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## Review Article

# Recent advances in cancer pain management

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**Abstract:** It is important to control of malignant pain and a related symptom is in cancer patients. To achieve the adequate pain control and best quality of life for patients, oncologists and palliative care clinicians must work together to understand problems related to psychologic, social, and spiritual pain. Pain is the primary problem targeted for control using the World Health Organization's (WHO) analgesic ladder to fulfil the broader objectives of palliative medicine. There are several classes of drugs that are currently used to treat cancer pain: 1) nonsteroidal anti-inflammatory drugs, with emphasis on cyclooxygenase-2 inhibitors; 2) opioid analgesics, with specific emphasis on methadone and its newly recognized value in cancer pain; 3) ketamine, an antagonist at N-methyl-d-aspartate receptors; and 4) bisphosphonates, used for pain resulting from bone metastases. This article tells about newer drugs and drug delivery approaches to cancer pain management.
**Keywords:** cancer, pain, fentanyl

## Introduction

After decades of publication of the world health organization's analgesic ladder, cancer pain is still a major cause of suffering in patients with cancer. Due to the increasing incidence of cancer, cancer-related pain has become a major health problem. Till the analgesic ladder approach has been outstandingly successful in alleviating pain and suffering when it is used appropriately. During last few decades, due to advancement in the use of chemotherapy, radiotherapy and other cancer treatments, patient survival have improved. But pain from cancer that may spread to involve nerve plexuses, the spinal canal and the brain has become a challenge. Previous studies have shown that at least 20-40% of cancer pain is not adequately relieved by application of the WHO analgesic ladder [1]. And also patients want to maintain a good quality of life without the side effect of analgesic drugs. The long-term adverse effects of opioids on cognitive function and on the immune and endocrine systems have been largely ignored in palliative care but are significant in those who survive cancer [2]. So search for ideal method of pain relief in these patients goes on. Research in cancer pain management should stress upon managing complex and difficult pain while minimising the adverse effects of analgesic drugs. We will be discussing some new drugs and new technique of drug delivery system.

## Advances in drug therapy

### New preparations of Fentanyl

Breakthrough cancer pain is widely recognized as a clinically significant complication of chronic cancer pain. With most breakthrough cancer pain episodes peaking in intensity within a few minutes and lasting for approximately 30 minutes, speed of onset of action is crucial for effective pain management. Fentanyl preparations, such as Fentanyl buccal tablet, sublingual Fentanyl citrate orally disintegrating tablet, and oral transmucosal Fentanyl citrate lozenge have all been proven to be efficacious in clinical studies [3].

### Nabiximols

Patients with advanced cancer who have pain the responds poorly to OPIOD therapy pose a clinical challenge. Nabiximols, a novel cannabinoid formulation, may be a useful add-on analgesic for patients with opioid- refractory cancer pain. A randomized, double-blind, placebo controlled, graded-dose study demonstrated efficacy and safety at low and medium doses [4].

### Denosumab

The food and drug administration approved denosumab to prevent skeletal-related events associated with metastatic solid tumors. This drug is a monoclonal antibody that inhibits the receptor activator of nuclear factor κB (RANK)-RANK ligand interaction. Clinical

trials have shown superiority over bisphosphonates for the prevention of skeletal-related events [5].

**Agents for neuropathic pain**

Chemotherapy-induced peripheral neuropathy (CIPN) is one the most serious complications associated with anticancer drugs. CIPN leads to a lower quality of life and dysfunction of the sensory motor and autonomic systems, and often causes patients to discontinue chemotherapy. To date, no agents have been shown to effectively prevent CIPN, leading to debate as to the standard protocol. Duloxetine has demonstrated a moderate therapeutic effect against CIPN. Although tricyclic antidepressants (such as nortriptyline or desipramine), gabapentin, and a topical gel containing baclofen (10 mg), amitripty line HCL (40 mg), and ketamine (20 mg) showed inconclusive results in CIPN trials, these agents are currently considered the best options for CIPN treatment [6].

**Tapentadol**

Tapentadol is a novel centrally acting analgesic that is both a noradrenaline uptake inhibitor and a mu opioid agonist A study by Mercadante *et al.;* Concluded that it is effective for cancer pain [7]. This 50 patient 4-week open label prospective study of opioid naive patients with moderate to severe cancer pain showed significantly improved pain scores and quality of life.

**Capsaicin**

Capsaicin, the active ingredient of the hot red chilli pepper, activates the transient receptor potential vanilloid 1 (TRPV) receptor expressed in nociceptive sensory nerves and defuctionalizes nociceptor activity. A recent Cochrane review suggests that low dose topical capsaicin is no better than placebo cream for peripheral neuropathic pain [8]. It is available as an 8% skin patch which is applied to a hypersensitive area after local anaesthetic as a "one off" treatment. If effective it can be repeated after 3 months. It is not licensed from cancer or chemotherapy-related neuropathic pain.

**Lidocaine**

Topical Lidocaine 5% medicated plasters are licensed for post herpetic neuralgia but are recommended in a recent review as first-line treatment for localized neuropathic pain from a variety of causes [9]. The plasters are cooling, liked by patients, and are remarkably safe. There are no studies of their use in cancer pain.

**Intrathecal drug therapy**

Epidural and intrathecal infusions of local anaesthetic agents with or without opioid make a most important contribution to the management of severe cancer pain. Indeed, it has been suggested that intrathecal morphine should be should be used when the usual pharmacological therapies have failed [10]. Intrathecal infusions are of low volume and can be delivered via a fully implanted pump.

The main indications for use of intrathecal drug delivery are:

a. Uncontrolled pain despite high doses of opioids and adjunct drugs;
b. Unacceptable side effects analgesics;
c. Cancer involving a nerve plexus, most commonly the lumbosacral plexus;
d. Widespread bony metastases.

Battery powered fully programmable pumps contain a drug reservoir of 20 or 40 ml. The intrathecal catheter and pump are inserted under general anaesthesia by a surgeon and are programmed via a computer and telemetric head held over the abdominal skin where the pump is sited. Drugs that can be used are: preservative-free morphine, hydromorphone, clonidine, baclofen, bupivacaine. Doses can be altered as often as necessary and the patient can deliver preset boluses via a hand held device called a personal therapy manager (PTM). A randomised controlled trial showed improved quality of life, sustained pain control and significantly fewer drugs – related toxicity with intrathecal drug delivery (ITDD) compared to comprehensive medical management [11]. Epidural infusions of local anaesthetic agents with opioid, targeting the oppropriate nerve roots, can be delivered by an external infusion pump.

**Vertebroplasty and kyphoplasty**

Metastatic spread of cancer to the vertebral in the spine occurs in one third of patients with cancer, most commonly in the thoracic spine [12]. Pain is a common symptom, presenting as back pain. There may be radiating pain in the distribution of compressed nerve roots if the tumour starts to invade the spinal canal. Vertebroplasty is a technique of injecting acrylic cement percutaneously into the effected vertebral body or bodies under fluoroscopic imaging. Kyphoplasty is a newer modification of vertebroplasty where a specialised balloon is inflated in the vertebral body prior to injection of cement. This minimises leakage of cement and reduces kyphotic deformity.

**Percutaneous cervical cordotomy**

In this technique, a radiofrequency lesion is made to the spinothalamic tract at C1-2level in the cervical spinal cord for pain on the opposite side of the body, usually from mesothelioma or breast carcinoma. Case series show effectiveness in 85-90% cases, and a reduction in drug related toxicity, with minimal adverse effects [13].

**Coeliac plexus block**

This is a neuro lytic block of the celiac ganglia, situated anterior to the body of L1 vertebra, which

innervate the organs of the upper abdomen through the sympathetic nervous system. Recent evidences point to effective pain relief and reduction in opioid use following a successful block. There are many approaches to the celiac ganglia described in the literature. But use of CT scanning or ultrasonography-guided blocks via the anterior route, or the video thorascopic approach adopted in recent years has improved safety [14].

**Intrathecal neurolysis**

This is the injection of phenol or alcohol into the dorsal roots of selected nerves via a spinal needle sited within the dural sac. Safety depends on correct positioning of the patient and skill of the operator. Selective dorsal thoracic root blocks are helpful for chest wall pain and saddle blocks for pelvi-sacral pain [15].

**Ultrasound guided nerve blocks**

Improvements in ultrasound technology have greatly improved accuracy of placement of needles and catheters adjacent to nerves, and there is increasing use by anaesthetists for regional anaesthesia. A literature review by tran *et al.;* concluded that for axillary blocks the use of ultrasound increases the likelihood of the block being successful [16]. Brachial plexus, lumbar plexus, femoral, intercostals, sciatic and other nerve blocks are now readily achievable and may become more effective again.

**The pain – relieving role of radiotherapy and chemotherapy**

Palliative radiotherapy is used to relieve pain from brain and bony metastases. A Cochrane review shows a complete response in 25% at one month, with a further 40% of patients with painful bony metastases getting 50% pain relief. The radionuclides strontium-89 and radium 223 have been used successfully to treat pain from prostate cancer bone secondaries [17].

Palliative chemotherapy is most successful in lymphoma, germ cell tumours, small cell lung tumours and breast carcinoma. Chemotherapy can also induce pain, especially neuropathic pain. Bisphosphonates reduce cancer bone pain in 50% of recipients regardless of the primary tumour [18] and should be considered where analgesics and / or radiotherapy are inadequate for the management of painful bony metastases.

**Neuromodulation**

Neuromodulation is the technique of changing nerve activity by the application of electric currents. The most common technique is spinal cord stimulation with wires/paddles adjacent to the dorsal columns. Modalities include peripheral stimulation, motor cortex and deep brain stimulation. Spinal cord stimulation has been shown to be particularly effective in neuropathic pain (15-40% of cancer pain), vascular pain and recently high-frequency stimulation has been shown to be effective in controlling nociceptive pain [19]. Despite its success in chronic pain, there has been little research into neuromodulation for cancer pain.

**Educational interventions:**

Although opioids are effective drugs at reducing cancer pain, there are significant psychological barriers that prevent physicians from prescribing them and patients from accepting them. These are illustrated in the recent national institute for Health and Clinical excellence (NICE) guidelines on opioids in palliative care several interview - based studies have highlighted patients concerns about opioids. They include concerns over addiction, tolerance, side effects and issues such as acceptance of palliation rather than treatment, and the feeling that starting opioids is a landmark for end-of-life care [20].

Educational interventions aim to reduce these barriers by providing information, thus increasing patient satisfaction and adherence to medication, leading to improved pain control. There have been many studies on the efficacy of educational interventions.

**In summary**

Cancer pain is complex and multifactorial in origin, which makes management of pain difficult in at least a quarter of patients. Careful assessment of the types and sources of pain must be made and then treated holistically, adapting treatment to the needs of the individual. Recent advances in drug thereapies, interventional techniques and the multiplicity of approaches that may be necessary are outlined in this short article; there are few rigorous trials in cancer patients and there remain many unknowns. The specialities of oncology, palliative care and pain medicine must work together to achieve the best possible pain management for patients.

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