Pharmacotherapy update:

Palliative care – supportive care & chemotherapy

Martin C Henman,
ESCP Research Committee & Trinity College Dublin

October 21st, 2022

ESCP

Disclosures

None.

In preparing this lecture…

- Where drugs are named as examples, this is not an endorsement.
- Where drugs are not mentioned does not imply deliberate exclusion.
- Published guidelines, systematic reviews and meta-analyses have been preferred to individual studies.

Trinity College Dublin

ESCP

Learning Objectives

- To explore the concept of Palliative Care
- To review recent developments in the pharmacological management of common symptoms
  - Pain
  - Breathlessness
  - Nausea and vomiting
  - Fatigue
- To outline research into the quality of prescribing in Palliative Care
- To identify useful resources

Trinity College Dublin

ESCP
European Society of Clinical Pharmacy

Palliative Care

Palliative care improves the quality of life of patients and that of their families who are facing challenges associated with life-threatening illness, whether physical, psychological, social or spiritual.

The quality of life of caregivers improves as well.

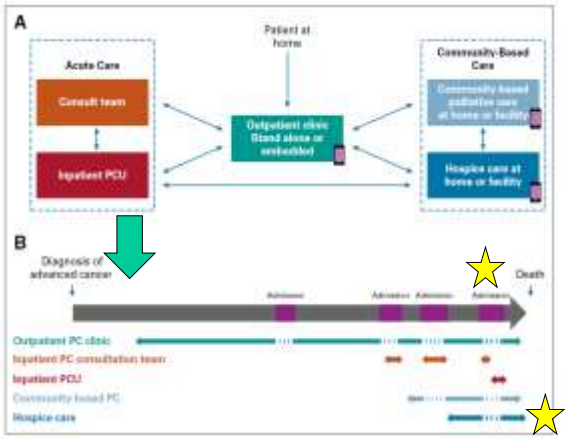
https://www.who.int/news-room/fact-sheets/detail/palliative-care

Trinity College Dublin

ESCP
European Society of Clinical Pharmacy

Models of Palliative care

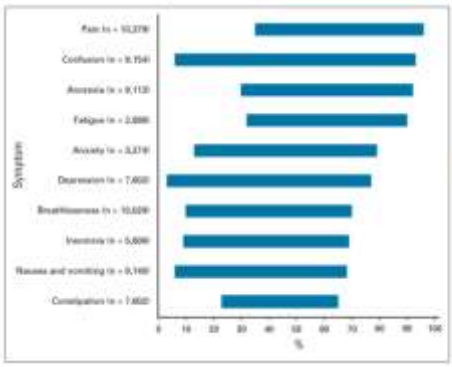
- From Hospice & care of the terminally ill
- To care over the disease course from diagnosis
- To outpatient and community-based Palliative care teams
- From cancer care to care of advanced, life-limiting diseases



Trinity College Dublin

ESCP
European Society of Clinical Pharmacy

Common symptoms



- While symptoms vary with the disease and stage, the four most prevalent and challenging to manage are pain, breathlessness, nausea and vomiting and fatigue
- Several symptoms usually need to be addressed at any time
- All of them require close attention

ESCP
European Society of Clinical Pharmacy

Pain

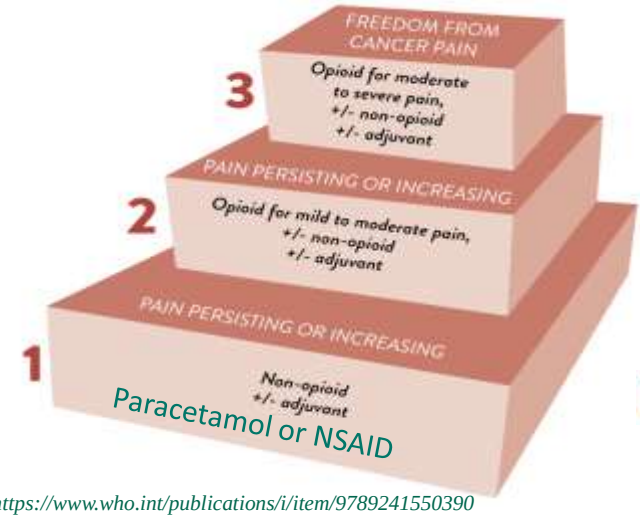
- Over 30% of patients with cancer receive inadequate analgesia for pain
- Pain varies according to whether it is nociceptive, neuropathic, or combined

TYPE			NEURAL MECHANISM	EXAMPLE
Nociceptive	Visceral		Stimulation of pain receptors on normal sensory nerve endings	Hepatic capsule stretch
	Somatic			Bone metastases
Neuropathic	Nerve compression		Stimulation of nervi nervorum	Sciatica due to vertebral metastasis with compression of L4, L5 or S1 nerve root
	Nerve injury	Peripheral	Lowered firing threshold of sensory nerves (deafferentiation pain)	Tumour infiltration or destruction of brachial plexus
		Central	Injury to central nervous system	Spinal cord compression by tumour
		Mixed	Peripheral and central injury	Central sensitization due to unrelieved peripheral neuropathic pain
	Sympathetically maintained		Dysfunction of sympathetic system	Chronic regional pain syndrome following fracture or other trauma

https://www.who.int/publications/i/item/9789241550390

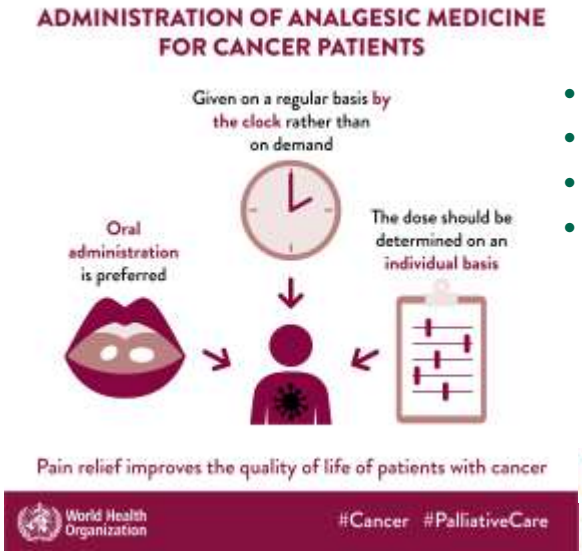
WHO analgesic ladder

- Guide to analgesic selection – '*However, it cannot replace individualized therapeutic planning based on careful assessment of each individual patient's pain.*'



https://www.who.int/publications/i/item/9789241550390

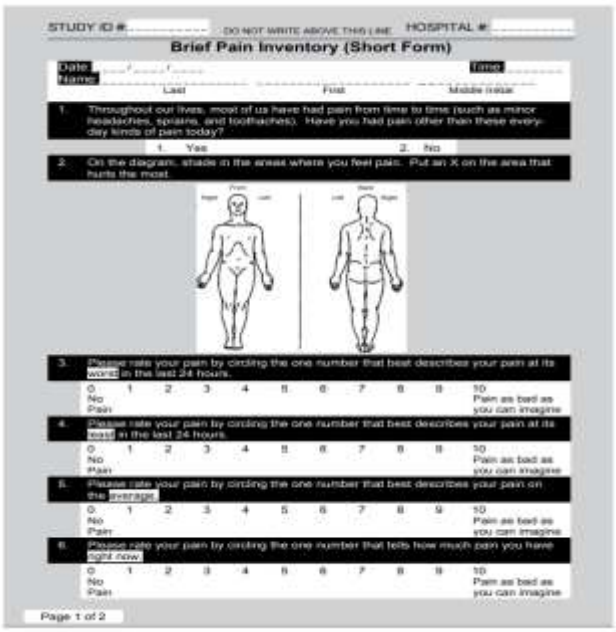
General principles of administration



- Titration
- Equivalence
- Switching
- Obesity

Trinity College Dublin
ESCP
European Society of Clinical Pharmacy

Evaluation of pain and its treatment



Trinity College Dublin
ESCP
European Society of Clinical Pharmacy

Analgesic summary for moderate or severe pain - aligned to WHO Ladder

Step 1. Paracetamol or NSAID - Mild analgesics should not be given alone for initiation of moderate or severe pain

Step 2. Codeine sulphate or Tramadol – evidence is weak

Straube C, et al: Cochrane Database Syst Rev (9):CD006601, 2014
Wiffen PJ, Derry S, Moore RA: Cochrane Database Syst Rev 5:CD012508, 2017

As an alternative to weak opioids, low doses of strong opioids could be an option, although this recommendation is not currently part of WHO guidance.

There is no evidence of increase in adverse effects from the use of low-dose strong opioids instead of the standard step 2 approach with weak opioids.

Fallon M, et al: ESMO clinical practice guidelines. Ann Oncol 29:iv166-iv191, 2018 (suppl 4)

Trinity College Dublin

ESCP
European Society of Clinical Pharmacy

Analgesic summary for moderate or severe pain - aligned to WHO Ladder

- Step 3. Opioid = oral morphine – 19 of 20 patients who receive and can tolerate opioids will have their pain reduced to mild or no pain within 14 days – with a low rate (6%) of reported intolerable adverse events.

Wiffen PJ, Wee B, Derry S, et al. Cochrane Database Syst Rev 7:CD012592, 2017

- No evidence of superiority across opioids for moderate to severe pain exists: morphine remains the first-line opioid of choice in international guidance because of its familiarity, availability, and cost.

Fallon M, et al: ESMO clinical practice guidelines. Ann Oncol 29:iv166-iv191, 2018 (suppl 4)

(Fentanyl patches, while similarly effective and tolerated are less readily available and more costly)

- There remains poor access to, and use, of opioids in Eastern and South Eastern Europe.

Berterame S, et al. Lancet 2016; 387: 1644–1656.
Knaul FM, et al. Lancet 2018; 391: 1391–1454.

ESCP
European Society of Clinical Pharmacy

Analgesic summary

- Adverse effects from opioid therapy are common and predictable.
  - Constipation (OIC), nausea, and vomiting are most commonly reported, and guidelines recommend the use of laxatives (for prophylaxis and management) with all opioid prescriptions.
- A different opioid should be considered in the absence of adequate analgesia (despite opioid dose escalation) or in the presence of unacceptable opioid side effects.
  - use of naloxone (in association with oxycodone) or methylnaltrexone to control OIC may be considered, but significantly increases costs
  - Naloxegol is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s).
- Fentanyl and buprenorphine (via the t.d. or i.v. route) are the safest opioids in patients with chronic kidney disease stages 4 or 5 (estimated GFR<30 mL/min)

Medical Cannabis

- Based on a review of 5 trials of nabiximols - (D9-tetrahydrocannabinol (27 mg/mL) and cannabidiol (25 mg/mL)
- For advanced cancer patients with pain not fully alleviated by opioid therapy, the additive effect of nabiximols to the ongoing opioid treatment remains unclear.

Fallon M, et al: ESMO clinical practice guidelines. Ann Oncol 29:iv166-iv191, 2018 (suppl 4)

Chronic Pain

- Moderate to high certainty evidence shows that non-inhaled medical cannabis or cannabinoids results in a small to very small improvement in pain relief, physical functioning, and sleep quality among patients with chronic pain, along with several transient adverse side effects, compared with placebo.

Wang L, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. BMJ. 2021 Sep 8;374:n1034. doi: 10.1136/bmj.n1034.

Cancer-related Neuropathic Pain (NP)

- ≥ 20% cancer patients experience NP
- Opioids are effective alone and combined with adjuvants, but,
- A meta-analysis of four randomized controlled trials (RCTs) found no analgesic benefit from adding pregabalin or gabapentin to opioids in patients with cancer-related pain

  Kane CM, et al. Palliat Med 32:276-286, 2018
- Antidepressants and anticonvulsants effective and well tolerated in patients with confirmed cancer-related neuropathic pain.

  Jongen JLM, et al: J Pain Symptom Manage 46:581-590.e1, 2013
- An opioid-sparing effect was found with the addition of pregabalin to opioid therapy

  Dou Z, Jiang Z, Zhong J: Asia Pac J Clin Oncol 13: e57-e64, 2017

- Gabapentin, pregabalin, Tricyclic Antidepressants may be useful, but adverse effects must be monitored
- Ketamine has not been shown to be effective

Trinity College Dublin

ESCP European Society of Clinical Pharmacy

Bone Pain

- Radiotherapy is highly effective - 8 Gy single dose
- Bisphosphonates did not provide analgesia in one systematic review

  Porta-Sales J, et al: Palliat Med 31:5-25, 2017
- But were superior to placebo or no treatment in a meta-analysis of patients with multiple myeloma

  Mhaskar R, et al: Cochrane Database Syst Rev 12: CD003188, 2017
- Bisphosphonates may be useful when pain is not localised
- Denosumab is indicated as an alternative to Bisphosphonates for the treatment of patients with metastatic bone disease from solid tumours and myeloma
- *Preventive dental measures are necessary before the use of Bisphosphonates or Denosumab*

Trinity College Dublin

ESCP European Society of Clinical Pharmacy

Breathlessness

- Refractory breathlessness - persists despite optimal treatment of the underlying condition
  - is associated with a shortened life expectancy
  - may result in use of acute hospital services
  - Is especially frightening for patients and families
  - because of the limited availability of effective interventions clinicians also experience distress
- Oxygen has a clear and accepted role for patients with hypoxia, but not others - a hand-held fan can be valuable
- Opioids by mouth and injection reduce breathlessness, but their effects are modest or small
  - the optimal dosing, titration, and potential issues from long-term use (eg, safety, tolerance, dependence, misuse) have not been determined - Jennings AL, et al: Thorax 57:939-944, 2002
- Evidence from Cochrane reviews only supports a role for benzodiazepines as second- or third-line treatment if opioids fail, because there is no overall evidence of benefit and some evidence of possible harms.

Simon ST, et al: Cochrane Database Syst Rev 10:CD007354, 2016

American Society of Clinical Oncology: Dyspnea - Summary of Recommendations

Recommendation 5.4

- Bronchodilators should be used for palliation of dyspnea when patients have established obstructive pulmonary disorders or evidence of bronchospasm.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Low	Weak

Recommendation 5.5

- Evidence remains insufficient for a recommendation for or against the use of anti-depressants, neuroleptics, or inhaled furosemide for dyspnea.

Insufficient evidence	
Evidence Quality	**Strength of Recommendation**
N/A	N/A

Nausea and vomiting

3 types of CINV with important implications for both prevention and management:

- Acute emesis, commonly begins within 1-2 hours of chemotherapy and peaks in 4-6 hours
- Delayed emesis, occurring more than 24 hours after chemotherapy
- Anticipatory emesis, occurring prior to treatment as a conditioned response in patients who have developed significant nausea and vomiting during previous cycles of chemotherapy

Emetogenic potential of chemotherapy agents and regimens;

- *Mildly emetogenic treatment*—fluorouracil, etoposide, methotrexate (<100 mg/m^2, low dose in children), vinca alkaloids
- *Moderately emetogenic treatment*—the taxanes, doxorubicin hydrochloride, intermediate and low doses of cyclophosphamide, mitoxantrone, and high doses of methotrexate (0.1– 1.2 g/m^2).
- *Highly emetogenic treatment*—cisplatin, dacarbazine, and high doses of cyclophosphamide.

Trinity College Dublin

ESCP European Society of Clinical Pharmacy

Antiemetics

Nausea and/or vomiting - 68% of patients with cancer at some point, while during the last 6 weeks of life, the prevalence is 40% or more.

Poorly controlled nausea and vomiting is associated with physical, cognitive, and psychosocial distress, including patient and family fears of death from dehydration and/or starvation.

- NK1 receptor antagonists e.g. aprepitant, rolapitant, fosaprepitant
- Serotonin (5-HT3) receptor antagonists e.g. granisetron, ondansetron, palonosetron
- Dexamethasone
- Olanzapine
- Metoclopramide
- Nabilone, Dronabinol (Medical Cannabis is not recommended by ASCO)

Trinity College Dublin

ESCP European Society of Clinical Pharmacy

ASCO recommendations

Adults treated with cisplatin and other high-emetic-risk single agents:

- should be offered a combination of - NK_1 receptor antagonist, a serotonin ($5\text{-}HT_3$) receptor antagonist, dexamethasone, and olanzapine (day 1).
- Dexamethasone and olanzapine should be continued on days 2 to 4.

Adults treated with carboplatin area under the curve (AUC) ≥ 4 mg/mL/min

- should be offered a combination of - NK_1 receptor antagonist, a $5\text{-}HT_3$ receptor antagonist, and dexamethasone (day 1).

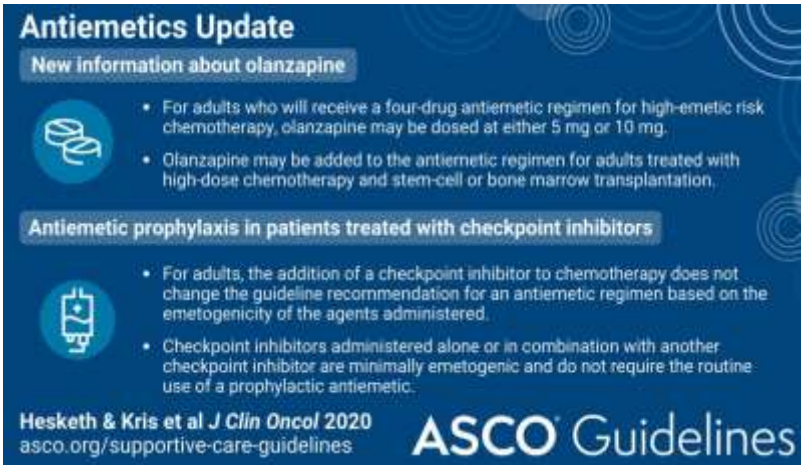
Adults treated with antineoplastic combinations should be offered antiemetics appropriate for the component antineoplastic agent of greatest emetogenic risk.

Trinity College Dublin

asco.org/supportive-care-guidelines

ESCP European Society of Clinical Pharmacy

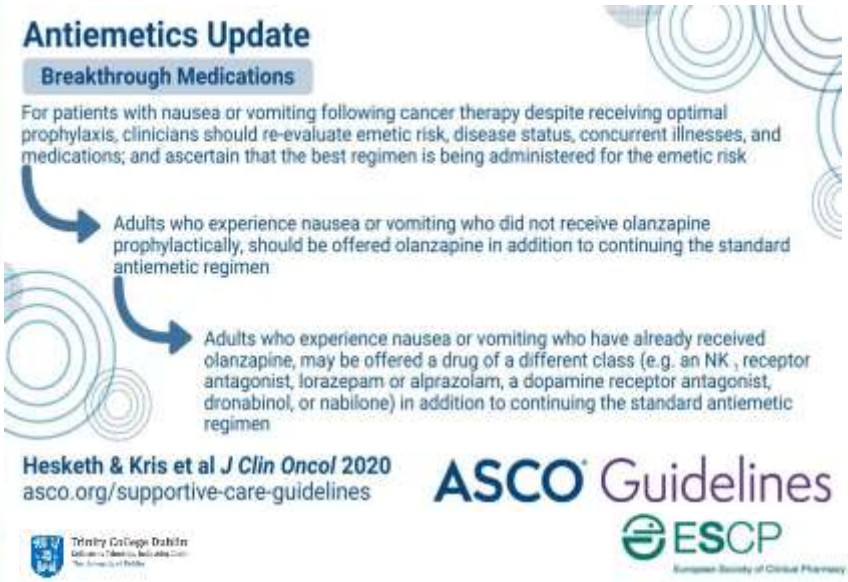
ASCO Recommendations



Checkpoint inhibitors: e.g. Pembrolizumab, Nivolumab, Atezolizumab, Avelumab, Ipilimumab, Relatlimab

ESCP European Society of Clinical Pharmacy

Nausea and Vomiting: breakthrough response



Fatigue

"a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals' ability to function to their normal capacity." Ream E, Richardson A: Int J Nurs Stud 33:519-529, 1996

- Methylphenidate - a meta-analysis of five psychostimulant trials, found an overall SMD for psychostimulant use of 20.28 (95% CI, 20.48 to 20.09). Minton O et al: J Pain Symptom Manage 41:761-767, 2011
- Other RCTs have found it to be ineffective for cancer-related fatigue. Evidence of benefit was limited to patients with narcotic-induced fatigue and/or depression.
- Modafinil - two trials concluded either no benefit or benefit only with severe fatigue.
- Patients with anaemia, including during chemotherapy, may benefit from erythropoietin - reduces fatigue (SMD, 20.36; 95% CI, 20.46 to 20.26) - evidence for darbepoetin is less consistent.
- Dexamethasone for up to 2 weeks, but efficacy and safety beyond this are undetermined.
- No evidence of benefit from L-carnitine, paroxetine, progestational steroids.

Quality of prescribing in Palliative Care

- Study characteristics: Observational cohort studies (52 studies) 14 prospective; 2 multinational, 16 hospice and 22 dedicated palliative care clinics.
- 21 assessed appropriateness of prescribing using general and specific tools; prevalence of ≥1 PIM ranged from 15 to 92%.
- Common PIMs included; lipid-modifying agents, antihypertensives, anti-thrombotic agents, and drugs for peptic ulcer and gastro-oesophageal reflux disease.
- Only one study reported on under-prescribing.

Conclusions:

- Medications prescribed were not differentiated according to treatment intention (i.e., preventative versus symptomatic relief)
- Studies that used general tools to assess appropriateness e.g. Beers, even though the tool is not designed for this population.

C.A. Cadogan et al. Prescribing practices, patterns, and potential harms in patients receiving palliative care: A systematic scoping review.
Exploratory Research in Clinical and Social Pharmacy 3 (2021) 100050

Final remarks

- Multidisciplinary palliative care teams have been shown to improve patient outcomes
- Patients and families want to be cared for at home as much as possible
- Co-ordination of care is vital to the success of multidisciplinary teams in every setting, but especially in Community/Primary Care

Resources

- WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents; https://www.who.int/publications/i/item/9789241550390
- Fallon M, et al: ESMO clinical practice guidelines. Ann Oncol 29:iv166-iv191, 2018 (suppl 4)
- American Society of Clinical Oncology - https://www.asco.org/practice-patients/guidelines
- Snaman J, et al. Pediatric Palliative Care in Oncology. J Clin Oncol 2020;38(9):954-962.
- Holmes HM, et al. Integrating palliative medicine into the care of persons with advanced dementia: Identifying appropriate medication use. J Am Geriatr Soc 2008;56(7):1306–1311.
- Lindsay J, et al. The development and evaluation of an oncological palliative care deprescribing guideline: The“ OncPal deprescribing guideline”. Support Care Cancer 2015;23(1):71–78.

Trinity College Dublin

ESCP

Martin C Henman BPharm, MA, PhD, FFIP, FESCP

Děkuji!

Thank you.

Go Raibh Maith Agaibh.

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

ESCP