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

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NCRI: Co-chair of Living With and Beyond Cancer Research Group

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Increasing cancer incidence + decreasing mortality = more survivors

Now – 2.5m in UK

GOOD NEWS!
Rise of cancer survivorship
Adverse events of targeted therapies

Jean A. Klastersky

Curr Opin Oncol 2014

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

<table>
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<tr>
<th>Targeted therapy</th>
<th>Fatigue/asthenia</th>
<th>Arthralgia/myalgia</th>
<th>Headache</th>
<th>Hypertension</th>
<th>Proteinuria</th>
<th>Creatinine</th>
<th>Rash and similar</th>
<th>Hand and foot syndrome</th>
<th>Stomatitis/mucositis</th>
<th>Anorexia</th>
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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

- Remission
- Cure
- Survivorship
- Death
- Remission
- Relapse

Diagnosis
Disease-directed therapy

- Procedural pain
- Surgical pain
- Treatment-related pains
- Pain at end of life
- Pain of metastatic disease

adapted from: Ahmedzai, Walsh Seminars in Oncol 2000
Sheffield model of supportive care
Cancer pain at all stages

- Remission
- Cure
- Survivorship
- Relapse
- Remission

Pain in long term survivors

Procedural pain
Surgical pain

39%
59%
67%

- Post-thoracotomy for lung cancer
  40% at 5 years (Maguire et al, 2006)
- Post-mastectomy for breast cancer
  47% at 2 years (Kehlet et al 2009)
- Neuropathic pain in multiple myeloma in remission
  50% at 2 years (Cachia et al, 2012)

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
## Persistent pain in cancer survivors

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

<table>
<thead>
<tr>
<th>System</th>
<th>Example of pain syndromes</th>
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<tbody>
<tr>
<td>Surgery</td>
<td>Lymphoedema</td>
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<tr>
<td></td>
<td>Breast implants/reconstruction</td>
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<td>Phantom limb</td>
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<td>Postmastectomy</td>
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<tr>
<td></td>
<td>Postthoracotomy</td>
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<tr>
<td>Chemotherapy (including adjuvant)</td>
<td>Arthralgia/myalgia</td>
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<td></td>
<td>Bisphosphonate-related osteonecrosis of jaw</td>
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<td></td>
<td>Chemotherapy-induced peripheral neuropathy</td>
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<td></td>
<td>Osteonecrosis</td>
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<td>Osteoporosis</td>
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<td>Radiation</td>
<td>Cystitis</td>
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<td>Enteritis/proctitis</td>
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<td>Fistula formation</td>
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<td>Plexopathies</td>
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<td>Haematopoietic stem cell transplant (including rescue)</td>
<td>Arthralgia/myalgia</td>
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<td>Corneal ulcersations</td>
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<td></td>
<td>Fibrosis/scleroderma</td>
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<td></td>
<td>Mucous membrane inflammation, strictures</td>
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<td>Peripheral neuropathy</td>
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<td></td>
<td>Osteonecrosis of joints</td>
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</table>

**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.
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
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?


THREE-STEP ANALGESIC LADDER

1. Pain persisting or increasing
   - Non-opioid
   - +/- Adjuvant

2. Pain persisting or increasing
   - Opioid for mild to moderate pain
   - +/- Non-opioid
   - +/- Adjuvant

3. Freedom from cancer pain
   - Opioid for moderate to severe pain
   - +/- Non-opioid
   - +/- Adjuvant

The main components of the WHO Guidelines are:

- INITIATION OF PAIN RELIEF
  (Non-opioids and opioids)

- MAINTENANCE OF PAIN RELIEF
  (Opioids)

- ADJUVANT MEDICINES
  for cancer pain (Steroids)

- MANAGEMENT OF PAIN RELATED TO
  BONE METASTASES
  (Bisphosphonates and radiotherapy)
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?

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

Analgesics

Nursing, psychological approaches
& Exercise

Surgery,
Nerve blocks,
Interventional techniques

Disease-modifying treatments (radiation, chemo, targeted drugs)
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]
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]
Side effects of analgesia may significantly reduce quality of life in symptomatic multiple myeloma: a cross-sectional prevalence study

Supp Care Cancer 2014

Analgesic side-effects adversely affect QoL

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<th>Pain medication</th>
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<td>Drowsiness</td>
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<td>Hallucinations</td>
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<td>Feeling sad, depressed</td>
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<td>Jerky movements</td>
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Severity of side effects

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HRQoL scores (95% CI)

WITH analgesic side-effects

48.3 (38.7–57.9)

WITHOUT analgesic side-effects

62.6 (53.5–71.7)
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

“I feel a lot better since I ran out of those pills you gave me.”
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

Morphine, fentanyl

Oxycodone

Buprenorphine
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
    - Naltemedidine - oral
“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).”
Oxycodone: a ‘strong opioid’ with reduced CNS side-effects

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### Morphine versus Oxycodone

<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Oxycodone</th>
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<tbody>
<tr>
<td>Oral bioavailability</td>
<td>16-68%</td>
<td>60-87%</td>
</tr>
<tr>
<td>Toxicity in renal failure</td>
<td>+++++</td>
<td>+</td>
</tr>
<tr>
<td>CNS adverse effects</td>
<td>+++++</td>
<td>+</td>
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<tr>
<td>Histamine adverse effects</td>
<td>+++</td>
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Buprenorphine – unique safety feature is relative lack of respiratory depression

Ceiling to respiratory depression

No ceiling to analgesic effect

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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 PCO₂ 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.

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.
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
Buprenorphine is anti-hyperalgesic
Buprenorphine: No dose adjustment needed for -

1. Elderly Patients
2. Renal Impairment

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

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