This update will cover four areas: episodic pain, neuropathic pain, management of opioid-induced adverse effects, and psychosocial and existential pain.

**Episodic pain**

Although the Expert Working Group of the European Association for Palliative Care recommended using immediate release oral morphine for episodic pain, measures with faster onset of action would be useful, especially for more severe episodic pain or pain emergencies. Intravenous morphine at a dose equivalent to 20% of the total oral daily dose has been evaluated. Eighty percent of patients achieved 50% or more reduction in the intensity of episodic pain within a mean of 16.6 minutes. Adverse effects included moderate to severe nausea and vomiting, drowsiness and confusion. Intravenous morphine, however, requires slow injection, because of the risk of hypotension. Intravenous fentanyl, which does not induce histamine release and does not carry the risk of hypotension, might offer additional benefit. Moreover, fentanyl is more lipophilic and has an even faster onset of action. Repeated administration of intravenous fentanyl every five minutes, at a dose equivalent to 10% of the total previous daily dose of morphine, was reported to be effective for pain emergencies. The procedure was safe; the major adverse effect being slight somnolence.

Other routes of administration have also been tried. Morphine gluconate is much more soluble in water than morphine sulphate or hydrochloride, and could be prepared at a concentration up to 20 mg/0.1 ml. This has been given in the form of nasal spray to 11 cancer patients for episodic pain. Perceptible pain relief was achieved in 10, with pain intensity significantly reduced, and the mean time of onset of 2.1 minutes only.

In addition to the dorsal root ganglia and periaqueductal grey area, opioids also act on peripheral nerves. Topical morphine and diamorphine has been demonstrated to be effective in alleviating pain in patients with painful skin conditions or sacral sores compared to placebo. Morphine gargle has been shown to be more effective than water in alleviating pain from chemotherapy or radiotherapy-induced stomatitis. It took on average only 28 minutes to achieve 50% or more reduction in pain, with the mean duration of relief of 216 minutes. As a result of the treatment, patients could take semi-solid or solid food and required little supplemental analgesics. It has also been demonstrated that excruciating bladder spasms resolved within hours after diamorphine 10 mg in 20 ml normal saline was instilled intravesically. The patient could be discharged with reduced dosage of analgesics, to perform the instillation of diamorphine three times a day at home, with intermittent self-catheterization.

Apart from morphine, intranasal ketamine (0.1 ml 10%) has also been shown to significantly alleviate episodic pain compared with placebo. Onset of pain relief occurred within 10 minutes, lasting up to an hour. Adverse effects included transient change in taste, rhinorrhea, nasal passage irritation, and transient elevation in blood pressure. None reported hallucinations.

**Neuropathic pain**

Pathophysiological changes that result after nerve injury include accumulation of sodium channels in the peripheral nerve (peripheral sensitization), reduction of gamma-aminobutyric acid (GABA) inhibition of pain transmission, alteration in calcium influx into the neuron, and increased activity of glutamate receptors, in particular the N-methyl-D-aspartate (NMDA) receptors (central sensitization). Neuropathic pain could be alleviated by modulation of peripheral sensitization by use-dependent sodium channel modulators, such as carbamazepine, phenytoin, mexiletine, flecainide, sodium valproate or tricyclic antidepressants. The inhibitory pathways of pain transmission could be modulated by opioids, serotonergic agents such as amitriptyline or paroxetine, as well as GABA agonists such as sodium valproate, clonazepam, gabapentin or baclofen.

Neuropathic pain could also be managed by modulation of calcium channels with gabapentin, or modulation of central sensitization with ketamine. Burst ketamine (100-500 mg/day by
continuous subcutaneous infusion for three to five days) has recently been shown to be effective in the alleviation of refractory neuropathic as well as somatic pain. After cessation of ketamine, 24 of the 29 patients maintained good pain control for a maximum of eight weeks.11

It would be more convenient to administer ketamine by mouth, instead of subcutaneously. Orally administered ketamine undergoes extensive first-pass metabolism, resulting in low concentrations of ketamine but high concentrations of norketamine in the blood and tissue. However, as norketamine is also an NMDA receptor antagonist, the first-pass metabolism does not affect the potency of the drug significantly. A conversion ratio of subcutaneous to oral ketamine of 1:1 has been reported.12

The starting dose of oral ketamine has been recommended to be 0.5 mg/Kg three times a day.13 The effective dosage could be as low as 0.6 mg three times a day,14 or as high as 3.2 mg/Kg every six hours.15 In one report from Macau, pain was controlled with oral ketamine 30-60 mg four times a day.16

While neuropathic pain has all along been considered opioid-less-responsive pain, modest relief has been demonstrated with morphine, oxycodone, fentanyl, levorphanol and tramadol, with improvement in steady pain, paroxysmal pain and allodynia.17-20 Despite its NMDA receptor antagonist effect, methadone has not been shown to be superior to morphine as first-line strong opioid for cancer pain, even though the proportion of patients with neuropathic pain in the methadone and the morphine groups were similar.21

**Management of opioid-induced adverse effects**

Opioid-induced adverse effects could be managed by treatment of the adverse effects, opioid substitution, use of opioid sparing drugs or neuraxial administration of the opioids.

It has been shown locally that opioid therapy is a major cause of delirium in advanced cancer patients.22 Cholinergic projections in the brain are considered essential to maintaining the state of consciousness, awareness, attention and sleep-wake cycling. Hallucinations may occur with disruption of the basal forebrain cholinergic pathways. Opioids have been demonstrated to inhibit cholinergic activity in multiple brain regions, and opioid-induced sedation and delirium has been shown to improve with donepezil or physostigmine.23-25

Another strategy in the management of opioid-induced adverse effects is opioid substitution. A fixed dose ratio conversion of morphine to methadone has been recommended.26 However, it has been demonstrated that the conversion ratio could be highly variable in different groups of patients. If pain is not controlled, rapid increase in methadone dosage may result in accumulation and overdose because of the long plasma half-life. Local experience of the effective use of an ad libitum schedule has been reported. On the day of conversion, oral morphine is discontinued. A fixed dose of methadone is given on request, calculated as 1/12 of the total daily dose of morphine, up to a maximum of 30 mg, but not more frequently than every three hours. When the total daily dose is stabilized, it is divided to be given two to three times a day.27

Various agents have been reported to have opioid sparing effect, including acetaminophen, midazolam, ketorolac, parecoxib, and even music. One way to reduce the requirement of opioids is to reverse opioid tolerance. It has been demonstrated that μ-receptor activation might initiate removal of the blockade of NMDA receptor by magnesium ion, eventually resulting in decreased responsiveness of μ-receptors and opioid tolerance. This could be reversed by the NMDA receptor antagonist, ketamine. It has been shown that the requirement of methadone could be reduced from 240 mg/day to 75 mg/day, by intravenous infusion of burst ketamine 100 mg daily for 2 days, repeated monthly.28

Systemic adverse effects could be minimized by neuraxial administration of opioids by the epidural or subarachnoid route. Intra-cerebroventricular administration of opioids has also been shown to be effective, starting with a low dose, titrating upwards. Adverse effects included dizziness, sleepiness, fatigue and nausea. The requirement of nurses to perform the injection disrupted the privacy of the patients. Intraventricular injection by the patients’ family members, however, increased the risk of infection.29
Psychosocial and existential pain

The concept of total pain is well established. Pain has been demonstrated to be associated with anxiety, depression, hostility, anger, fear of future progression of pain, worry about pain, negative mood, lower quality of life score for psychosocial well-being, decreased social activities, lower levels of social support, reduced social functioning and lower resiliency of the social network.30

Existential pain, however, may have different meanings to different people. It has been shown that 97.3% of chaplains, 65.8% of palliative care physicians and 48.9% of pain specialists described existential pain as suffering that had no clear connection to physical pain. Only 1% of chaplains thought that in certain cases, strong existential suffering could be expressed as physical pain. On the other hand, 32% of palliative care physicians and 32% of pain specialist considered that existential suffering could be a primary cause of pain, and could reinforce physical pain that already existed. This carried an implication to treatment, suggesting the possibility of alleviation of existential pain by analgesic therapy in combination with existential support.31

References