This review is a summary of a presentation by Emeritus Professor Sam H. Ahmedzai (UK), which was given to pain and palliative care specialists and generalists in Sydney on 29 June 2016 as part of his international speaking tour sponsored by Mundipharma.

Cancer pain in the 21st century: Stepping off the ladder, stepping up to new challenges.

Prof. Ahmedzai’s lecture challenged the relevance of the 1986 WHO guidelines in modern day cancer pain management and covered options for individualising pain management in patients with cancer and the need to treat cancer pain as chronic pain.

**Professor Sam H. Ahmedzai**

Sam is Emeritus Professor at the Medical School at University of Sheffield, with 30 years’ experience of being consultant physician in palliative medicine. He set up and for 20 years he was chair of the UK’s first academic department of Supportive Care. His research covers - cancer pain and opioid drugs; symptom management in advanced diseases; holistic needs and quality of life assessment, improving supportive care services for cancer and chronic disease patients; advocating patient and public involvement in cancer research.

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According to the 2007 European Pain In Cancer survey, 73% of patients surveyed had pain, 94% had experienced moderate-severe pain at some point, and 33% had cancer pain sometimes so bad that they wanted to die. The researchers concluded that the management of cancer pain was suboptimal and recommended that pain management guidelines should be revised to improve pain control in patients with cancer. In 2012, Fisch et al. published the results of a prospective observational study that found that two-thirds of cancer outpatients determined as being at risk of pain required or used analgesics. What was surprising, and disappointing, is that analgesic prescribing was still inadequate in one-third of these patients.

The 1986 WHO guidelines were developed to be a simple, pragmatic, ‘one size fits all’ approach to pain management so that they could be used in all countries, particularly under-resourced developing countries where morphine is relatively affordable. Indeed, oral morphine is the drug of choice in the guidelines with all other analgesic agents regarded as ‘adjuvant’ or ‘co-analgesic’. Furthermore, as the WHO three-step ladder was wedged with cancer pain and was part of the WHO’s cancer control strategy, palliative care embraced the WHO three-step ladder approach and championed opioids, morphine in particular, above all other methods of pain relief.

While a morphine-based approach to pain control may make sense in certain settings, it has become clear that it is not necessarily appropriate in the hospitals and clinics of countries with better resourced healthcare systems and with the availability of newer analgesics in the twenty-first century.

Management of cancer pain in the 2010s is still based on the WHO three-step analgesic ladder, which was published in 1986 (Figure 1). Essentially, it recommends administration of oral analgesics in the following order: non-opioids (aspirin and paracetamol) for mild pain; then, as necessary, mild opioids (codeine) for moderate pain; then strong opioids, such as morphine, for severe pain, until the patient has achieved ‘freedom from cancer pain’. With advances in knowledge and understanding of cancer pain and with the availability of many new analgesic agents it seems reasonable to question why palliative medicine is still using 30-year-old guidelines that emphasise the use of opioids.

![Figure 1. Cancer pain relief: the WHO three-step analgesic ladder (1986).](image)

Twentieth century view of cancer pain

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Reasons for the problem of cancer pain

The main reason that management of cancer pain continues to be a problem in the 2010s is that a twentieth century model of cancer pain is still being applied, resulting in an over-simplistic opioid-dominated view of analgesia, the assumption that cancer pain control has to be ‘cheap’ (based on oral morphine), and cancer pain being associated with end of life. In the 1980s, following publication of the 1986 WHO guidelines and with increased access to pain clinics and palliative care services, it looked as if the problem of cancer pain would soon be solved. However, in the 2010s cancer pain has not yet been beaten because:

- Cancer has not yet been cured – as long as there is cancer there will always be cancer pain.
- Palliative care is not yet universal – there are wide variations in levels of care.
- Pain services are being cut back – they are easy targets for healthcare cost savings.
- Oncology is still focused on survival – quality of life is not always at the forefront of treatment.
- Cancer pain is a complex phenomenon – cancer itself is a multifaceted disease and pain is caused by both cancer and cancer treatment.

Are the WHO guidelines still relevant?

Despite the WHO’s emphasis on oral morphine for the treatment of cancer pain, the clinical evidence does not appear to support this position. A 2003 Cochrane systematic review of published randomised controlled trials reporting on the analgesic effect of oral morphine in patients with cancer pain, and subsequent updates of the 2003 review, conclude that ‘the randomised literature for morphine is small given the importance placed on this medicine’, with most trials having populations that were insufficient (<100 patients) to provide appropriate data for meta-analysis. In the 2013 update, it was stated that ‘there is qualitative evidence that oral morphine has much the same efficacy as other available opioids’. Similarly, the European Association for Palliative Care (EAPC) review and update of its guidelines concluded that there are no clinically important differences among oral morphine, oxycodone, and hydromorphone and that any of the three drugs could be used as the first-choice opioid for management of moderate to severe cancer pain.

Side effects of opioids

The side effects of opioids used to control cancer pain are a barrier to adequate pain control and have a negative impact on patient quality of life. This was the conclusion of an analysis of differences in the prevalence and severity of side effects associated with different types of opioid in patients with chronic cancer pain. It found a significant positive correlation between the severity of side effects and the total dose of opioid taken.

The main reason that side effects are experienced with the use of morphine is that opioid receptors are highly prevalent, with multiple subtypes being found throughout the body. Indeed, opioid receptors play a role in the regulation of most of the major organ systems, including the gastrointestinal, cardiovascular, respiratory, renal, and immune systems. Consequently, opioid adverse effects are essentially just opioid effects.

In the 2007 European Pain in Cancer survey, the most common side effect with opioids was constipation, which affected at least one-third of patients. Constatipn has a major effect on patients and their families. This was clearly demonstrated in a 2013 qualitative study that explored the psychological distress and illness burden associated with opioid-induced constipation in cancer patients. It revealed a wide range of consequences of constipation for cancer patients, including:

- Intrusion into daily life.
- Anticipatory anxiety, general distress.
- Negative perceptions about using opioids.
- Negative effects on nutrition.
- Physical symptoms, in addition to cramp and pain.
- Feelings of shame, and loss of dignity.

Moreover, there is a poor evidence base for laxatives being effective in the treatment of opioid-induced constipation. Laxatives are palliative and do not treat the cause of constipation.

Oxycodone/naloxone – A targeted treatment

The problem of opioid-induced constipation, and the lack of an effective treatment for constipation, supports the need for drugs that provide more targeted pain relief.

An example of a targeted treatment is the oral sustained-release fixed-dose combination of oxycodone and naloxone (in a 2:1 ratio). The oxycodone component is responsible for the pain-relieving effects. The naloxone component blocks the opioid effects of the oxycodone on the gastrointestinal tract but does not act on the CNS itself because it is highly metabolised in the liver after oral dosing.

A comprehensive review of randomised controlled trials in patients with chronic non-malignant or cancer-related pain indicates that oxycodone/naloxone in daily doses up to 80mg/40mg provides equally effective analgesia with improved bowel function compared with oxycodone administered alone. One of these trials was a randomized, double-blind, 4-week investigation involving 185 patients with moderate to severe cancer pain who had opioid-induced constipation. It demonstrated a significant improvement in constipation within 1 week of starting oxycodone/naloxone ≤120 mg/day and analgesic efficacy equivalent to that of oxycodone ≤120 mg/day alone (Figure 2). In addition, oxycodone/naloxone was associated with 20% less laxative use and the average rate of analgesic rescue medication use was low and similar in the two treatment groups.

Quality of life, which was comparable for the groups, was not reduced and greater improvements in constipation-specific quality of life assessments were observed with oxycodone/naloxone. Rates of adverse drug reactions were generally similar in both treatment groups.

Figure 2. Effect of oxycodone/naloxone prolonged-release tablets (OXN PR) and oxycodone prolonged-release tablets (OxyPR) on: (A) mean (SE) bowel function index (BFI) score; and (B) mean (SE) Brief Pain Inventory Short-Form (BPI-SF) score in patients with cancer pain. Importantly, there was no evidence of opioid withdrawal (measured using the modified Subjective Opiate Withdrawal Scale) with oxycodone/naloxone. Furthermore, in the open-label extension phase of the study, the reduction in constipation, with maintenance of pain control, was sustained for a further 24 weeks.
Transdermal and transmucosal opioid delivery
With the development of improved sustained-release drug delivery systems in the form of transdermal patches (e.g., fentanyl [72 hours] and buprenorphine [7 days]), and the development of transmucosal delivery for rapid breakthrough pain (e.g., fentanyl buccal/ sublingual lozenges, tablets, and nasal sprays), more options for opioid drug delivery are available in the twenty-first century. The availability of alternative routes of administration that provide effective analgesia challenges the standard practice of using the oral route, as advocated in the 1986 WHO guidelines.

A meta-analysis of studies that compared transdermal opioids with long-acting oral morphine in the treatment of cancer pain indicates significantly (p<0.001) less constipation with transdermal opioids (fentanyl and buprenorphine) than with oral morphine and a significantly (p=0.014) higher patient preference for transdermal opioids. Similarly, a pooled analysis of data from published uncontrolled and randomised controlled trials (with sustained-release oralmorphine as comparator) showed significantly (p=0.002) improved pain relief with transdermal fentanyl compared with sustained-release oral morphine and 2- to 3-times lower likelihood of causing constipation, nausea, vomiting, and somnolence. These data confirm that cancer pain can be controlled with transdermal opioids with fewer side effects. Therefore, there is no compelling reason to continue to use oral morphine above all other forms of analgesia.

With regard to treating breakthrough pain, the time to meaningful pain relief with oral/transmucosal opioids has been demonstrated to be shortest with oral transmucosal fentanyl in a prospective study. This finding is supported by those of a randomised, double-blind study that showed that oral transmucosal fentanyl was more effective than morphine sulphate immediate-release in controlling breakthrough pain and that substantially more patients preferred oral transmucosal fentanyl than oral morphine.

Buprenorphine – a complex opioid
Buprenorphine elicits different effects at different opioid receptors, including partial agonism at mu, antagonism at kappa, and agonism at ORL-1 receptors. Largely due to this unique profile of receptor activity, buprenorphine behaves differently from other opioids. Until recently, buprenorphine has largely been ignored by the pain medicine community because of a lack of understanding of its receptor activities and concerns about antagonism with other opioids. However, a better appreciation of its actions and that the antagonist effect (originally demonstrated in animal studies at high dosages) does not manifest in clinical practice has led to increasing use of buprenorphine.

Moreover, because of its opioid receptor activity profile, there is a ceiling (or apparent maximum) to the degree of respiratory depression with therapeutic doses of buprenorphine. However, a better appreciation of its actions and that the antagonist effect (originally demonstrated in animal studies at high dosages) does not manifest in clinical practice has led to increasing use of buprenorphine.

Take-home messages
• Thirty years after publication of the 1986 WHO guidelines on cancer pain relief, cancer pain continues to be a major problem.
• With its emphasis on oral morphine, the WHO guidelines overlook the benefits of other analgesic drugs and pain interventions.
• Oxycodone/naloxone results in reduced constipation with no loss of analgesia and no opioid withdrawal in cancer patients with opioid-induced constipation compared with oxycodone alone.
• Cancer pain can be controlled with transdermal opioids with fewer side effects than with oral opioids.
• Cancer pain should be managed as chronic pain not end-of-life pain, i.e. at all stages of the disease course.
• Re-engagement with pain medicine is needed in the twenty-first century, including intrathecal, neurolytic, and electrostimulation approaches.
References


