WHO Ladder

A/Prof Franco began his talk by introducing the WHO Ladder (see Figure 1), which provides a well-established approach to cancer pain management, but he believes it needs to be tailored and updated. He commented that having three steps on the ladder (nonopioids on step 1, weak/mild opioids on step 2 and strong opioids on step 3) is something that needs to be reviewed.

WHO’s Pain Relief Ladder

Russell K Portenoy*, a well-known figure in cancer pain management, said about the WHO Ladder a number of years ago “…while the analgesic ladder approach provides a framework for the stepwise and systematic approach to managing cancer pain, it should not be viewed as evidence-based or a best practice guideline. Clinical competency in cancer pain management requires a more detailed understanding of the principles of appropriate drug selection, dosing, and other processes of care.” A/Prof Franco went on to talk about reasons he believes Dr Portenoy said this, including the idea that jumping straight to strong opioids may not be uncommon for oncologists when they ‘inherit’ a physician-referred patient who has presented with pain at diagnosis and may already be receiving weaker opioid therapy. Often the question for managing such patients is should they be switched, or should we be encouraging other clinicians not to use such treatment?

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This is a summary of a presentation by A/Prof Michael Franco, from Monash Health, Victoria, who spoke on the current evidence for treating chronic cancer pain as part of Breakfast Session 6 at the MOGA (Medical Oncology Group of Australia) 2018 Annual Scientific Meeting, which was held on Aug 1–3 in Adelaide. A/Prof Franco’s talk covered the WHO ladder for managing cancer pain, opioid switching/rotation, two specific opioids (TARGIN® tablets [modified release oxycodone/naloxone] and methadone) and novel techniques. This Breakfast Session was sponsored by Mundipharma, and we hope you find this summary enlightening.
Low-dose morphine similar to weak opioids

A trial by Bandieri et al. published in 2016 concluded that patients with moderate pain due to cancer have similar tolerability and an earlier effect with low-dose morphine compared with weak opioids.1 The authors of this study also commented that removing the second step on the WHO Ladder would simplify treatment and possibly provide better pain control, but qualified this statement with a recommendation for more phase 3b/4 studies. While A/Prof Franco supports the need for more research, he also commented on his personal experiences, noting that the idea of going straight to a lower dose of a step 3 agent rather than via a weaker agent first is potentially beneficial, including an earlier and better analgesic effect. It also makes things simpler for the patient, who is likely already dealing with a significant pill burden for their active anticancer treatment, by avoiding switching them to another agent, and the associated re-education that entails, in the near future. He noted that compliance is likely to be better when the complexity of a patient’s regimen is minimised.

Opioid switching/rotation

Opioid switching is often utilised as a therapeutic manoeuvre for patients who are losing analgesic efficacy. However, it is a difficult area to study, so there is little evidence available. A 2016 review by two eminent palliative care specialists, Sebastiano Mercadante and Eduardo Bruera, found that satisfactory pain control with decreased intensity of adverse effects was reported by 50–90% of patients who switched opioids.2 They did also note that there have been no randomised clinical trials investigating the efficacy of opioid switching, but they do encourage a pragmatic approach, which A/Prof Franco agreed with. He stated that for patients who are losing efficacy or are experiencing intolerable toxicity, it is reasonable to consider switching opioids. Furthermore, a number of guidelines all include opioid switching as part of cancer pain control, including five that are summarised in a recent systematic review on the subject.3 This review analysed data from nine studies involving 725 patients, along with three prior systematic reviews covering 2296 patients. The review’s authors concluded that analgesia and patient satisfaction can both be improved by opioid rotation.

Specific opioids

TARGIN® tablets (modified release oxycodone/naloxone)

TARGIN combines oxycodone and naloxone in a 2:1 ratio in tablet form to be taken orally.4 The original recommended maximum dosage was 40mg/20mg twice daily, but there is now good evidence from randomised clinical trials that 80mg/40mg twice daily is effective and safe.5,6 However, A/Prof Franco commented that if higher doses are to be prescribed, an understanding of how the product/agents being prescribed works is important, and he believes there are a number of prescribers who are not familiar with how TARGIN works. The analgesia provided by oxycodone in TARGIN is not reversed by naloxone, and opioid withdrawal does not occur (see Figure 2).7 However, if a patient has hepatic dysfunction, the attenuated first-pass metabolism of oral naloxone can result in loss of therapeutic effect. Therefore, if higher doses of TARGIN are to be considered, the patient’s hepatic function needs to be carefully assessed, particularly if opioid switch/rotation is being considered. Note, TARGIN should be used with caution in patients with mild hepatic impairment, and it is contraindicated in patients with moderate-to-severe hepatic impairment. As always with opioids at any dose, bowel function should also be monitored.

Patient scenario

To illustrate this point, A/Prof Franco described a scenario where a patient is initially well controlled on TARGIN, but the analgesia gradually becomes less effective, and the TARGIN dose is increased. This initially results in some increased analgesia, but is followed by steady loss of efficacy again. The patient is then switched to an alternative opioid, but if this is a one-to-one switch (i.e. oxycodone to another opioid) then in an extreme situation, the patient may become narcotised. This scenario could arise from inadequate monitoring of the patient’s hepatic function and naloxone entering their central nervous system. A one-to-one opioid swap in this scenario (which removes naloxone and only considers the oxycodone) leads to an elevated morphine equivalent daily dose. It is recommended to start with a lower equivalent dose of the new opioid (>50% reduction of the calculated approximate equi-analgesic dose) and to monitor the patient carefully for analgesia, adverse effects and toxicity.8

![Mechanisms of opioid agonist/antagonist combinations](image)

Figure 2. Mechanisms of opioid agonist/antagonist combinations (adapted from Leppert W. Drug Des Devel Ther 2015;9:2215–31)
What does watching hepatic function mean?

Hepatic dysfunction for the purposes of monitoring during treatment with TARGIN specifically means a Child-Pugh score of B or worse. The most sensitive measures of first-pass metabolism (which are considered in the Child-Pugh assessment) are: i) low albumin level and presence of ascites; ii) elevated bilirubin level; and iii) INR/prothrombin time – aminotransferase levels can be useful adjuncts.

Methadone

Methadone, a synthetic, atypical opioid, exhibits NMDA (N-methyl-D-aspartate) antagonism, δ- and κ-receptor agonism, and inhibition of 5-HT (serotonin) and noradrenaline (norepinephrine) re-uptake. There is increasing evidence for the use of methadone for treating chronic cancer pain, including a recent case series reporting good efficacy with low-dose methadone (<10mg twice daily) when combined with haloperidol for managing cancer pain. However, methadone can be difficult to prescribe due to its long and unpredictable half-life and difficult conversion ratios (see Text box), which were detailed in a recent review. A/Prof Franco’s preference is the Ayonrinde method developed by Ayonrinde and Bridge from Perth, where ratio of methadone to morphine changes as the morphine equivalent daily dose increases. Despite the difficulties with its use, methadone can be valuable for patients with difficult, refractory pain who do not respond well to other opioids.

Various conversion methods for switching WHO level 3 opioids to methadone

- Stop and go, or rapid conversion
- Progressive method
- Three-day switch, or Edmonton method
- German model
- Ayonrinde method
- Friedman method
- Ad libitum method, or Morley-Makin method
- Outpatient titration
- Methadone production information

Novel treatments for cancer pain

NGF (nerve-growth factor) inhibitors

Monoclonal antibodies against NGF may be useful for patients with cancer pain due to bone metastases; a detailed graphic of the mechanisms of NGF inhibitors has been published in a review by Chang D et al. There is some recently published clinical evidence of short-term efficacy in osteoarthritis and diabetic peripheral neuropathy. There are three monoclonal antibodies currently in development, including one currently being investigated in an international phase 3 clinical trial for bone metastasis-related pain. These agents typically have a long half-life, and are suitable for subcutaneous administration, for 3–6 monthly doses.

Guided interventional pain techniques

Guided interventional pain techniques can be useful for patients with very difficult-to-treat ongoing pain. Coeliac and splanchnic nerve blocks are often used at large centres with the appropriate medical staff. Vertebroplasty (injection of cement into vertebral bodies) is controversial due to conflicting evidence of efficacy. Much of the original evidence came from insufficiently fractures in patients with osteoporosis. A/Prof Franco mentioned a published case report of a patient with bone metastases in whom the treatment was promising when performed by highly trained staff.

Take-home messages

- Three-step WHO guidance needs revision
  - Low-dose morphine similar to mild-weak opioids
- Limited good trial evidence for opioid switching/rotation
  - Pragmatic approach is advocated
- Monitor hepatic function if increasing TARGIN dose or unusual symptoms such as reduced pain relief or withdraw symptoms are experienced
- Caution must be exercised in administering TARGIN tablets to patients with mild hepatic impairment
- TARGIN tablets are contraindicated in patients with moderate-to-severe hepatic impairment

References