”New” WHO cancer pain guidelines

Jo Thompson – Nurse Consultant

Supportive & Palliative Care

NHS Royal Surrey NHS Foundation Trust

@JoThompson71

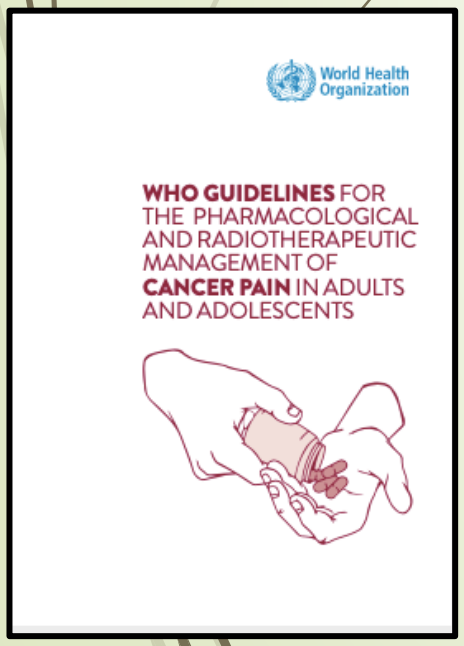
Florence Nightingale Foundation

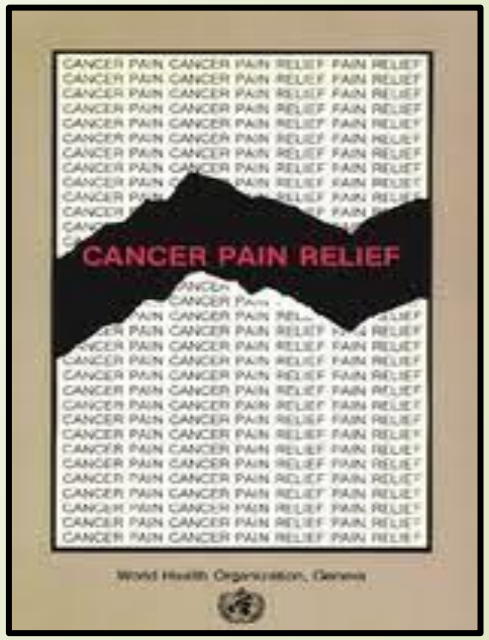
Disclosures

- I have received honoraria for preparing educational material and sitting on advisory boards for:
  - Kyowa Kirin
  - Sandoz
  - Convatec

Overview

- Brief refresher of the "old" guidelines
- Discuss the "new" guidelines
- Consider the relevance of the ladder today



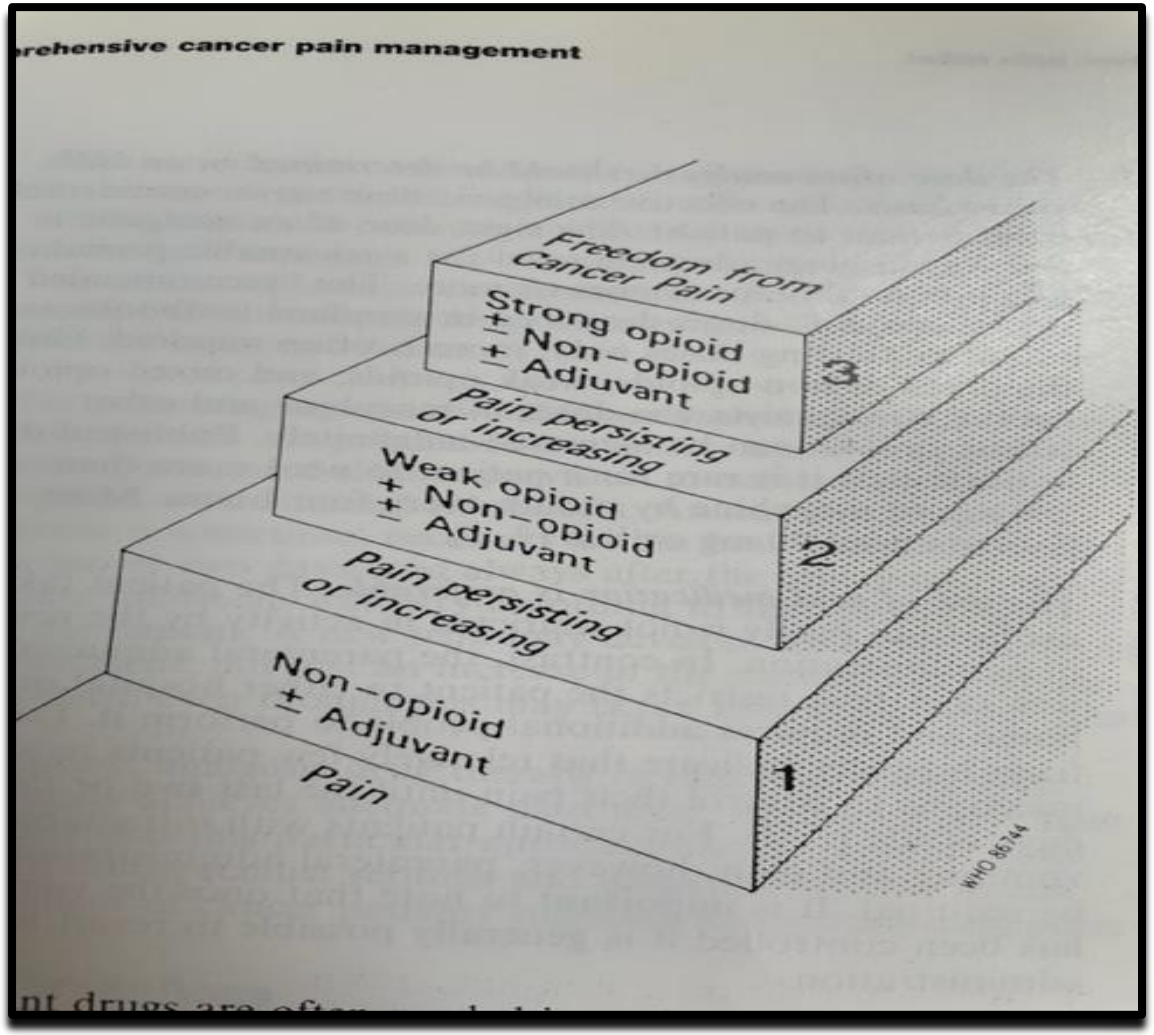


Cancer pain relief – The initial guidelines

- Finalised in 1984 by a group of experts, released in 1986
- Consensus that using a limited number of drugs, cancer pain relief was a realistic target
- Core principles: by mouth, by the clock …

And by the ladder

"Drs and other health care professionals should learn to use a few drugs well"



Why an update?

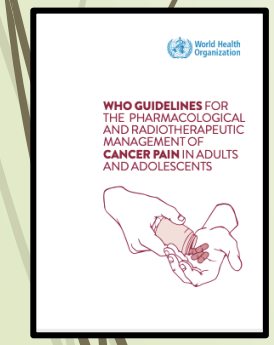
- Recognition of the need for new up to date guidelines
- Recognition of an increasing incidence of cancer & availability of new treatments
- Need to provide guidance suitable for the realities of low / middle income countries – instructions on the use of opioids as accessibility and knowledge remains poor
- Oral morphine WHO list of essential medicines for primary health care:
  - 77% high income countries
  - 15% lower-middle
  - 13% low

The updated guidelines

- Published in 2018
- Covers both pharmacological and radiotherapeutic management
- Involved a GDG reviewing available evidence (according to the GRADE criteria) and making a series of recommendations

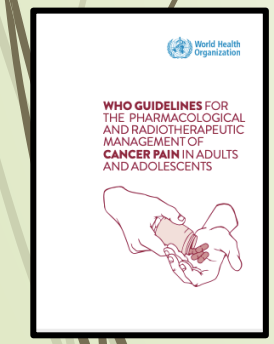
Guiding principles

- Optimum management is to reduce pain to allow an acceptable quality of life
- Global assessment of the person should guide treatment, people experience and express pain differently
- Safety must be assured
- Should include psychosocial and spiritual care



Guiding principles

- Analgesics, including opioids must be accessible: both available and affordable
- Administration : by mouth, by the clock, for the individual and with attention to detail
- Cancer pain management should be integrated as part of cancer care



Opioids – the highlights

Recommendation

In adults (including older persons) and adolescents with pain related to cancer, NSAIDs, paracetamol and opioids generally should be used at the stage of initiation of pain management, either alone or in combination depending on clinical assessment and pain severity, in order to achieve rapid, effective and safe pain control. (*Strong recommendation; low-quality evidence*)

Opioids – the highlights

6.2.1. CHOICE OF OPIOID

6.2.2. TREATMENT OF BREAKTHROUGH PAIN

6.2.4. CHOOSING BETWEEN IMMEDIATE-RELEASE MORPHINE AND SLOW-RELEASE MORPHINE

Switching / rotating

No recommendation

In the absence of evidence, WHO makes no recommendation for or against the practice of opioid switching or rotation.

Considerations

In the absence of any evidence, practitioners may wish to consider an individual trial of therapy and to switch to another opioid for those patients who do not achieve adequate analgesia or have side-effects that are severe, unmanageable, or both.

Ideally, clinicians should identify active clinical trials testing the efficacy of opioid rotation in patients with cancer pain and, wherever possible, encourage eligible patients to enrol into such trials.

Summary of the evidence

No RCTs were identified that evaluated switching or rotating opioids in patients with cancer pain.

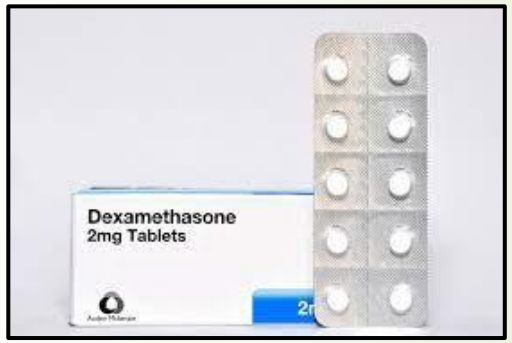
Cessation / reduction of opioids

- Can enable the reduction of opioids
- Unclear protocols

Adjuvant medicines

No recommendation for

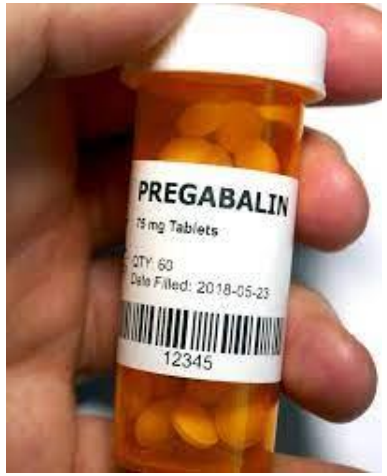
or against using (evidence not sufficient)



Steroids should be prescribed when indicated:
strong recommendation ; moderate quality evidence

Adjuvant medicines

- No recommendation for or against
- Evidence retrieved for the SR to inform the guidelines was discounted
- Practitioners may wish to consider an individual trial



Gabapentin

- Evidence retrieved for gabapentin was discounted following a revelation of fraud

- Whilst widely prescribed, it was rejected for inclusion in the *WHO Model list of essential medicines in 2017*


EDITORIAL

Gabapentin Approvals, Off-Label Use, and Lessons for Postmarketing Evaluation Efforts

Joshua D. Wallach, MS, PhD; Joseph S. Ross, MD, MHS

Bisphosphonates & MABs

Recommendation

In adults (including older persons) and adolescents with bone metastases, a bisphosphonate should be used to prevent and treat bone pain. (*Strong recommendation; moderate-quality evidence*)

No recommendation

WHO makes no recommendation for or against the use of monoclonal antibodies to prevent and treat bone pain.

Bisphosphonates vs MABs

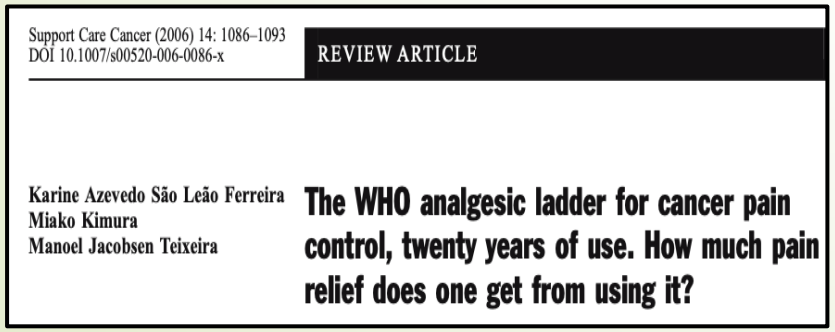
Radiotherapy

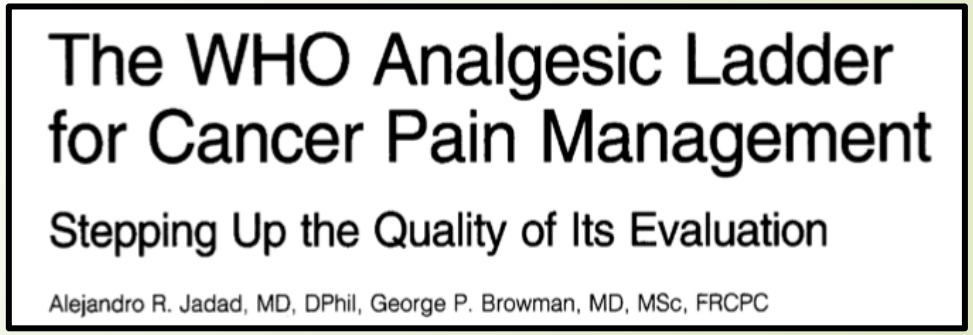
Single dose hyperfractionated

What's wrong with the ladder?

Testing

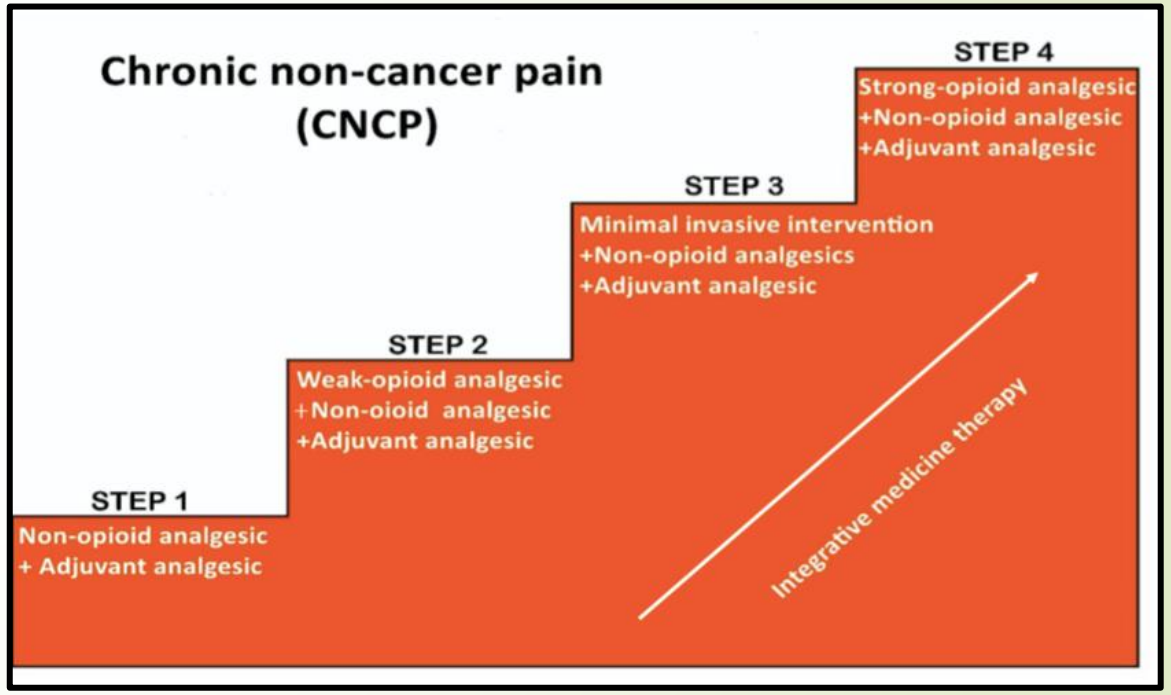
- Studies aimed at testing the effectiveness of the ladder
- Poor methodological quality
- Brought into question the evidence base behind some of the suggested drugs / drug combinations





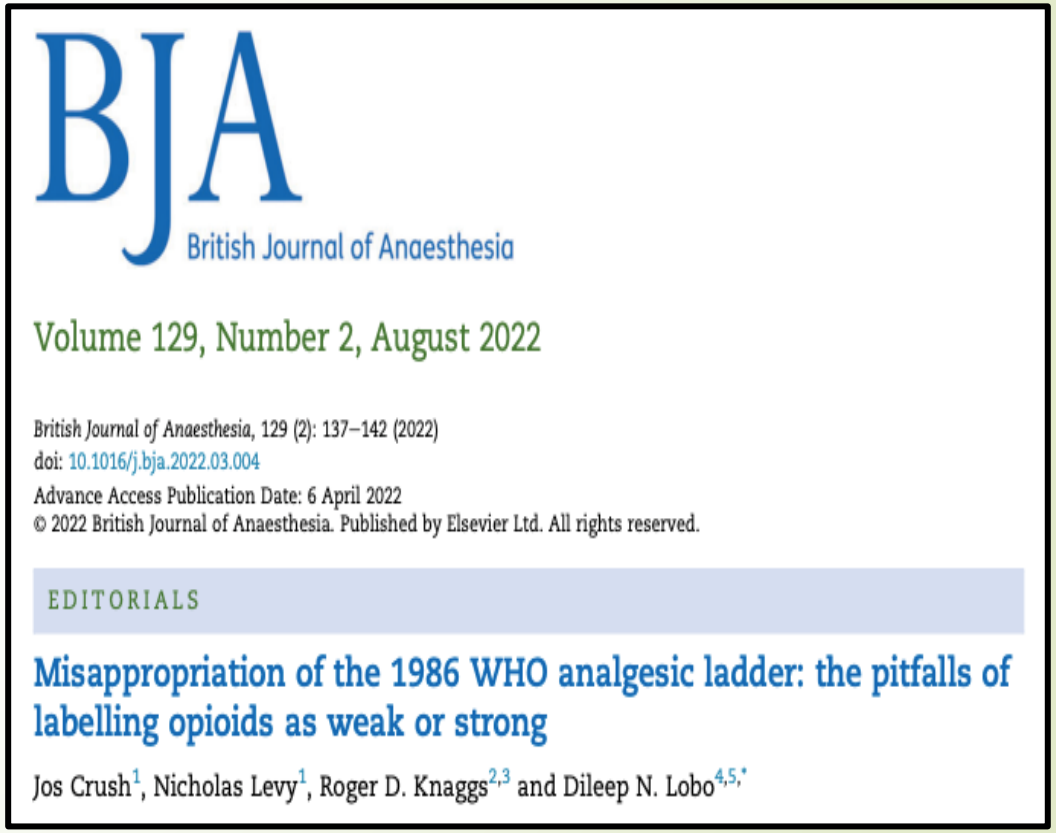
Misinterpretation

- Evolved and used to manage other types of pain
  - Chronic cancer / non-cancer pain
  - Pain related to surgery
- Ladder ‘adapted’



Labelling opioids

- Labelling opioids as ‘weak’ or ‘strong’ unhelpful and misleading
- Harm though opioid use intrinsic to all opioids
- ‘weak’ opioids – variable response due to polymorphisms



BJA
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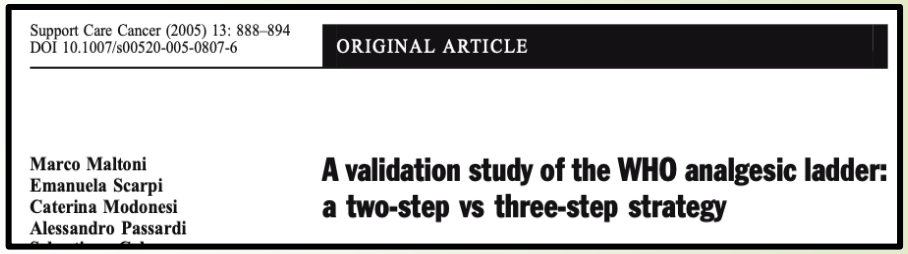
EDITORIALS

Misappropriation of the 1986 WHO analgesic ladder: the pitfalls of labelling opioids as weak or strong

Jos Crush[1], Nicholas Levy[1], Roger D. Knaggs[2,3] and Dileep N. Lobo[4,5,*]

Challenging the steps

- Study of 900 patients showed > 50% switched from step 2 to 3 within 2 weeks (DeConno 2006)
- 54 patients randomised (study closed early)
- Followed up for median 42 days
- Recorded : worst, average and least pain daily
- Other symptoms monitored (Maltoni et al 2005)


Support Care Cancer (2005) 13: 888–894
DOI 10.1007/s00520-005-0807-6

ORIGINAL ARTICLE

Marco Maltoni
Emanuela Scarpi
Caterina Modonesi
Alessandro Passardi

A validation study of the WHO analgesic ladder: a two-step vs three-step strategy

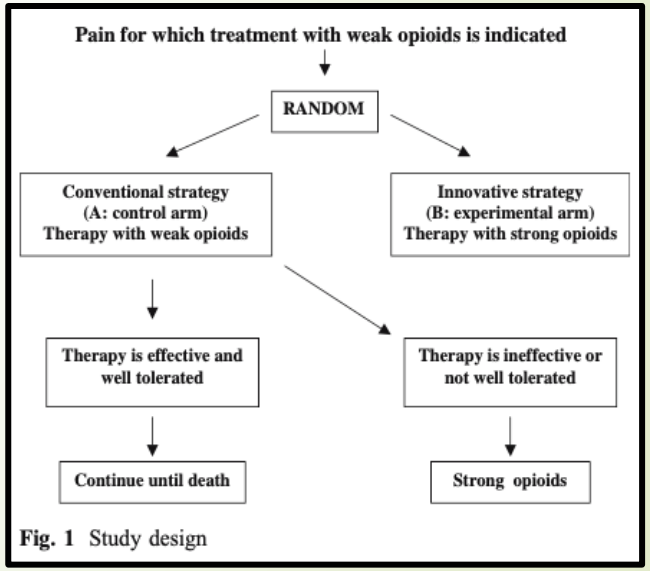


Fig. 1 Study design

Results

- 2 step group worst pain ≥ 5 on 22.8% days vs 28.6% in 3 step group
- 2 step group worst pain ≥ 7 on 8.6% days vs 11.2% in 3 step group
- 'strong' opioids used on 21% of treatment days in 3 step group
- Conclusion: Direct move to step 3 is feasible

Challenging the steps

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

An international, open-label, randomised trial comparing a two-step approach versus the standard three-step approach of the WHO analgesic ladder in patients with cancer

M. Fallon[1*], K. Dierberger[2], M. Leng[3], P. S. Hall[1,2], S. Allende[4], R. Sabar[5], E. Verastegui[4], D. Gordon[1], L. Grant[6], R. Lee[3], K. McWillams[7], G. D. Murray[2], L. Norris[1], C. Reid[8], T. A. Sande[1], A. Caraceni[9†], S. Kaasa[10,11†] & B. J. A. Laird[1,12†]

Challenging the steps

- 153 patients randomized
- Step 2 = codeine or tramadol / step 3 = morphine or oxycodone
- 20 days follow-up
- Participants recorded: average pain, worst pain, analgesia use on a daily basis
- Primary outcome measure: time to achieving stable pain (3 consecutive days ≤ 3)

Results and observations

- No difference in the 2 groups in time to stable pain control
- More than 50% patients in the control arm moved from step 2 to 3
- Moving directly to step 3 was safe (fewer SE in experimental arm)
- Cost of experimental arm less (significant as cost of ‘weak’ opioids high in low / middle income countries)

Evidence for individual drugs

- Evidence absent or very limited for several adjuvant therapies despite these being part of established practice for cancer pain management

7. RESEARCH AGENDA

- Heterogeneity in clinical trials particularly in measuring pain outcomes meant limited opportunities to pool data – a validated scale recommended
- Research prioritized in low / middle income countries
- Risk for substance misuse should be evaluated / opioid cessation protocols

The future of the ladder

"The WHO analgesic ladder, introduced in 1986 and disseminated world wide, remains recognized as a useful educational tool but not as a strict protocol for cancer pain management" WHO 2018

The ladder as an educational tool

- Teach its history
- Include explanations surrounding the language in the ladder
- Challenge the use of opioids for mild to moderate pain - no role
- Offer a critique / the evidence

In conclusion

- New WHO cancer pain guidelines are much more extensive, evidence based, and promote a more individualized approach including radiotherapeutic management
- The original ladder is now outdated and should be challenged
- If used as an educational tool teaching should focus on its critique


THANK
YOU
for
LISTENING TO
MY PRESENTATION