Advances in cancer pain management

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Extensive experience suggests that cancer pain can be relieved in 80% to 90% of patients using a simple opioid-based analgesic regimen [1–4]. For most patients, a satisfactory outcome follows an opioid dose adjustment period that culminates in a favorable balance between analgesia and side effects. In some cases, however, this favorable balance between analgesia and side effects cannot be achieved or maintained over time. Pain cannot be controlled with dose escalation because of moderate to severe opioid-related side effects. This kind of pain may be considered “poorly responsive” to the opioid. Poor opioid responsiveness is an important clinical phenomenon; the management of which requires careful assessment and working knowledge of a broad range of therapeutic options. This article describes some of the possible mechanisms underlying poor opioid responsiveness and the clinical strategies that might be considered to improve the balance between analgesia and side effects. Those interested in a more detailed synopsis of current strategies for treating cancer pain and the mechanisms underlying poor opioid responsiveness are referred to the following reviews [5–9].

Definition of opioid responsiveness

Opioid responsiveness has been defined as the degree of analgesia achieved as the dose is titrated to an endpoint defined by intolerable side effects. If analgesia is generally inadequate because side effects impose a practical limit on dose escalation, the pain may be said to be relatively poorly responsive to the specific drug and route of administration. If a favorable balance between analgesia and side effects can be attained, the pain may be said to be relatively responsive to the drug and route.
Mecanism implicat in opioid responses

Poor opioid responsiveness may be related to mechanisms that increase the likelihood of side effects, such as accumulation of metabolites, and mechanisms that reduce the likelihood of analgesia, such as tolerance.

Mechanisms that increase the likelihood of side effects

Demographic and disease-related variables may predispose to side effects and thereby reduce responsiveness. For example, the elderly may be less likely to experience a favorable outcome during opioid therapy because of a propensity to develop cognitive impairment from centrally acting drugs. Comorbidities, such as dementia, and factors directly related to the cancer, such as brain metastases, may have the same effects.

Other mechanisms may be drug related. The predominant metabolic pathway for morphine is glucuronidation to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) [10]. The accumulation of morphine metabolites may be associated with side effects, such as myoclonus and chronic nausea [15,16].

Probably as a consequence of first-pass glucuronidation through the liver, the ratios of M6G:morphine and M3G:morphine are higher with oral than parenteral administration [11,12]. Liver dysfunction has a small effect on morphine kinetics [14]; however, renal insufficiency results in accumulation of M3G and M6G [13].

Mechanisms that reduce the likelihood of analgesia

Tolerance and the development of mechanisms that underlie neuropathic pain may reduce the likelihood of analgesia by shifting the opioid dose–response curve to the right.

Tolerance

Although opioid doses usually stabilize for prolonged periods, analgesic tolerance is a potential problem that could result in loss of responsiveness. Tolerance is a complex receptor-selective phenomenon. It may involve interactions among multiple receptor subtypes [17,18]; activation of varied non-opioid systems, including those activated by agonist activity at the N-methyl-D-aspartate (NMDA) receptor [19–21]; and characteristics (such as intrinsic activity) that are drug specific [22–25]. One important strategy for managing poor opioid responsiveness—opioid rotation—presumably works by relying on incomplete cross-tolerance among drugs to overcome these processes (see below).

Neuropathic pain

Neuropathic cancer pain usually results from injury to peripheral nerves, which may be caused by tumor invasion (eg, malignant brachial plexopathy),
cancer treatment (eg, chemotherapy-induced painful polyneuropathy or postmastectomy syndrome), or other factors (eg, postherpetic neuralgia). Although neuropathic pain may respond well to opioids [2], it is, overall, less responsive to opioids than pain caused by other pathophysiologies [26,27].

The pathophysiology of neuropathic pain is based on unique mechanisms in the peripheral and central nervous system. In the presence of nerve injury, nociceptors may acquire new characteristics; regenerating nerve sprouts may discharge spontaneously (which may be associated with spontaneous dysesthesia); activation thresholds may be decreased (resulting in pain after non-noxious stimuli or allodynia); and the stimulus-response function may shift to the left (such that a noxious stimulus causes more pain than normal or hyperalgesia). These characteristics may be caused by any of numerous mechanisms. Activation of the NMDA-receptor is involved, providing evidence for a common intracellular mechanism of neuropathic pain and tolerance [28–30].

**Strategies to improve the balance between analgesia and adverse effects**

Patients whose pain is poorly responsive to an opioid must be comprehensively reassessed as the initial step in management. This evaluation has two goals. The first goal is to determine whether specific contributing factors can be identified, which may be amenable to primary therapeutic strategies. The most common example is probably the role of radiotherapy to address disease progression associated with loss of analgesic effectiveness. Chemotherapy also may be helpful in selected cases, as discussed below.

The second goal is to determine the risks and potential benefits associated with each of four strategies for improving the balance between analgesia and side effects: (1) more effective management of opioid side effects; (2) opioid rotation or switching the route of opioid administration; (3) pharmacologic interventions to reduce the systemic opioid requirement; and (4) nonpharmacologic interventions to reduce systemic opioid requirement. Each strategy comprises numerous specific therapies. Unfortunately, comparative trials have not been done, and the decision to pursue one or another is a matter of clinical judgment based on a comprehensive assessment of the patient.

**Symptomatic management of opioid side effects**

Effective management of opioid side effects can open the “therapeutic window” and convert a poorly responsive pain into one that can be managed. The Steering Committee of the European Association of Palliative Care Research Network has developed evidence-based guidelines for the management of side effects of oral morphine [31]. The most important advance in these techniques is the now commonplace use of a psychostimulant to reduce the somnolence or cognitive impairment that may be limiting therapy.
Switching the opioid administration route

As described above, the accumulation of metabolites is higher with oral than with parenteral administration of morphine. Therefore, changing the route of opioid administration may be useful in patients suffering from side effects that may be related to accumulation of M6G and M3G, such as myoclonus and nausea.

In a prospective study of 36 cancer patients, a continuous subcutaneous infusion of morphine produced significantly less nausea, constipation, and drowsiness than oral morphine [32]. In another study of 164 patients, switching from oral to subcutaneous morphine resulted in significant improvements in nausea and vomiting but no change in drowsiness [33]. Comparative studies between oral or subcutaneous morphine and rectal morphine showed comparable analgesia and side effects [34–36].

Opioid rotation

Sequential opioid trial (opioid rotation) is now widely accepted as a strategy for addressing poorly responsive pain. In a retrospective analysis of 191 patients, 80 underwent opioid rotation secondary to cognitive failure, hallucinations, uncontrolled pain, myoclonus, and nausea. Seventy-three percent experienced an improvement of side effects and pain control [37]. In another retrospective analysis, the incidence of agitated delirium among patients with advanced cancer decreased from 26% to 10% after a more frequent use of opioid rotation and hydration [38]. In a case series of six terminally ill cancer patients suffering from severe pain despite increasing doses of morphine or hydromorphone, conversion to methadone resulted in adequate pain control [39]. In a recent prospective study, 50 cancer patients with uncontrolled pain and moderate to severe opioid adverse effects were switched from oral morphine to oral methadone. Although 80% experienced a significant reduction in pain intensity, nausea and vomiting, constipation, and drowsiness, there were no significant changes in myoclonus, xerostomia, confusion, and sweating [4]. Some evidence has shown that switching from morphine to fentanyl can decrease the incidence of constipation [40]; this effect, if confirmed, may be related to the change in drug or route.

The opioids commonly used in the United States for severe pain include morphine, hydromorphone, fentanyl, oxycodone, and methadone. Guidelines for switching from drug to drug, using equianalgesic dose ratios as a starting point, have been proposed (Table 1) [41].

The most important advance in the use of opioid rotation relates to the expanding role of methadone. Although methadone may be difficult to use because of its large interindividual variation in pharmacokinetics (with half-lives ranging from 8 to more than 120 hours) [14,44], recent experience suggests that it may be an attractive alternative μ opioid analgesic. Its advantages include no neuroactive metabolites, elimination pathways that are independent of renal
Table 1
Equianalgesic doses for representative opioid-receptor agonists used to manage severe cancer pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>PO</th>
<th>IM</th>
<th>Half-life (h)</th>
<th>Duration (h)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>20–30</td>
<td>10</td>
<td>2–3</td>
<td>2–4</td>
<td>Standard for comparison for opioids</td>
</tr>
<tr>
<td>Morphine CR</td>
<td>20–30</td>
<td>10</td>
<td>2–3</td>
<td>8–12</td>
<td>Various formulations are not bioequivalent</td>
</tr>
<tr>
<td>Morphine SR</td>
<td>20–30</td>
<td>10</td>
<td>2–3</td>
<td>24</td>
<td>A recent study suggested that hydromorphone:morphine = 3:1, rather than 7:1, during prolonged use [42]</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
<td>1.5</td>
<td>2–3</td>
<td>2–4</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td></td>
<td>2–3</td>
<td>3–4</td>
<td>Although a 1:1 ratio with morphine was used in a single-dose study, there is a change with repeated administration and a large dose reduction (75% to 90%) is needed when switching to methadone. Another study suggested that the equianalgesic doses depend on the previous opioid dose (see text).</td>
</tr>
<tr>
<td>Oxycodone CR</td>
<td>20</td>
<td></td>
<td>2–3</td>
<td>8–12</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>20</td>
<td>10</td>
<td>8–12</td>
<td>4–12</td>
<td>Although a 1:1 ratio with morphine was used in a single-dose study, there is a change with repeated administration and a large dose reduction (75% to 90%) is needed when switching to methadone. Another study suggested that the equianalgesic doses depend on the previous opioid dose (see text).</td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
<td></td>
<td>7–12</td>
<td></td>
<td>Can be administered as a continuous IV or SC infusion; based on clinical experience, 100μg/h is roughly equianalgesic to morphine 4mg/h IV</td>
</tr>
<tr>
<td>Fentanyl TS</td>
<td></td>
<td></td>
<td>16–24</td>
<td>48–72</td>
<td>Based on clinical experience, 100μg/h is roughly equianalgesic to morphine 4mg/h IV. A recent study indicated a ratio of oral morphine:transdermal fentanyl of 70:1 (the recommended converting ratio was 100:1) [43]</td>
</tr>
</tbody>
</table>

Abbreviations: CR, controlled-release; IM, intramuscular; IV, intravenous; SR, sustained-release; TS, transdermal system; SC, subcutaneous.

* Studies to determine equianalgesic doses of opioids have used morphine by the IM route. The IM and IV routes are considered to be equivalent, and IV is the most common route in clinical practice. Equianalgesic dose tables are guidelines. There may be big interindividual differences. The relative potency of some opioids may increase with repetitive dosing. The dose therefore needs to be individualized and carefully titrated to effect.

* Although the PO:IM morphine ratio was 6:1 in a single-dose study, other observations indicate a ratio of 2–3:1 with repeated administration.

function, good oral bioavailability, and extremely low cost. Perhaps most important, the racemic formulation available in the United States contains the \( \text{d-isormer} \), which is a noncompetitive NMDA receptor antagonist [4].

Several approaches have been described to facilitate the switch from morphine to methadone [24,45,46]. In a recent publication, morphine was stopped and immediately substituted with methadone using a different methadone:morphine ratio based on the patients’ daily morphine doses: 1:4 (1 mg oral methadone =
4 mg oral morphine) for patients receiving less than 90 mg morphine per day; 1:8 for patients receiving 90 to 300 mg/day; and 1:12 for patients receiving more than 300 mg/day of morphine [4]. This changing equianalgesic ratio is based on the observation that the potency of methadone increases in patients with substantial prior opioid exposure. This observation may be explained by reversal of tolerance produced by the d-isomer. A simpler guideline for conversion to methadone suggests that the calculated equianalgesic dose of methadone be decreased by 75% to 90% and administered in four divided doses per day. Access to a “rescue” dose (preferably an alternative short-acting opioid) will ensure that pain is not poorly relieved at the start of methadone treatment.

**Pharmacologic interventions to reduce systemic opioid requirement**

**Coanalgesics**

Nonsteroidal anti-inflammatory drugs (NSAID) have an opioid-sparing effect that may help prevent the occurrence of dose-related side effects [47]. Advanced age, history of peptic ulcer disease, being male, and concurrent corticosteroid therapy are among the most important risk factors for upper gastrointestinal tract bleeding and perforation associated with NSAIDs [48]. Antineoplastic therapy also may induce damage to upper gastrointestinal tract mucosa [49]. Proton pump inhibitors have been found to be most effective and well tolerated in preventing gastrointestinal damage induced by NSAID [50–52] or antineoplastic therapy [49]. No comparative studies have been performed concerning the analgesic efficacy of cyclooxygenase-2 (COX-2) inhibitors and nonselective NSAIDs in the cancer population; the increased safety of the COX-2 selective drugs is likely to be an advantage in those with serious medical illness.

The adjuvant analgesics comprise numerous drugs in diverse drug classes (Table 2). Although they are all commercially available for indications other than pain, they are also analgesic in selected circumstances. In cancer patients, these drugs are typically used to help manage several challenging pain syndromes, such as neuropathic pain, bone pain, and pain related to bowel obstruction [53]. The most recent advances have occurred in the treatment of neuropathic pain and are discussed below.

**Intraspinal opioid therapy**

The clearest indication for intraspinal opioid delivery is intolerable somnolence or confusion in patients who are not experiencing adequate analgesia during systemic opioid treatment of pain located below the level of midchest. In a randomized trial comparing the oral and the epidural route of morphine, pain relief was similar after 24 hours, and side effects were less frequent in the epidural group [54]. Somatic incident pain, neuropathic pain, and visceral pain from bowel distension have been described as being relatively less responsive to spinal opioids [55]. The intraspinal administration of local anesthetics or other drugs (eg, clonidine) with an opioid may provide additional analgesia and permit the successful treatment of patients unresponsive to spinal morphine alone [56].
Therapeutic strategies that target the cause of the pain

As noted, primary therapy directed at the etiology of the pain should be considered whenever assessment of the patient with poor opioid responsiveness suggests that such an approach is viable. Patients who suffer from pain during the course of a highly chemosensitive or radiosensitive tumor, such as lymphoma or small cell lung cancer, can benefit from tumor-specific treatments. There is less evidence, however, concerning the benefit of chemotherapy or radiotherapy in the palliation of pain caused by less sensitive tumors. Most of the existing phase II chemotherapy trials place emphasis on response rate, which is not a direct measure of patient benefit. In phase III trials, quality of life or symptom distress is increasingly considered one of the secondary endpoints. Specific chemotherapy regimens have been shown to be analgesic in patients with non–small-cell lung cancer [57], breast cancer [58], prostate cancer [59,60], esophageal cancer...
[61], pancreatic cancer [62], and ovarian cancer [63]. The analgesic effectiveness of radiotherapy has been documented in treatments for painful bone metastases [64], non–small-cell lung cancer [57,65], and headache secondary to brain metastasis [66].

**Other interventions**

Invasive techniques, such as neural blockade, may reduce analgesic requirements in poorly responsive pain syndromes (see discussion below). Other techniques, including psychological interventions (eg, guided imagery, hypnosis, and other approaches), physiatric strategies (eg, physical therapy), and neurostimulatory approaches (eg, transcutaneous electrical nerve stimulation) are suggested by clinical experience.

**Treatment of neuropathic pain**

Given its poor opioid responsiveness, neuropathic pain is often a target of the diverse strategies described above. Because the pharmacologic options available for this type of pain have advanced rapidly, clinical experience suggests that most patients with neuropathic cancer pain that is poorly responsive to an opioid can be managed by adding an adjuvant analgesic. In a retrospective study of 593 cancer patients with nociceptive (n = 380), mixed (n = 181), and neuropathic (n = 32) pain, nonopioid or opioid analgesics were given to 99%, 96%, and 79%, antidepressants to 8%, 25%, and 19%, anticonvulsants to 2%, 22%, and 38%, and corticosteroids to 26%, 35%, and 22% of patients, respectively. Analgesic treatment resulted in a significant pain relief in all groups of patients, with a decline in mean pain intensity (measured on a 100-mm visual analogue scale) from 66 (nociceptive), 65 (mixed), and 70 (neuropathic) on admission to 26, 30, and 28 after 3 days and 18, 17, and 21 at the end of the survey [2].

**Corticosteroids**

The corticosteroids are important adjuvant drugs in the cancer population, particularly in the setting of advanced disease. The pain-related indications for corticosteroids include refractory neuropathic pain, bone pain, pain associated with capsular expansion or duct obstruction, and headache caused by increased intracranial pressure.

**Anticonvulsants**

The use of anticonvulsants in the treatment of cancer-related neuropathic pain is based on studies in chronic nonmalignant neuropathic pain syndromes, such as trigeminal neuralgia, postherpetic neuralgia, and diabetic neuropathy. Controlled studies, such as those that evaluated carbamazepine and gabapentin, show that as many as two thirds of patients may obtain good pain relief [67]. In an
uncontrolled study of 22 cancer patients whose neuropathic pain was not completely controlled with opioids, the addition of gabapentin resulted in decreased pain in 20 patients [68]. In a phase II study of the efficacy and toxicity of sodium valproate in patients with cancer-related neuropathic pain, 55.6% of patients responded to the treatment [69].

At present, gabapentin is the most commonly used adjuvant analgesic for neuropathic pain. It has an acceptable adverse effect profile, is not metabolized in the liver, and has no known drug–drug interactions. Treatment usually starts with 100 to 300 mg/day, and dose titration usually continues until benefit occurs, side effects supervene, or the total daily is at least 2700 to 3600 mg/day. Some patients do not reach a maximal response until the dose is increased to 6000 mg/day or even higher.

Other anticonvulsants also have established analgesic effects. Phenytoin and clonazepam have been used for many years. Clonazepam may be particularly useful if pain is associated with anxiety. A variety of observations, including several controlled trials, also support the potential efficacy of the newer anticonvulsants, including lamotrigine, topiramate, tiagabine, oxcarbazepine, and zonisamide.

**Antidepressants**

Although widely accepted as adjuvant drugs, no randomized trials have evaluated the use of antidepressants for cancer-related neuropathic pain, and no studies have compared the effects of anticonvulsants and antidepressants.

Amitriptyline, a tertiary amine tricyclic drug, is the best studied and, on this basis, may be preferred in patients with cancer-related neuropathic pain once gabapentin has failed. This drug has been shown to increase the plasma concentration of morphine in cancer patients [70], and its side effect liability is relatively high. In a study of 15 patients with post-mastectomy syndrome, for example, five of the eight women who had a good response did not want to continue because of adverse events (the order of importance being tiredness, dry mouth, and constipation) [71]. Patients who are unable to tolerate the common side effects of a tertiary amine tricyclic drug might be considered for a trial with a secondary amine tricyclic, such as desipramine [72]. Adverse effects are even less likely with the selective serotonin reuptake inhibitors and other newer antidepressants; however, evidence of analgesic efficacy for these drugs is very limited. Several controlled studies, however, do suggest efficacy for drugs, such as paroxetine. Because of the relatively better side effect profile, trials with paroxetine or another of the newer antidepressants are appropriate for those who cannot tolerate a secondary amine tricyclic drug or who have contradictions to a tricyclic trial [73].

**Local anesthetics**

Oral local anesthetics have been found to effectively treat nonmalignant [74] and cancer-related neuropathic pain syndromes [75] and should be considered once trials of anticonvulsants or antidepressants have failed. In the United States,
mexiletine has been the preferred oral local anesthetic. Treatment usually begins with a low dose (150 mg/day), which is followed by gradual dose escalation. In cancer patients with severe, progressive neuropathic pain, brief intravenous local anesthetic infusions also can be tried. Treatment usually involves the infusion of lidocaine (1 to 4 mg/kg) over 30 minutes. Because of a dose response, a prudent approach involves an initial low dose infusion, which, if unsuccessful, is followed by infusions at incrementally higher doses.

NMDA-receptor antagonists

NMDA-receptor antagonists have been shown to suppress hyperalgesia in animal models [76–78]. Controlled trials have shown that drugs with this mechanism can be effective in treating nonmalignant neuropathic pain syndromes [79,80]. Because of its NMDA-receptor blocking properties, methadone may have relatively good efficacy in the treatment of cancer-related neuropathic pain; however, no randomized trials have addressed this hypothesis. Substantial benefit has resulted from the addition of ketamine (a dissociative anesthetic with antagonistic effects on the NMDA receptor) to opioid therapy in cancer patients with difficult pain problems, including neuropathic pain, who had lost an analgesic response to high doses of morphine [81–84]. In one protocol, ketamine was given at an initial starting dose of 100 to 150 mg/day, and the opioid dose was reduced by 50%; the ketamine dose was then titrated against effect [85]. Ketamine can cause severe psychomimetic effects, such as nightmares and delirium, and the potential for this toxicity limits its use in the clinical setting. Haloperidol [85] or diazepam [81] often is coadministered to reduce the risk of these problems, and patients with intracranial hypertension or seizures should not receive this drug [85]. Dextromethorphan, an antitussive, is another commercially available NMDA receptor antagonist. In a randomized trial, the addition of dextromethorphan 90 mg/day to conventional treatment with either an NSAID, dextropropoxyphene, or morphine did not have any significant analgesic effect [86]. Other controlled trials of a morphine–dextromethorphan combination tablet, however, suggest that the adjuvant does have an analgesic effect. Animal studies have shown that much higher doses of NMDA receptor antagonists are necessary to treat neuropathic pain than are necessary to inhibit the development of opioid tolerance [20]. In a study of patients with diabetic neuropathy, a mean dose of 381 mg/day was needed to reduce the pain by a mean of 24% [80]. Amantadine is also a NMDA receptor antagonist and, in a small, randomized trial, it was found to be effective in treating surgical neuropathic pain in cancer patients [87].

Other drug classes

Several other drug classes may help manage neuropathic pain. The \( \gamma \)-amino-butyric acid agonist baclofen has been shown to effectively treat trigeminal
neuralgia [88] and may be useful for treating neuropathic pain in the medically ill. The therapeutic dose appears to vary widely, ranging from 30 to 200 mg/day.

The alpha-2-adrenergic agonists, including clonidine and tizanidine, have established analgesic efficacy in a variety of pain syndromes. Epidurally administered clonidine has proven efficacy in cancer pain and was shown to be relatively more effective for neuropathic pain [89].

Benzodiazepines also may have salutary effects in patients with chronic cancer pain, and it may be impossible to determine the degree to which psychotropic or primary analgesic actions contribute to this outcome. The efficacy of clonazepam was noted previously, and a survey of patients with mixed types of cancer-related neuropathic pain suggested that alprazolam also may have analgesic effects [90]. Patients with cancer pain also commonly experience anxiety and muscle spasms; phenomena that may exacerbate the intensity of pain and respond well to other benzodiazepines, such as diazepam.

**Topical analgesic therapies**

Topical local anesthetics can be administered by patch or cream. Recently, a lidocaine-impregnated patch (Lidoderm) was approved for patients with post-herpetic neuralgia. This formulation appears to be well accepted and should be considered for any patient who has a very localized neuropathic pain syndrome [91].

Patients with neuropathic pain caused by peripheral nerve injury also can be considered for a trial of topical capsaicin; a peptide that depletes substance P in small primary afferent neurons. A recent study of cancer patients with surgical neuropathic pain found that capsaicin significantly decreased pain and was preferred by 60% of the patients despite side effects, such as skin burning [92].

**Summary**

Although most patients with cancer pain can attain a favorable balance between analgesia and side effects with a conventional approach to opioid therapy, a substantial minority cannot. For these patients, an important subgroup of whom have neuropathic pain, alternative therapeutic strategies are needed. With a detailed assessment, clinicians should be able to choose among the large and diverse group of options available and implement an approach, or combination of approaches, that have a high probability of improving analgesic outcomes.

**References**


