + Exercise**
- **Smart, targeted pain management** – maximum efficacy, minimum adverse effects

20th or 21st century models? You decide

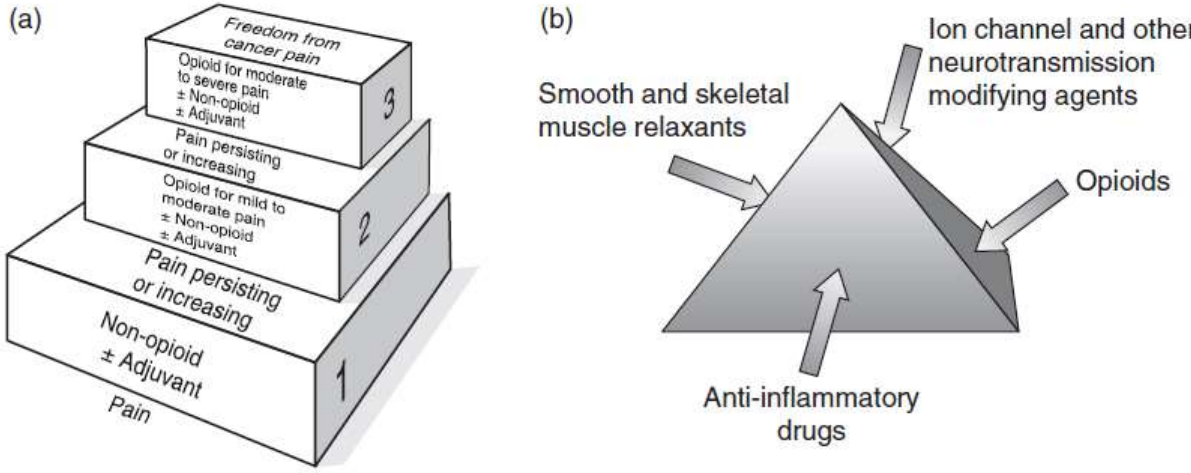


Fig. 18.2 (a) WHO analgesic ladder (http://www.who.int/cancer/palliative/painladder/en/). (b) Pyramid model (25).

Boland, Cachia, Portenoy, Ahmedzai (2011)

Accompanying the cancer patient and family - on the whole journey – to recovery or death

Thank you