LEADING ARTICLE

Management of Cancer Pain: Optimal Pharmacotherapy and the Role of Interventions

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This article provides an up to date review of the pharmacological and non-pharmacological therapy of cancer pain and considers the role of interventional approaches, such as anesthetic techniques and neurosurgical procedures, for difficult-to-treat cancer pain syndromes. The management of cancer-related pain is an essential component of comprehensive care for the oncology patient. Optimal pharmacotherapy requires ongoing clinical assessments, rational opioid prescribing and titration, management of common side effects, effective treatment of breakthrough pain and the appropriate use of adjuvant analgesics, especially for difficult to treat pain syndromes. Multiple non-pharmacological approaches are available and have various levels of evidence supporting their use in the treatment of cancer related pain. Anesthetic procedures, most importantly spinal drug delivery and neurolytic blocks, are supported by controlled trials and should be offered to select patients. In patients with refractory pain despite aggressive pharmacological, non-pharmacological, and anesthetic interventions, neurosurgical interventions should be considered.

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Managing pain in cancer patients is a fundamental component of comprehensive care. Uncontrolled pain can cause physical, psychological, and spiritual distress [1,2]. Indeed, studies have shown cancer patients' quality of life to be negatively affected when pain and other symptoms are prevalent [3–5]. Initial prevalence studies found that approximately 30–50% of cancer patients undergoing treatment for their disease and up to 90% of patients with advanced disease have chronic pain severe enough to warrant the use of opioid therapy [6–8]. Pain in cancer patients may be due to direct effects of the tumor (e.g. invasion of bone, nerve compression, and/or visceral stretching), due to complications of cancer therapy (e.g. radiation-induced fibrosis or chemotherapy-induced neuropathy), or it may be unrelated to the cancer or its treatment (Tables 1–3).

Studies show that 85–95% of all cancer pain can be controlled with systemic analgesics and non-pharmacological modalities [9,10]. However, for those patients with unrelieved pain, invasive procedures play an important role in decreasing pain and improving quality of life. Despite increased efforts in education and quality improvement measures to increase awareness, cancer pain continues to be under-treated [11,12]. This article reviews the pharmacological and non-pharmacological therapy of cancer pain and considers the role of interventional approaches, such as anesthetic techniques and neurosurgical procedures, for difficult-to-treat cancer pain syndromes.

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Pharmacotherapy of cancer pain

In the 1980s an expert panel for the World Health Organization (WHO) developed a model algorithm – the analgesic ladder – to guide clinicians in the selection of analgesic drugs for cancer pain [8]. In short, this approach recommends that moderate-to-severe cancer pain should be treated with an opioid-based regimen. Thus, an understanding of opioid pharmacotherapy is essential for the management of cancer-related pain. In addition, effective pain management requires expertise in the use of the nonsteroidal anti-inflammatory drugs (NSAIDs) and adjuvant analgesics, especially for the treatment of metastatic bone pain and neuropathic pain syndromes.

Non-opioid analgesics

Acetaminophen

Acetaminophen is an effective analgesic for mild-to-moderate pain treatment and it has only minimal

Table 1. Acute pain syndromes in cancer patients.

Acute pain associated with diagnostic procedures
- Lumbar puncture headache
- Bone marrow biopsy
- Lumbar puncture
- Venipuncture
- Paracentesis
- Thoracentesis

Acute pain associated with analgesic techniques
- Spinal opioid hyperalgesia syndrome
- Acute pain after radiotherapy of metastatic bone pain

Acute pain associated with other therapeutic procedures
- Pleurodesis
- Tumor embolization
- Nephrostomy insertion
- Pain associated with bone marrow transplantation

Acute pain associated with chemotherapy
- Pain from intravenous or intra-arterial infusion
- Intraperitoneal chemotherapy
- Headache due to intrathecal chemotherapy
- Painful oropharyngeal mucositis
- Painful peripheral neuropathy
- Bone or muscle pain from colony-stimulating factors or chemotherapies
- 5-fluorouracil-induced angina

Acute pain associated with hormonal therapy
- Painful gynecomastia
- Luteinizing hormone-releasing factor tumor flare in prostate cancer
- Hormone-induced acute pain flare in breast cancer

Acute pain associated with immunotherapy
- Arthralgia and myalgia from interferon and interleukin

Acute pain associated with radiation therapy
- Painful oropharyngeal mucositis
- Acute radiation enteritis or proctitis
- Early onset brachial plexopathy following radiation for breast cancer

Acute tumor-related pain
- Vertebral collapse and other pathological fractures
- Acute obstruction of hollow viscus (e.g. bowel, ureter, and bladder outlet)
- Headache from intracranial hypertension
- Hemorrhage from tumor

Acute pain associated with infection
- Myalgia and arthralgia associated with sepsis
- Pain associated with superficial wounds or abscesses

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anti-inflammatory effects. Unlike aspirin, acetaminophen has no effect on platelet function and fewer adverse effects compared with other non-opioid analgesics. Adverse effects include renal toxicity and hepatotoxicity at high doses. The daily intake of acetaminophen should not exceed 4 g/day and should be <3 g/day in patients with liver disease or chronic alcoholism.

NSAIDs

NSAIDs have a well-established role in the treatment of cancer pain [15]. They can be effective as an initial monotherapy for cancer pain and, when combined with opioids, may lead to a slight short-term improvement in pain compared with either agent alone [16]. The long-term safety and efficacy of NSAIDs for cancer pain have not been established. For patients with mild pain, a NSAID may be used as the sole analgesic, but should be considered for combination therapy when pain is moderate or severe. NSAIDs appear to be especially useful in patients with nociceptive somatic pain, particularly bone pain, and for inflammatory pain; it is less useful in treating neuropathic pain [17–19]. Recent research in the pathophysiology of bone pain suggests that there may be an even greater role for NSAIDs in treating pain secondary to bone metastases [20–22].

Unfortunately, the side-effect profile of NSAIDs limits their therapeutic value in treating cancer pain. All NSAIDs have the potential to cause nephrotoxicity, ranging from peripheral edema to renal failure. Serum creatinine levels should be monitored closely after initiating therapy with these agents, especially in medically frail or elderly patients. NSAIDs should be used with caution in patients with a history of aspirin allergy or asthma because they can precipitate bronchospasm in as many as 20% of these patients [23]. Significant edema can occur in patients with cirrhosis or congestive heart failure [23,24]. The relatively selective cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib, etodolac, meloxicam, and nabumetone, have a lower risk of gastrointestinal side effects than nonselective NSAIDs [24]. Thus, in patients with a history of significant gastritis or ulcer disease, or in those who are or elderly, COX-2 inhibitors or concomitant proton-pump inhibitors should be considered [25,26]. Recently, there has been recognition that COX-2 inhibition can increase the risk of thrombotic disease [27] and although this risk appears to be relatively small, it may influence the decision to offer a NSAID to patients at relatively high risk of such complications.

Opioid analgesics

The administration of opioid analgesics is the mainstay of cancer pain management. The clinician should have knowledge of opioid pharmacology and a rational approach to dosing.

Table 2. Chronic pain syndromes in patients with cancer: tumor-related pain syndromes.

Nociceptive pain syndromes

Bone, joint, and soft-tissue pain syndromes

- Multifocal or generalized pain (focal metastases or marrow expansion)
- Base of skull metastases
- Vertebral syndromes
- Pain syndromes of the bony pelvis and hip
- Tumor invasion of joint, or soft tissue, or both

Paraneoplastic pain syndromes

- Hypertrophic osteoarthropathy
- Tumor-related gynecomastia

Neoplastic involvement of viscera

- Hepatic distension syndrome
- Rostral retroperitoneal syndrome
- Chronic intestinal obstruction and peritoneal carcinomatosis
- Malignant pelvic and perineal pain
- Chronic ureteral obstruction

Neuropathic pain syndromes

- Painful peripheral mononeuropathies
- Painful polyneuropathies
- Plexopathy (cervical, brachial, lumbosacral, sacral)
- Radiculopathy
- Epidural spinal cord compression

Adapted with permission from [195].

Table 3. Chronic pain syndromes in patients with cancer: treatment-related pain syndromes.

Nociceptive pain syndromes

Painful osteonecrosis

- Radiation-induced or corticosteroid-induced necrosis of femoral or humeral head
- Osteoradionecrosis of other bones

Painful lymphedema
Painful gynecomastia
Chronic abdominal pain

- Due to intraperitoneal chemotherapy
- Due to radiation therapy

Radiation-induced chronic pelvic pain

Neuropathic pain syndromes

Postsurgical neuropathic pain syndromes

- Postmastectomy syndrome
- Post-thoracotomy syndrome
- Post-radical neck dissection syndrome
- Postnephrectomy syndrome
- Stump pain and phantom pain

Postradiotherapy pain syndrome

- Radiation fibrosis of cervical, brachial, or lumbosacral plexus
- Radiation-induced neoplasm
- Radiation myelopathy

Postchemotherapy pain syndromes

- Polyneuropathies

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Opioid selection

The WHO analgesic ladder makes a distinction between "weak" and "strong" opioids. Weak opioids are conventionally administered orally for moderate pain and in those with limited prior opioid exposure. Strong opioids are used to treat severe pain and those already receiving opioid therapy. The former group includes codeine, dihydrocodeine (only with aspirin), hydrocodone (only with acetaminophen or ibuprofen), oxycodone (combined with aspirin, acetaminophen, or ibuprofen), propoxyphene, and occasionally, meperidine. Tramadol, a unique centrally acting analgesic with a mechanism that is partly opioid, is also generally included in this group. Opioids used for severe pain include fentanyl, hydromorphone, levorphanol, methadone, morphine, oxycodone (without acetaminophen or aspirin), and oxymorphone. There is considerable variability with respect to the side-effect profile of the various opioids in each patient; therefore, it is often useful to rotate to another agent if a patient is experiencing dose-limiting side effects. Although methadone is not a new drug, it is increasingly used for patients with moderate-to-severe cancer pain. It can be given via oral, rectal, intravenous, or epidural routes; and may be particularly useful in patients with neuropathic pain [28]. Methadone is an opioid receptor agonist and a presynaptic inhibitor of *N*-methyl-D-aspartic acid (NMDA) [29]. Patients with chronic pain and those on opioids for long periods of time have increased NMDA activitation in the dorsal horn of the spinal cord. Activation of the NMDA receptor is associated with hyperalgesia and opioid tolerance [30]. Blockade of the NMDA receptor may enhance the analgesic effect of externally administered opioids and decrease opioid tolerance or opioid-induced hyperalgesia. Indeed, methadone has been suggested to be useful for patients with a high tolerance to opioids and refractory pain [31,32]. Methadone interacts with inducers and inhibitors of the cytochrome P450 (CYP) system. It is extensively metabolized by CYP1A2, CYP3A4, and CYP2D6; the first two are induced by a number of drugs and other substances (e.g. cigarette smoke), and the third enzyme has a genetic polymorphism. Drugs that lower the levels of

methadone via CYP induction include carbamazepine, effavirenz, phenobarbital, phenytoin (by 50%), rifampicin, and risperidone, each of which has been shown to precipitate withdrawal symptoms [28]. Drugs that raise the serum methadone levels include fluconazole, ketoconazole, and the selective serotonin-reuptake inhibitors (SSRIs; except venlafaxine), which raise methadone levels in CYP2D6-positive patients (rapid metabolizers) [28]. In addition, there are important drug–drug interactions that can occur in those on methadone, for example, levels of desipramine and zidovudine both increase when patients are receiving methadone. Other difficulties related to the use of methadone lie in its variable and long biological half-life and in the controversy regarding its equianalgesic dosing range.

Methadone can cause prolongation of the QT interval; although the clinical significance of this effect is under debate. Methadone blocks cardiac repolarization through specific potassium channels that are composed of subunits expressed by the human *ether-a-go-go*-related gene [33]. Oral methadone can cause a QTc prolongation in approximately one-third of patients [34,35]; however, QTc >500 msec is not seen frequently in these patients. In one study, a QTc >500 ms was observed in 16% of chronic methadone maintenance patients who were subsequently hospitalized, although drug interactions were a predisposing factor [36]. Furthermore, there are inconsistent data regarding the correlation of methadone dose and QTc; two studies have shown that methadone dose and serum levels do not correlate with QTc [37,38] and in another study, methadone dose was associated with longer QT interval of 0.140 ms/mg (p=0.002) [35]. Methadone doses >120 mg/day have been associated with a QTc prolongation >450 ms [39] and a mean methadone dose of 400 mg/day (standard deviation 283 mg) was found in 17 patients with torsade de pointes (TdP) [40]. Finally, in an evaluation of reports of methadone-related adverse events submitted to the Food and Drug Administration, approximately 1% of >5000 reports demonstrated QT prolongation or torsades de pointes. The median dose was 345 mg (range of 29–1680 mg) [41]. Intravenous methadone is associated with a greater risk for prolonged QTc and TdP, likely due to the preservative chlorambutanol, which is also associated with QT prolongation [40]. Drugs that prolong the QT interval, such as metoclopramide and olanzapine, should be used with caution in patients receiving significant doses of methadone.

A new opioid to the US market that is now available as both extended-release and immediate-release formulations is oxymorphone. Extended-release oxymorphone has been found to provide safe and effective pain relief for those with cancer pain [42,43]. It is administered twice daily and is approximately twice as potent as oxycodone [44]. Levorphanol, which is chemically similar to dextromethorphan (an NMDA antagonist and a cough suppressant), is a potent opioid that can be considered for patients with severe cancer pain. It was originally synthesized as an alternative to morphine >40 years ago. It has a greater potency than morphine, being approximately five times as potent in its parenteral formulation. Analgesia is achieved through its agonistic activity at μ, δ, and κ opioid receptors, and its antagonism of NMDA receptors. Levorphanol can be given orally, intravenously, and subcutaneously [45]. Buprenorphine has long been used to treat patients with addiction as an alternative to methadone. A new buprenophine patch is available in Europe and has been found to be effective in patients with cancer and non-cancer pain [46,47]. In addition, buprenorphine can be used parenterally to treat moderate-to-severe pain, although its opioid antagonist property may limit its usefulness in patients with high opioid tolerance.

Routes of administration

Oral route

Numerous oral formulations are available and the long-acting, modified-release drugs are usually preferred in an effort to improve therapeutic adherence and convenience. The modified-release drugs include oral morphine (with dosing intervals of 12 or 24 h), oxycodone (with a 12-h dosing interval), and oxymorphone (that has a 12-h dosing interval). The typical time of onset of short-acting opioids via the oral route is 30 min to 1 h with a typical duration of action of approximately 3–4 h. When tablets and capsules are not feasible, many liquid forms are available in various concentrations.

Rectal route

Rectally administered opioids (e.g. morphine and hydromorphone) replace subcutaneous or intramuscular injections in patients who are unable to tolerate oral medications. They have approximately the same potency and half-life as orally administered agents [48–51]. In single-dose bioavailability studies of sustained-release morphine preparations, despite delayed absorption from the rectal route, total morphine absorption over 24 h was equivalent to the oral route, whether the drug was given orally or rectally [48–51].

Transdermal route

The transdermal fentanyl patch delivers lipophilic fentanyl into the fat-containing subcutaneous tissue below the skin. The drug diffuses continuously from the reservoir in the patch through a rate-controlling membrane, and is absorbed

from the skin depot into the bloodstream where it is rapidly metabolized [52]. The onset of pain relief occurs at approximately 12 h; constant plasma concentration is not reached until around 14–20 h after the initial patch is placed [52]. Liberal rescue medication should be provided during the first 24 h of using the patch [53]. If a patient develops signs of fentanyl overdose, naloxone must be given until the skin reservoir has become depleted [54]. It has been demonstrated that approximately 50% of the drug is still present 24 h after patch removal [55]. Converting patients from oral or parenteral medication to the patch is easily accomplished [56]. A new patch is applied every 72 h, although up to 25% of patients require a new patch every 48 h. The transdermal route is an effective method of delivering pain medication for patients with stable, moderate-to-severe pain, poor gastrointestinal absorption, or an inability to swallow pills. Side effects include those due to the contact adhesive, along with those commonly associated with other opioids, but may be better tolerated than those caused by morphine [55–57]. The transdermal system should not be used in septic patients, those experiencing acute pain, those with markedly fluctuating opioid requirements, cachectic patients, or individuals with significant dermatological insults (i.e. skin graft versus-host-disease or diffuse varicella). When the patient's temperature rises to 40°C, drug absorption from the skin can increase by as much as 35% [52]. If hepatic function is impaired, or sepsis or shock develop and blood flow to the liver decreases, plasma concentrations may rise sharply [55]. Patients with cachexia lack the subcutaneous tissue necessary for formation of a drug reservoir. Lower doses may be more appropriate in elderly patients [58], or in those with respiratory insufficiency.

Transmucosal route

Oral transmucosal fentanyl citrate induces rapid analgesia with a short duration of effect and is an effective treatment in the management of breakthrough pain [59,60]. A new commercially available fentanyl buccal tablet employs an effervescent delivery technology to enhance the rate and extent of absorption through the buccal mucosa. The fentanyl buccal tablet was found to be both efficacious and safe for the treatment of cancer-related breakthrough pain [61].

Subcutaneous and intravenous routes

Continuous subcutaneous or intravenous administration of opioids can provide pain relief in the shortest amount of time. Drugs can be delivered by a portable infusion pump and initiated or continued in the home [62–64]. Guidelines for their use are available [65,66]. Patient-controlled analgesia (PCA) systems for subcutaneous or intravenous drug delivery have the advantage of responding to the individual's threshold for pain while eliminating delays when nurses must administer supplemental medication [67].

Spinal route

This route of administration is discussed in the intraspinal therapies section.

Dosing

Patients will require dose titration to achieve optimal opioid therapy. As the dose is titrated, patients should experience a favorable balance between analgesia and side effects. The absolute dose of the opioid is not important; it is the balance between analgesic effect and side effects that should be considered. Conventionally, the size of the increment at each dose escalation is between 30% and 100% of the total daily dose on the previous day. The lower end of this range is used if the pain is not severe or the patient is medically frail; the upper part of the range is appropriate for severe pain in the patient who is more robust. An around-the-clock dosing schedule is preferred when the pain is persistent or frequently recurring. Given the high prevalence of breakthrough cancer pain, a short-acting drug along with a long-acting baseline regimen should be used. An oral "rescue dose" can be prescribed every 2–4 h as needed at a dose that is equal to 5–15% of total daily opioid consumption [68]. Opioid rotation is often used when a patient has a poor response to a particular opioid. When patients are switched from one opioid to another, the dose of the new drug is calculated based on standard equianalgesic doses (Table 4) [69]. The calculated dose of the new drug is reduced to account for incomplete cross-tolerance and individual variation. However, some exceptions should be noted. A reduction in dose by 25–50% to account for incomplete cross-tolerance is typical practice for most opioids. The factor of safety has already been incorporated into the conversion to transdermal fentanyl, and the dose of this formulation is usually not reduced. When converting to methadone, the dose should be reduced by 75–90% due to the possibility of a greater than expected potency from this drug [69].

Management of side effects

The most common opioid side effects during long-term therapy are constipation, sedation, and fatigue. The management of side effects is a fundamental component of opioid therapy (Table 5) [70]. Poor tolerability may lead to poor adherence to treatment; thus, patients who experience poor responsiveness during the titration of an opioid may become more responsive when the treatment-limiting toxicity is addressed.

Table 4. Opioid analgesics used for the treatment of persistent cancer pain. Patients are placed in one of five classes according the number of points received: class I (age <50 years, no comorbidities), class II (<71 points), class III (71–90 points), class IV (91–130 points), and class V (>130 points). Admission to the intensive care unit is recommended for patients in class V.

	Dose (mg) equianalgesic to 10 mg intramuscular morphine*		Half-life	Duration	Comment
Drug	Orally	Intramuscular	(hrs)	(hrs)	
Morphine	20–30**	10	2–3	2–4	Standard for comparison
Morphine modified-release	20–30	10	2–3	8–12	Various formulations are not bioequivalent
Oxycodone	20	–	2–3	3–4	
Oxycodone modified-release	20	–	2-3	12	
Hydromorphone	7.5	1.5	2–3	2–4	Potency may be greater during prolonged use (i.e. hydromorphone:morphine ratio of 3:1 rather than 6.7:1)
Methadone	20	10	12–190	4–12	Although 1:1 intramuscular:intramuscular potency ratio with morphine was found in single dose study, there is a change with chronic dosing and large dose reduction (75–90%) is needed when switching to methadone
Oxymorphone	10	1	2–3	2–4	Available in rectal and injectable formulations
Levorphanol	4	2	12–15	4–6	
Fentanyl	–	–	7–12	–	Can be administered as a continuous intravenous or subcutaneous infusion; based on clinical experience, 100 μg/h is roughly equianalgesic to morphine intravenous 4 mg/h
Transdermal fentanyl	–	–	16–24	48–72	Based on clinical experience, 100 μg is roughly equianalgesic to intravenous morphine 4 mg/h. A ratio of oral morphine: transdermal fentanyl of 70:1 may also be used clinically
Oral transmucosal fentanyl citrate	–	–	7–12	1–2	Recommended starting dose for breakthrough pain, 200–400 μg, even with high "base-line" opioid doses

*Studies to determine equianalgesic doses of opioids have used morphine by the intramuscular route. The intramuscular and intravenous routes are considered to be equivalent and intravenous is the most common route used in clinical practice.
**Although the oral:intramuscular morphine was 6:1 in single dose study, other observations indicate a ratio of 2–3:1 with repeated administration.
Adapted with permission from [196].

Adjuvant analgesics

Adjuvant analgesics are a diverse class of medications, and they typically have indications for conditions other than pain. They have analgesic properties and are often used when an opioid regimen is unable to provide sufficient analgesia or when it is associated with dose-limiting side effects (Table 6).

Neuropathic pain

Adjuvant agents are often needed to treat patients with neuropathic pain. Several classes of medications may be considered for the treatment of neuropathic pain. Anticonvulsants, antidepressants, α-2-adrenergic agonists, corticosteroids, topical agents, γ-aminobutyric acid (GABA) receptor agonists, and NMDA receptor antagonists have

Table 5. Commonly used approaches in the management of opioid side effects.

Side effect	Treatment
Constipation	**General approach** • Increase fluid intake and dietary fiber • Encourage mobility and ambulation if appropriate • Ensure comfort and convenience for defecation • Rule out and treat impaction if present **Pharmacological approach** • Contact laxative plus stool softener (e.g. senna plus docusate) • Osmotic laxative (e.g. milk of magnesia) • Lavage agent (e.g. oral propylethylene glycol) • Prokinetic agent (e.g. metoclopramide) • Oral naloxone or methylnaltrexone
Nausea	**General approach** • Hydrate as appropriate • Progressive alimentation • Good mouth care • Correct contributory factors • Adjust medication **Pharmacological approach** • Vertigo treated with an antihistamine (e.g. meclizine or scopolamine) • Early satiety treated with a prokinetic (e.g. metoclopramide) • Dopamine antagonists (e.g. chlorpromazine, haloperidol, metoclopramide, and prochlorperazine)
Somnolence or cognitive impairment	**General approach** • Reassurance • Education • Treatment of potential etiologies **Pharmacological approach** • If analgesia is satisfactory, reduce opioid dose by 25–50% • If analgesia is satisfactory and the toxicity is somnolence, consider a trial of psychostimulant (e.g. methylphenidate)

Adapted with permission from [194].

Table 6. Adjuvant analgesics for neuropathic and bone pain.

Indication	Class	Examples
Neuropathic pain	Steroids	Dexamethasone Prednisone
	Antidepressants Tricyclics	Amitryptiline Desipramine Nortriptyline
	SSRIs/SNRIs	Duloxetine Venlafaxine Citalopram Paroxetine
	Anticonvulsants	Pregabalin Gabapentin Lamotrigine Carbamazepine Clonazepam Valproate
	Sodium channel blockers α-2-adrenergic agonists	Mexilitine Tocainide Tizanidine Clonidine
	NMDA receptor antagonists	Ketamine Dextromethorphan Amantadine Memantine
	GABA agonists	Baclofen
	Topical agents	5% Lidocaine patch Local anesthetic creams Capsaicin
Bone pain	Bisphosphonates	Pamidronate Ibandronate Zolendronate
	Other osteoclast inhibitor	Calcitonin
	Radiopharmaceuticals	^{89}Strontium ^{153}Samarium

GABA: γ-aminobutyric acid; NMDA: *N*-methyl-D-aspartic acid; SSRI: selective-serotonin reuptake inhibitors; SNRI: serotonin–norepinephrine reuptake inhibitors.

demonstrated some efficacy in the pharmacological management of neuropathic pain [72–74]; however, the antidepressants and anticonvulsants are typically preferred for treating neuropathic pain that is secondary to cancer [75].

The anticonvulsant gabapentin has the fewest side effects of all anticonvulsants and is very effective in patients with neuropathic pain from a tumor, peripheral neuropathy from a tumor or treatment, and post-herpetic neuralgia [72–75]. It does not actually mediate its effects via GABA receptors, but rather binds to the α-2-δ subunit of the *N*-type calcium channels in neurons within the dorsal horn, thus inhibiting calcium influx and diminishing neuronal hyperactivity [76]. To minimize sedation, doses should be initially low (e.g. 100 mg three times daily or 300 mg at

bedtime) then then increased as tolerated every 3–5 days until analgesia is achieved. The effective dose varies between 900 mg/day and 3600 mg/day in divided doses. The pharmacokinetics of gabapentin are unique in that it has a ceiling effect related to a saturable transport mechanism in the gut, this means that the effects of this drug may plateau during dose escalation [75]. The most common dose-limiting side effect is sedation. Gabapentin needs to be renally dosed in patients with a lower than average creatinine clearance. Peripheral edema related to gabapentin may require therapy with diuretics. Pregabalin has the same mechanism of action and binding site as gabapentin and has been found to be effective in patients with neuropathic pain [77,78]. Pregabalin can be started at 50 mg twice or three times daily, with the usual effective dose between 150 and 300 mg twice daily. Pregabalin is efficiently absorbed through the gastrointestinal tract and absorption is proportional to the dose throughout the effective dose range [78], making titration simpler. In addition to the gabapentinoids – gabapentin and pregabalin – there is some evidence for the use of other anticonvulsants such as carbamazepine, lamitrogine, phenytoin, tiagabine, and topiramate in treating non-malignant neuropathic pain syndromes [74,75]. These anticonvulsants should also be considered in the management of neuropathic pain syndromes secondary to cancer.

The tricyclic antidepressants, including amitriptyline, desipramine, imipramine, and nortriptyline, are effective agents for neuropathic pain independent of their antidepressant effects [79]. When used as adjuvant analgesics, the tricyclic antidepressants are effective at lower doses and typically have faster analgesic effects than when they are used in the treatment of depression [79]; however, due to their anticholinergic side effects, they should be used with caution in the elderly or in patients who have cardiac conduction abnormalities, orthostatic hypotension, or bladder outlet obstruction. Since nortriptyline has been shown to be as effective and better tolerated than amitriptyline in post-herpetic neuralgia [80], and desipramine seems to be comparable with amitriptyline in diabetic neuropathy [81], the use of secondary amines (desipramine and nortirptyline) should be preferred in patients who are unlikely to tolerate the side effects of the tertiary amines (e.g. amitriptyline). Common side effects are tiredness, dry mouth, and constipation; less common side effects are urinary retention, confusion, and orthostatic hypotension. Selective serotonin- and norepinephrine-reuptake inhibitors, for example, duloxetine and venlafaxine, have been shown to be analgesic for a number of neuropathic pain syndromes [81–84]. Twice daily 150 mg bupropion (a dopaminergic agonist) has been found to be effective in patients with painful diabetic neuropathy [85]. There is less evidence supporting the use of SSRIs for neuropathic pain.

Corticosteroids given epidurally, intravenously, or orally are useful as antineoplastics, for example, in leukemia, lymphoma, and myeloma, and can provide nonspecific relief for patients with spinal cord compression and plexus infiltrations. Doses of dexamethasone 16–100 mg/day are needed to reduce vasogenic edema in spinal cord compression [86], but lower doses (6–20 mg/day) may be helpful in patients with plexus involvement [87]. Patients must be monitored for the development of oral or esophageal candidiasis and steroid-induced delirium.

Topical agents such as lidocaine patches, local anesthetic creams, capsaicin, and other topical creams, including doxepin and diclofenac, can be used over areas of hyperesthesia related to neuropathic pain.

Bone pain

Adjuvants for bone pain include NSAIDs, corticosteroids, bisphosphonates [88,89], and the radiopharmaceuticals, strontium chloride (^{89}Sr) [90] and ^{153}Sm-lexidronan [91]. Multiple studies have demonstrated the efficacy of bisphosphonates in reducing skeletal complications and pain from bone metastases [92–95]. Pamidronate and zolendronate are recommended in patients with multiple myeloma and other malignancies with painful bone lesions [96,97]. It should be noted that the long-term use of bisphosphonates is associated with a small, but meaningful, risk of osteonecrosis of the jaw [98]. The limitations of radiopharmaceuticals include their cost and the potential for development of cytopenias [24]. Calcitonin was once thought to be a potential therapeutic in bone pain; however, given the limited evidence available, a recent Cochrane review did not support the use of calcitonin for control of pain from bone metastases [99].

Breakthrough pain

Breakthrough pain, as a result of its variable presentations and etiologies, as well as its poor responsiveness to routine pharmacological interventions, presents a unique challenge in the management of cancer pain. Its prevalence in cancer patients ranges from 19% to 95% [100] and it is associated with significant functional impairment, psychological distress, and a poor prognosis [101–103]. Breakthrough pain has been defined as "a transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain" [104]. It is usually classified as incident pain (volitional, non-volitional, or procedural), idiopathic (or spontaneous), and end-dose failure.

The management of breakthrough pain requires a careful assessment, the treatment of any underlying etiology (e.g. vertebroplasty for incident pain related to vertebral compression fracture), and symptomatic treatment with pharmacotherapy. Treatment of end-dose failure typically involves decreasing the dosing interval of long-acting opioids (e.g. from 12 h to 8 h) or increasing the standing dose. Breakthrough pain that is lancinating, shocking, or burning is likely to be neuropathic and so may respond to adjuvant medications (e.g. those described above) in conjunction with short-acting opioids for severe paroxysmal episodes. Immediate-release formulations of morphine, hydromorphone, and oxycodone are reasonable for treating "predictable" pain episodes such as those caused by dressing changes or physical therapy. Given the delayed onset of action, these medications should be given at least 15–30 min prior to the episode to ensure adequate blood levels of the drug at the time when the pain is expected to begin. Some investigators recommend using between 5% and 15% of the dose of the background opioid analgesic as a starting dose for breakthrough pain [105]; however, an Expert Working Group of the European Association for Palliative Care claims that "the optimal dose for breakthrough pain can only be determined by titration" [106]. Indeed, in one clinical trial no relationship was found between the dose of opioid used for breakthrough pain and the dose of opioid needed to control the background pain [107].

Few controlled studies have been published on the pharmacological management of breakthrough cancer pain. Oral transmucosal fentanyl citrate (OTFC) has been shown to be effective for treating breakthrough cancer pain [60,108–110]. The fentanyl buccal tablet has also shown good results in controlling breakthrough cancer pain in a randomized, double-blind study [61], and a more rapid and efficient delivery of fentanyl when compared with OTFC [111]. Oral and sublingual methadone has been shown to be effective for breakthrough pain [112,113]. Intranasal ketamine has also been described for breakthrough pain with promising results [114].

Optimizing pharmacotherapy

Optimizing pharmacotherapy for cancer pain requires careful ongoing clinical assessment. The clinician should determine responsiveness to opioid therapy; something that should be accomplished with a careful patient history and physical exam. Intolerable side effects or poor analgesic efficacy suggest poor response to opioid therapy. Opioid rotation should be considered early on in the treatment if patients are determined to have dose-limiting side effects or signs of neurotoxicity. The use of adjuvants and co-analgesic agents should be considered, especially for bone and neuropathic pain. Steroids can be useful in patients with pain secondary to hepatic capsular stretch, and in cases of hollow viscera obstruction or lymphadenopathy. Treatment of opioid-related side effects is critical to ensure patient compliance with therapy and reduce unnecessary iatrogenic suffering. Also, non-pharmacological modalities should be offered in conjunction with pharmacotherapy when necessary.

Non-pharmacological therapy of cancer pain

Cognitive–behavioral interventions

Education and reassurance

Patients with cancer are often required to undergo extensive diagnostic testing, which can include painful procedures. A rehearsal of the planned test or procedure, including a description of the appearance of the room and the length of time that would be spent undergoing the procedure, can minimize the patient's anxiety. Such explanations, offered prior to the testing, lessen the need for post-procedure medication and shorten the patient's hospital stay [115]. If conscious sedation is not planned, a pleasant distraction may be helpful to divert attention from certain procedures – such as bone marrow aspiration or biopsy – that take place in the physician's office or in the patient's room [116]. Patients with a good imagination can pretend to be in a place they have previously enjoyed (e.g. at the beach or in the mountains); they can dissociate themselves [117] from the procedure by concentrating on those pleasant memories, thereby diminishing the pain associated with the procedure.

Hypnosis

Practitioners with formal training in hypnosis can use elaborate hypnotic techniques to help their patients deal with painful procedures or conditions [116,117]. Hypnosis takes advantage of people's natural ability to enter a trance-like state. Patients who are trained to enter a trance can modify their perception of pain and diminish sleeplessness, anxiety, and the anticipation of discomfort [118]. Hypnotic training in patients with sickle cell anemia has been demonstrated to decrease the frequency and pain intensity of painful events [119].

Cognitive–behavioral techniques and counseling

The cognitive–behavioral approach addresses a number of psychosocial and behavioral factors that contribute to the patient's experience of pain [120]. Such techniques have demonstrated clinical utility in patients with a wide range of chronic pain syndromes [120]. Psychological counseling, as part of a multidisciplinary approach to pain treatment, provides education, support, and skill development for patients with pain. It can improve patients' abilities to communicate their pain to healthcare personnel and may be effective in overcoming anxiety and depression. Spiritual

counseling may help patients who have lost hope, can find no meaning in their lives, or feel they are being punished or have been forsaken by God [121]. They may experience pain in light of these feelings. Through counseling, they can regain a sense of worth and belonging, which may mitigate their painful experience.

Cutaneous techniques

Acupuncture, massage, vibration, and applying either a cold compress or heat to the skin over injured areas are often very effective techniques for decreasing pain. Cold wraps, ice packs, or cold massage using a cup filled with water that has frozen into a solid piece of ice, relieves the pain of muscles that are in spasm from nerve injury. Heat from heating pads, hot wraps, or paraffin treatments can soothe injured joints, but should not be used over areas of vascular insufficiency [122]. Transcutaneous electrical nerve stimulation devices are suggested for use in patients with dermatomal pain, such as post-herpetic neuralgia or radiculopathy caused by spinal cord compression [123]. For optimal effect, a physiatrist or physical therapist familiar with the device should train the patient in its use.

Topical anesthetic creams, for example, the eutectic mixture of lidocaine and prilocaine (EMLA; 2.5% lidocaine and 2.5% prilocaine) may be used, particularly in children, to decrease the pain of superficial cutaneous procedures such as venous cannulation, bone marrow aspiration, or biopsy [124–126]. In adults, it can be used before accessing implanted vascular access devices or central nervous system ports. To achieve anesthesia, the EMLA cream must be applied 1–1.5 h before the planned procedure in a mound under a semipermeable dressing such as Opsite™ (Smith & Nephew, Hull, UK) or Tegaderm™ (3M, Minnesota, USA) [127,128]. ELA-Max™ (Ferndale Laboratories, Michigan, USA), a cream containing 4% lidocaine, is available over the counter and is an alternative to EMLA cream. As it does not contain prilocaine, there is no risk of methemoglobinemia.

Lidocaine patches can be used over areas of hyperesthesia, a side effect that can occur in patients with post-herpetic neuralgia or nerve entrapment caused by vertebral body collapse [129]. The patch is applied to the affected area for no more than 12 consecutive hours per day and can be cut to size. Its use should be avoided over areas of broken skin and in patients undergoing radiation therapy. Extended application of lidocaine patches has been safely applied for up to 24 h/day for up to 4 days with minimal systemic absorption in healthy volunteers and post-herpetic neuralgia patients [130].

Radiation therapy

Radiation therapy is commonly used in the management of painful bone lesions, spinal cord compression, bulky lymphadenopathy, and symptomatic splenomegaly in patients with hematological malignancies [131]. Radiotherapy is the treatment of choice for local metastatic bone pain in most circumstances, although patients with underlying pathological fractures may require surgical fixation prior to radiotherapy. It may take up to 4 weeks for 50% of the patients to demonstrate pain relief from the radiation [132]. Randomized trials have shown that single fraction radiotherapy is as effective as multifraction radiotherapy in relieving pain due to metastases [133]; however, there are higher rates of re-treatment, and single fraction radiotherapy may not prevent pathological fractures or spinal cord compression [133]. In patients with poor performance status or a short life expectancy, a single dose (8 Gy) of radiation or a hypofractionated course (20 Gy taken over five fractions) may be preferable and less burdensome.

Surgery

Surgical intervention is often required in patients with impending or actual pathological fractures or an unstable spine [134,135]. Surgery may additionally be helpful in rectal pain related to recurrent rectal cancer [110,136], painful skin metastases [137], abdominal pain, pain secondary to bulky tumor, organomegaly, or hernia [138]. The functional status and quality of life of the patient are important factors when considering the appropriateness and timeliness of surgical intervention.

Vertebroplasty and kyphoplasty

Vertebroplasty and kyphoplasty are relatively new surgical techniques that are used to stabilize vertebral compression fractures and reduce pain. Vertebroplasty is a procedure in which bone cement, usually polymethylmethacrylate, is injected into the vertebral body. During kyphoplasty, a balloon is first inserted into the vertebral body, which is then inflated and deflated, before cement is added. Balloon kyphoplasty has been shown to stabilize pathological vertebral fractures caused by multiple myeloma and significantly reduce pain [139,140].

Interventional approaches

Intraspinal therapies

Epidural and intrathecal drug delivery systems (IDDS) have an established role in the management of severe pain when systemic opioids fail to provide adequate pain relief or are associated with unacceptable side effects [141–147]. Spinal administration allows opioids to block pain transmission by binding to receptors in the dorsal horn of the spinal cord [148]. As the drug is infused in close proximity to the receptors, a smaller amount of medication is needed, thus reducing systemic side effects. The choice of the catheter

placement (epidural or intrathecal) and the type of delivery system (implantable pump, tunneled catheter, or percutaneous catheter) needs to be tailored to the specific patient. The advantage of epidural delivery is that it allows analgesia to be limited to a few dermatomes. Intrathecal administration allows for one tenth of the dose of epidural medication, but there is a decrease in the time of onset of analgesia and a prolongation of effect following bolus dosing compared with epidural morphine administration [149]. Percutaneous epidural catheters are the simplest means of providing spinal analgesia and may be used for days to weeks; however, there is a greater risk of infection and the possibility of dislodgement compared with tunneled epidural catheters, such as epidural Port-A-Cath® (Smiths Medical, Minnesota, USA); DuPen catheters (Bard, Utah, USA), which can be used for a longer period of time [150]. Implantable pump systems are used in patients with a life expectancy of ≥3 months, whereas external pumps should be used in patients with a shorter life expectancy [151]. Both fixed-rate and programmable pumps are available. Contraindications for intraspinal drug delivery include unstable vital signs, anticoagulant therapy, and ongoing infection. Other factors that affect surgical risk include hematological abnormalities, wound infections, malnutrition, and the presence of tumors in the spinal canal [152].

Spinal opioids can be delivered by intermittent bolus injection, PCA, or continuous infusion. Morphine is the most commonly administered agent, although hydromorphone, fentanyl, and sufentanil, can be successfully used. The addition of a local anesthetic, such as bupivicaine, an α-adrenergic agent (e.g. clonidine), or other agents, to the spinal infusion may be initiated when spinal opioids do not provide adequate analgesia or in patients with refractory neuropathic pain syndromes [152–155]. In a recent controlled trial, a continuous intrathecal infusion of morphine via an implanted drug delivery system yielded better pain control, less fatigue, and improved survival compared with comprehensive medical management alone [156]. In 2005, a multidisciplinary expert panel published clinical guidelines for the use of intrathecal drug delivery in the management of cancer pain (Fig. 1) [152]. Oncologists and palliative care clinicians with a basic understanding of the technology, medication dosages, and titration regimens used for delivering drugs in the intrathecal space can incorporate IDDS into their clinical practice when treating cancer-related pain syndromes [152].

While intraspinal catheters may allow for a reduction in the total opioid dose and thus have fewer side effects than systemic opioids, they have important limitations and complications associated with its use. One concern with intrathecal delivery systems is the potential for cephalad spread of morphine in the cerebrospinal fluid (CSF), which can result in respiratory depression seen 12–18 h after injection. Another early complication is the development of an intraspinal hematoma following the procedure [157]. Infections of the spinal catheter systems that can cause meningitis and epidural abscess, which are thought to be relatively uncommon with proper maintenance, are a serious concern with long-term spinal analgesia [157]. Other delayed complications include CSF hygroma, pump pocket seroma, epidural fibrosis of the catheter site, migration of the catheter, and catheter tip granuloma, especially with high concentrations and high daily doses of opioids [150,157]. Implantable pumps are more convenient to manage and are less likely to become infected. Although opioid side effects are less common with spinal delivery, patients may still complain of pruritus, urinary retention, somnolence, and may develop myoclonus. The main limitations for using spinal delivery are the small volume of medication reservoir within the implantable pumps, which require custom-made solutions from pharmacists, adequate nursing assistance, and regular physician evaluations. Hospices and home care staff may not have the experience or proper training to manage such devices in terminally ill, homebound patients. Further education and standardized nursing regulations are needed to ensure that this population has access to intraspinal delivery systems when indicated.

Anesthetic techniques

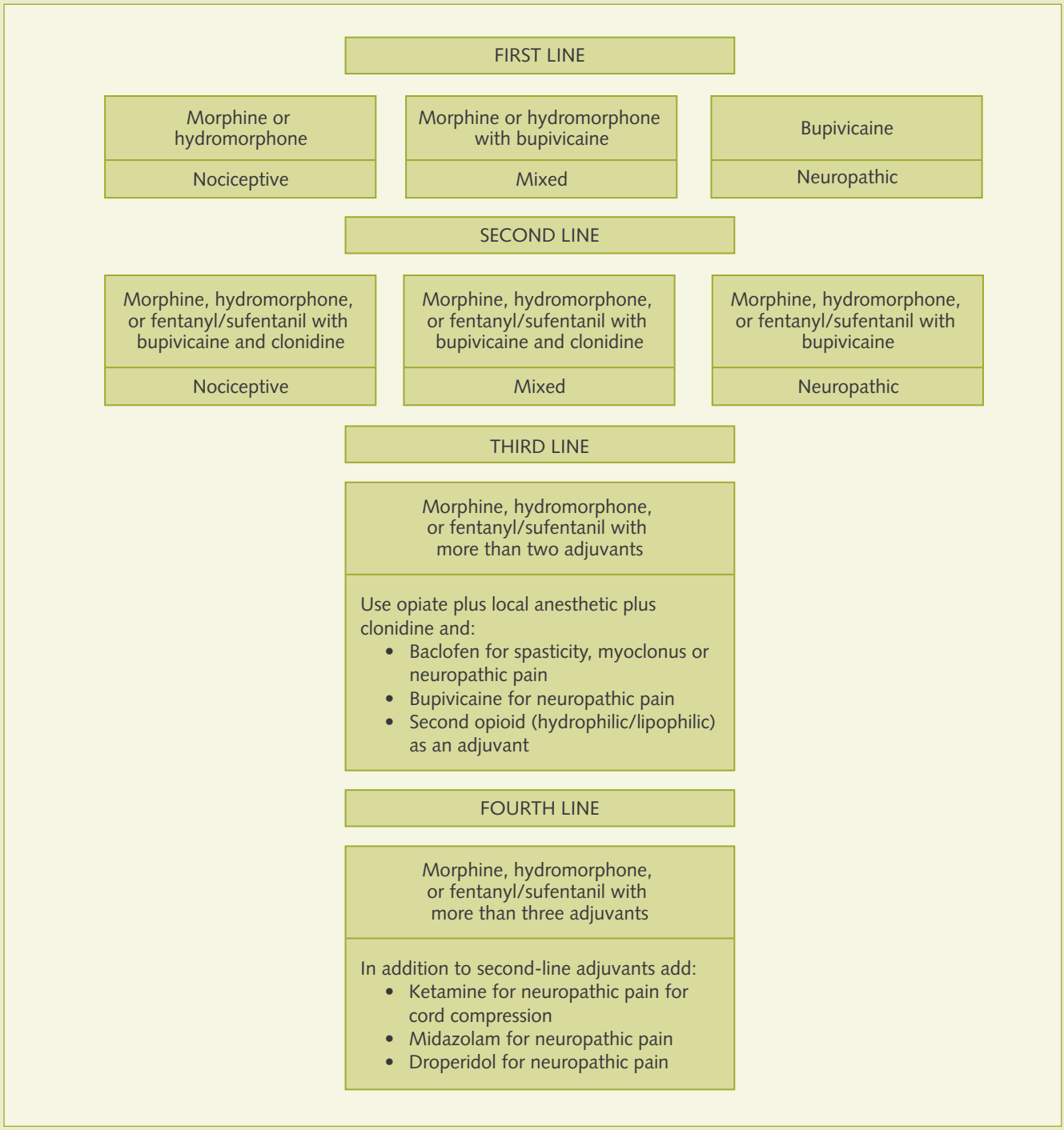
Somatic nerve blockade

Local anesthetic blockade of peripheral nerves is useful for the treatment of somatic and neuropathic pain that is localized to a single nerve, plexus, or dermatome distribution. Although the pain relief is rapid and can be quite dramatic, the local anesthetic effect may last for only a day; therefore, a catheter may be inserted for continuous local delivery to a nerve or plexus in order to sustain pain relief for longer periods. Examples of continuous block techniques for terminally ill patients include brachial plexus block for extremity pain [158,159], suprascapular nerve block for shoulder pain [160], and sciatic and femoral nerve block for lower-extremity pain [158].

Neurolytic blockade of peripheral nerves

Neurolytic blockade of peripheral nerves can be performed following successful local anesthetic blockade to extend pain relief for weeks or even months [161,162]; however, up to 30% of patients may develop neuritis of deafferentation neuralgia in the weeks following neurolytic block administration [150]. Unfortunately, this post-neurolysis neuropathic pain syndrome may be even more severe than the initial somatic pain and so neurolytic blockades of

Figure 1. Algorithm for intrathecal drug delivery in cancer pain.



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peripheral nerves should be reserved for those with severe pain and a limited life expectancy (usually <6 months). Phenol and ethanol are most commonly used for chemical neurolysis. Radiofrequency and cryonalgesia may also be considered and are thought to have a lower associated incidence of neuritis and deaffenteration pain [163–165]. Examples of neurolytic blocks that may be considered for cancer patients are neurolytic intercostal nerve blocks and neurolytic paravertebral blocks for the management of intractable chest wall pain caused by chest wall invasion [166]. Unfortunately, only a few case series have been published describing analgesic efficacy of this method [167].

Given the lack of evidence and the risk of complications, these techniques should be limited to intractable pain in cancer patients with a poor prognosis.

Neurolytic sympathetic blockade

In patients with advanced cancer, neurolytic sympathetic blocks may be used for the management of pain from upper abdominal viscera (celiac plexus block), pelvic viscera (superior hypogastric plexus block), and perineal viscera (ganglion impar block). In addition, pain from cancer treatment, e.g. phantom and post-thoracotomy pain, may also be amenable to sympathetic blockade [150,157].

Celiac plexus block

There is good evidence for the use of neurolytic celiac plexus block (NCPB) for the relief of upper abdominal or back pain from pancreatic or other abdominal malignancies, with up to 85–90% of patients achieving good to excellent pain relief during the first 2 weeks after gaining NCPB and 70–90% of patients have long-lasting benefit, even until death [166–170]. The celiac plexus contains afferent splanchnic nerve fibers (innervating the upper abdominal viscera) as well as preganglionic sympathetic fibers from T5 to T12 and postganglionic sympathetic fibers. Hypotension, back pain, and diarrhea are the expected side effects of this treatment [166,170]. Less common complications include unilateral paresis from somatic neurolysis, paraplegia from subarachnoid neurolysis or anterior cord infarction, pneumothorax, and retroperitoneal bleeding [166].

Superior hypogastric plexus block

Neurolytic superior hypogastric plexus block is a safe and effective treatment for pain relief in patients with pelvic visceral pain from gynecological, colorectal, or genitourinary cancer with poor pain control due to progression of disease or unacceptable side effects from systemic analgesics [171]. The superior hypogastric plexus contains afferent fibers from the pelvic viscera and sympathetic postganglionic fibers. Injury to sacral nerves, bladder or bowel perforation, intravascular injection, and urinary or fecal incontinence are potential complications. If there is significant somatic pain from sacral or muscle involvement, or neuropathic pain from nerve root compression or infiltration, then an analgesic response to this treatment would not be expected as only visceral pain responds to sympathetic blockade. Such patients should be considered for spinal analgesia [150].

Other sympathetic blocks

Neurolytic ganglion impar (or sacrococcygeal ganglion) block may be used for the relief of intractable rectal or perineal pain [150]. Stellate ganglion block may be used for cancer pain in the head and neck area [157] while thoracic and lumbar sympathetic ganglia blocks may be useful for phantom pain sensations, postmastectomy pain, and posthoracotomy pain [172,173].

Intrathecal and epidural neurolysis

Intrathecal (or subarachnoid) injection of ethanol or phenol should be restricted to patients with advanced cancer and pain limited to a few dermatomes when spinal analgesics are contraindicated or not available [150]. This procedure, essentially a chemical version of a dorsal rhizotomy, selectively interrupts dorsal root function and the pain pathways from the affected innervated area. Intrathecal neurolysis may be useful for treating perineal pain in patients with colostomy and a permanent bladder catheter or in relatively localized (somatic) chest-wall pain [169]. Analgesic effects are obtained in approximately 50% of patients and may last for up to 6–12 months [169]. Complication rates are between 1% and 14% and include irreversible spinal cord damage resulting in bowel and bladder incontinence and motor paresis.

Epidural neurolysis may be considered for pain within cervical dermatomes as intrathecal neurolysis injections would be rapidly diluted given the high-flow CSF circulation that could cause subsequent spread to adjacent neural structures. It can additionally be used at lower thoracic and lumbar levels [169]. Essentially, both neurolytic procedures are infrequently used given the advances in spinal analgesic therapies.

Interpleural analgesia

Interpleural analgesia (IPA), which involves administration of local anesthetics into the pleural space, can be used to treat pain caused by metastatic disease to the neck, arms, chest, brachial plexus, thorax, or abdomen, and acute pancreatitis, herpes zoster, and post-herpetic neuralgia. The local anesthetic is thought to diffuse through the pleura to block the intercostal nerves, thoracic sympathetic chain, splanchnic nerves, and brachial plexus. The most common complications seen with this technique are pneumothorax (approximately 2% of patients) and systemic toxicity (1.3% of patients). IPA may be used for a period of weeks to months with a simple percutaneous catheter or with a subcutaneously implanted injection portal [150].

Trigger point injections (myofascial injections)

Myofascial pain syndromes are common and may be the primary source of pain or occur secondary to another pathology such as a vertebral compression fracture. If a hypersensitive spot in skeletal muscle, or "trigger point", is located following a physical examination, the patient may benefit from an injection of local anesthetic into this point.

Aseptic injection of 1–3 mL of dilute local anesthetic into this point in the muscle may offer pain relief for days to weeks [157].

Neuroma and intralesional injection

Painful neuromas may also be treated with an injection of local anesthetic. A corticosteroid can be added to prolong the anesthetic effect [174,175]. In addition, painful surgical scars and post-herpetic neuralgia, associated with post-thoracotomy and postmastectomy syndromes, may be treated with local anesthetic and steroid injection.

Spinal cord stimulation

Spinal cord stimulation is rarely used in patients with advanced cancer; however, it may have some benefit in patients with neuropathic pain related to surgery such as phantom limb pain [176].

Neurosurgical procedures

With advances in anesthetic pain management techniques and a wide range of available pharmacological agents, few patients require surgical intervention to interrupt central or peripheral nociceptive pathways. However, some patients may have refractory pain despite aggressive pharmacological, non-pharmacological, and anesthetic interventions. In this subpopulation of cancer patients with pain, neurosurgical interventions may be appropriate.

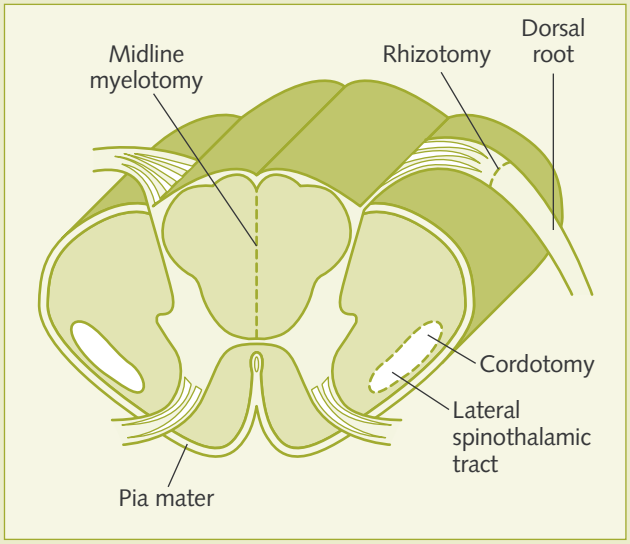
Cordotomy

The most commonly performed neurosurgical procedure for cancer pain relief is anterolateral cordotomy, which ablates the spinothalamic tract effectively, blocking pain signals from the contralateral body to the thalamus (Fig. 2). A percutaneous method has resulted in this becoming a minimally invasive procedure. It is most useful for the treatment of unilateral somatic pain below the C5 dermatome. It is ineffective for deafferentation pain and has only limited use in visceral pain. Immediate pain relief is achieved in the majority of patients, but pain recurs in roughly half of these individuals at 6–12 months [177,178]. Many patients in whom pain recurs also develop paresthesias or dysesthesias.

Dorsal rhizotomy

Interruption of the dorsal roots blocks all pain sensations from innervated areas, which is useful for somatic pain that is limited to several dermatomes of the trunk or functionless limbs [157]. Motor function may be impaired if proprioception is blocked; however, using a highly selective rhizotomy technique, pain sensation may be selectively interrupted without a loss of normal sensation or proprioception (Fig. 2). Rhizotomy results in pain relief in 50–80% of patients with chest wall pain from tumor invasion [157], but it is not effective for neuropathic pain.

Figure 2. Anatomic areas and neurosurgical procedures.



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Cranial rhizotomy

Cranial rhizotomy may be considered for somatic or neuropathic orofacial pain that is not responsive to pharmacological or anesthetic interventions [179,180]. It may result in pain relief, but neurological deficit and recurrent pain are common with the procedure.

Midline myelotomy

There is evidence for a dorsomedially located pathway for pain transmission in the human spinal cord that is separate from the spinothalamic tract and mediates both pelvic and more proximal visceral pain. Lesions to the dorsal column result in visceral pain relief that far exceeds that predicted from a midline interruption of decussating spinothalamic axons [181–185]. Thus, midline/commissural myelotomy (Fig. 2) is considered only for visceral lower body pain in patients with advanced cancer in whom other procedures are unsuccessful or cannot be performed. Although experience with this technique is limited, significant pain relief has been noted in 70% of patients with rare complications or side effects resulting from other techniques [186,187].

Hypophysectomy

Hypophysectomy is occasionally considered for patients with widespread cancer pain, especially above the clavicles, in whom antitumor treatments and other approaches have

failed. One theory postulates a hormonal mechanism involving changes in humoral substances in the CSF or hormonal changes via a direct neural mechanism [188]. Side effects include CSF leakage, diabetes insipidius, infection, coma, and cranial nerve palsies.

Thalamotomy

The thalamus is the termination site of the spinothalamic tract. It transmits information about pain and temperature from the body to the brain. A thalamotomy has been reported for, and shown to be effective in the treatment of, neuropathic cancer pain [189–191].

Neurostimulation

Deep brain stimulation has been used successfully in a small number of cancer pain patients who were refractory to intraspinal or systemic opioid treatment, but more conservative approaches are at least as effective for most patients [192].

Intraventricular opioid delivery

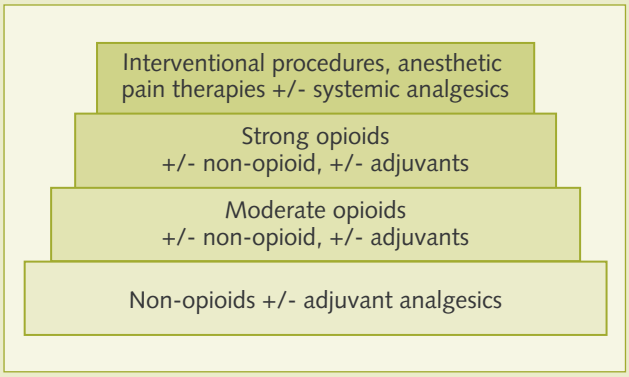
Placement of an Ommaya reservoir under the scalp, connected to a catheter whose tip lies within the lateral cerebral ventricle, may provide satisfactory analgesia with relatively few side effects [193]. This method could be considered in patients with pain from head and neck cancer, although no studies have demonstrated superiority of intraventricular delivery over systemic opioid delivery.

Role for interventional approaches in cancer pain

Patient selection

While there are no algorithms to suggest appropriate situations in which interventional approaches should be considered in the management of cancer pain, there is certainly evidence of its efficacy in select patient populations. One suggestion is to consider an extension of the WHO analgesic ladder to include a fourth level consisting of "interventional, anesthetic pain therapies with or without systemic analgesics" (Fig. 3) [150]. Obviously, patients with refractory pain who have undergone aggressive pharmacological and non-pharmacological modalities, including high-dose systemic opioid therapy and appropriate adjuvant analgesics, will likely need an interventional approach. Procedures such as neurolytic sympathetic blocks can be considered early on in specific visceral pain syndromes (e.g. NCPB for pancreatic cancer). Intraspinal analgesia should be offered in cases of refractory pain or when systemic opioids are causing intolerable side effects. Certain patients, particularly those with mostly somatic pain and poor prognosis, may be eligible for neurolytic blocks that act at peripheral nerves. If these measures fail to provide relief, neurosurgical procedures should be considered. The risks and benefits, prognosis, and goals of care should be considered together with the patient and their family when deciding on a treatment approach for the management of cancer pain. Moreover, hospice patients should not be denied aggressive or invasive procedures for palliation of pain and other symptoms at the end of life.

Figure 3. Four-step analgesic ladder for stratified use of analgesic therapies.



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Other considerations

Patients are typically managed in the in-patient hospital setting after an interventional procedure to ensure that there are no early-onset side effects or complications from the therapy. Rarely, interventional pain specialists are able to perform bedside procedures on non-ambulatory and bedbound hospice patients in the home. Before the patient is discharged from the hospital, the primary care team, home care nurse, or hospice team should be educated in the maintenance of pumps and equipment, as well as in the assessment of late-onset complications or treatment failure, for example, catheter migration in an epidurally placed intraspinal delivery system resulting in worsening pain. In most patients, systemic analgesic therapies will be continued; however, an opioid dose reduction may be necessary if the patient has a good analgesic response following the intervention. For example, one might consider reducing patients' long-acting opioid dose by 25–50% when there is a marked reduction in pain following a neurolytic sympathetic block. Breakthrough medications for pain and a "backup plan" should be in place to ensure a successful transition to the home setting and to provide comfort to caregivers at home – should the interventional approach not be sufficient. Careful assessment and monitoring of the symptoms of opioid toxicity and withdrawal should be made on an ongoing basis. Follow-up appointments with interventional pain specialists and/or neurosurgeons may be

necessary and should be anticipated prior to discharge from the hospital. Coordination with palliative care services or local hospice programs, when appropriate, will likely be helpful in assuring that patients' needs are being met and their ongoing follow-up is appropriate.

Conclusion

Treating pain in cancer patients is a fundamental component of comprehensive care. The majority of cancer patients can be managed with pharmacological and non-invasive modalities. The pharmacological management of cancer pain involves an understanding of opioid pharmacotherapy and dosing, the use of co-analgeiscs and adjuvant analgesics, and careful assessment and treatment of side effects. In patients with unrelieved pain or intolerable side effects from systemic analgesics, invasive procedures, including anesthetic and neurosurgical techniques, should be considered. Careful patient selection and collaboration are essential components to successful treatment.

Disclosure

The author has no relevant financial interests to disclose.

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