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Advances in Pain Management is designed to bring a critical analysis of the world pain medicine literature, to an international, multidisciplinary audience. Our mission is to promote a better understanding of pain medicine by providing an active forum for the discussion of clinical and healthcare issues.

Leading Articles – These major review articles are chosen to reflect topical clinical and healthcare issues in pain medicine. All contributions undergo a strict editorial review process.

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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. *Adv Pain Manage* 2008;**1**(4):122–40.

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 anti-inflammatory effects. Unlike aspirin, acetaminophen has

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

Adapted with permission from [194].

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, an 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 an 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

Post-surgical neuropathic pain syndromes

- Post-mastectomy syndrome
- Post-thoracotomy syndrome
- Post-radical neck dissection syndrome
- Post-nephrectomy syndrome
- Stump pain and phantom pain

Post-radiotherapy pain syndrome

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

Post-chemotherapy pain syndromes

- Polyneuropathies

Adapted with permission from [195].

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 ms 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 buprenorphine 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.

Drug	Dose (mg) equianalgesic to 10 mg intramuscular morphine*		Half-life (h)	Duration (h)	Comment
	Oral	Intramuscular			
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 "baseline" 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 $\alpha_2\delta$ 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) 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], as reviewed in *Adv Pain Manage* Vol. 1 Iss. 1. 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 has 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 from the procedure by concentrating on those pleasant memories [117], 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]. Additionally, surgery may 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

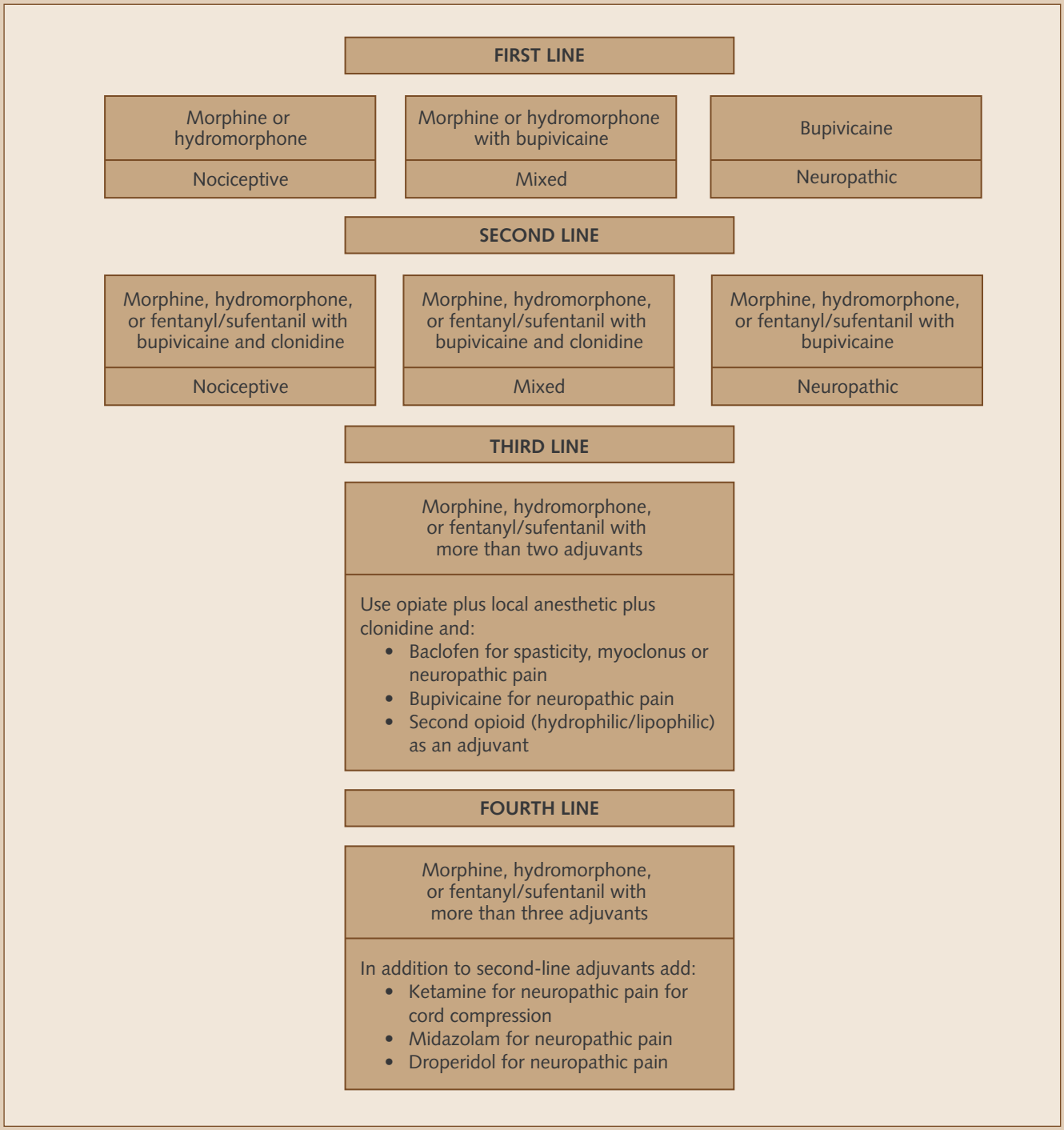
Somatic nerve blockade

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.



Adapted with permission from [197].

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 deafferentation 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 post-ganglionic 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 sub-arachnoid neurolysis or anterior cord infarction, pneumo-thorax, 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 post-ganglionic 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, post-mastectomy pain, and post-thoracotomy 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 post-mastectomy 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.

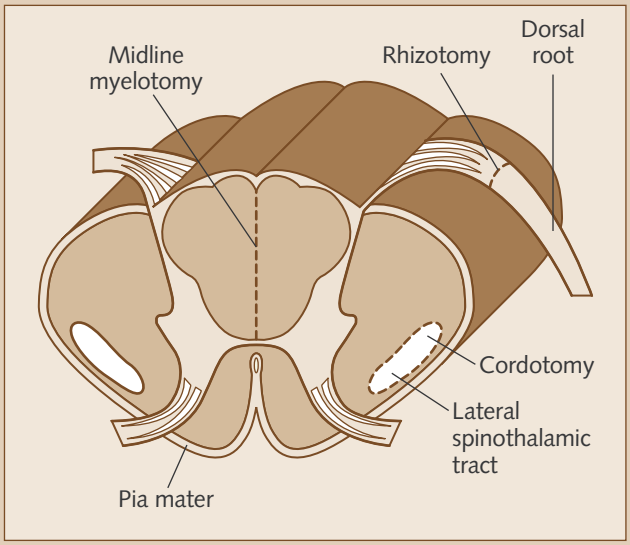
Cordotomy

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

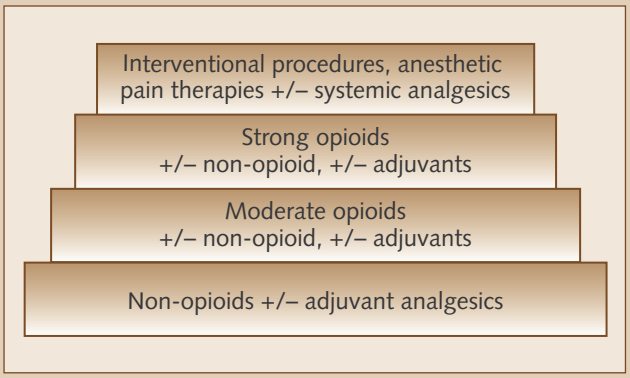
Placement of an Ommaya reservoir under the scalp, connected to a catheter whose tip lies within the lateral cerebral ventricle, may provide satisfactory analgesia with relatively few side effects [193]. This method could be considered in patients with pain from head and neck cancer, although no studies 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 "back-up 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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Evidence-Based Management of Chronic Low Back Pain

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LEADING ARTICLE

Low back pain (LBP) is one of the most prevalent and costly health problems in the industrial world. While the prognosis of acute LBP is generally quite good, recurrences are common. There is an extensive body of published evidence on the treatment of LBP; however, methodological challenges, heterogeneous populations, and often conflicted results make drawing evidence-based conclusions about the optimal management of chronic LBP very difficult. Nonsteroidal anti-inflammatory drugs, muscle relaxants – particularly the benzodiazepines – and tri/tetracyclic antidepressants appear to provide some pain relief in chronic LBP sufferers and represent a reasonable starting point for therapy; judicious and careful use of opioids may have a role in the appropriate setting. Massage, spinal manipulation, and perhaps acupuncture are potential options with reasonable expectations for pain reduction. Exercise and cognitive–behavioral therapy can improve pain and functional outcomes. Intensive, multi-disciplinary rehabilitation programs have the strongest support in the literature for improving both short- and long-term outcomes. Spinal fusion surgery may be an option in properly selected patients, but the outcomes are likely to be similar to intensive multidisciplinary rehabilitation. The specific characteristics of a patient's back pain, as well as their personal goals and values, need to be incorporated into the choice of treatment.
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Low back pain (LBP) is one of the most prevalent and costly health problems in the industrial world. Approximately 80% of Americans report having symptoms of LBP at some point in their lives [1,2]. The annual prevalence of back pain ranges for 15% to 45% with a point prevalence of approximately 30% [3]. LBP is second only to the common cold as patients' reason for primary care office visits and it is the most frequently occurring reason why individuals consult orthopedic surgeons, neurosurgeons, and occupational medicine physicians [4]. Approximately 2% of the US workforce receive compensation for back injuries each year [3] and back pain has been estimated to account for 40% of all lost work days [5]. Estimated costs for patients with LBP are >$90 billion/year [6].

The prognosis of acute LBP is generally quite good; recovery occurs in approximately 60% of cases after 6 weeks and in 80–90% at 12 weeks [3], but recovery after 12 weeks is much less certain. Of the individuals disabled for >6 months, fewer than half ever return to work, and after 2 years of disability, return to work is quite rare [3]. Among those who recover from an acute back pain episode the recurrence of significant LBP occurs in up to 35% of patients within 2 years [5]. A systematic review of the prognosis of acute LBP found that pain and disability decreased, on average, by 58% over 1 month, and an average of 82% were back to work at 1 month; however, at least one recurrence within 12 months occurred in an average of 73% of patients [7].

The impact of patients who do develop chronic pain and disability on healthcare and the economy of a country can be devastating. The small minority of patients with chronic pain and disability represent the majority of the costs for treating this disorder. In those patients diagnosed with industrial back pain, approximately 10% of workers with chronic pain and disability account for 70–80% of the total costs [8,9]. In a prospective study by Engel et al., 20% of patients with low back problems accounted for approximately 70% of the total costs [10].

The management of chronic LBP is challenging because the effectiveness of most existing treatments is either disappointing or controversial [11]. One potential reason for this challenge is the lack of a coherent and reliable classification system that allows for the selection of subgroups who might respond better (or worse) to specific treatments. By lumping together a heterogeneous group of all LBP patients, there is the potential

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to wash out real effects that might appear were well-selected subgroups evaluated [12]. The identification of well-defined subgroups within the population of LBP subjects has been identified as a key research priority [13]; however, while some recent studies have begun to make progress in defining subgroups of acute LBP [14], less progress has been made for specifying chronic LBP subgroups.

Some authors recommend a so-called "reductionist" approach and imply that a large proportion of patients with chronic LBP can be given an anatomically specific diagnosis, such as lumbar zygapophysial joint pain or sacroiliac joint (SIJ) pain [15]. Although the facet joint was identified as a potential pain generator in LBP >70 years ago, there remains significant controversy and uncertainty regarding the prevalence and clinical features of this entity [16]. The prevalence of the pain in response to placebo-controlled, anesthetic injections of the facet joints has been reported to be between 10% and 40%, although these figures have generally been observed in pre-selected referral populations [16,17]. Similarly, the SIJ, in the absence of trauma or inflammatory sacroiliitis, remains controversial as a purported cause of LBP [18]. Trials of controlled injections clearly demonstrate that some individuals do have a pain relief response to the SIJ injection; however, the prevalence of this condition remains uncertain. Some studies have been cited as showing that SIJ injection-responsive pain makes up approximately 20% of chronic LBP [15], but this is extremely misleading because the study looked at pre-selected cohorts of patients with pain patterns believed to represent SIJ problems. The identification of specific subgroups of chronic LBP patients who respond better to specific treatments remains an important priority for ongoing research. Currently, the true prevalence of these specific conditions among all individuals with chronic LBP – and so the overall benefits of a reductionist approach to chronic LBP – remains unclear.

The field of LBP has been described as an excellent example of evidence-based healthcare due to the extensive body of published evidence consisting of >500 randomized controlled trials and a large number of systematic reviews [19]. While this description is true, frequent methodological challenges, heterogeneous populations, and often conflicted results, combined with conflicting interpretations of results, make drawing evidence-based conclusions about the optimal management of LBP difficult.

This review focuses on the current evidence for the management of chronic non-specific LBP; it is not based on a formal meta-analysis or systematic review of the literature, but draws evidence from various published meta-analyses and systematic reviews. Non-specific LBP, as herein defined, excludes back pain caused by fractures, inflammatory spondylitis, infection, tumor, or other systemic disease in addition to radiculopathies related to intervertebral disc herniation and spinal stenosis. Chronicity is generally defined as symptoms persisting for ≥12 weeks.

Treatment options

Medication

Medication is often the first line of treatment for the management of chronic LBP (Table 1). Medications that are commonly prescribed include acetaminophen (paracetamol), nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, antidepressants, and opioids. In The Netherlands, approximately 20% of patients with chronic LBP are treated with medications: 4% are given acetaminophen or aspirin, 16% receive NSAIDs, and approximately 4% are administered muscle relaxants [20].

Some authors advocate acetaminophen as a reasonable first step in the treatment of chronic LBP [20,21], although others suggest that while it is reasonable in acute LBP, it should not be recommended for treating chronic LBP [6]. There is evidence that acetaminophen has a similar efficacy to NSAIDs in acute LBP patients; however, there is little direct evidence regarding the efficacy of acetaminophen in chronic LBP [19]. The possible beneficial effects of long-term acetaminophen use must be weighed against potential hepatic and renal adverse events [22].

There is strong evidence that both traditional and cyclooxygenase-2-specific NSAIDs are more efficacious than placebo for reducing LBP in the short term, although the effects tend to be small [19]. One small randomized study suggested the NSAID diflunisal had a greater efficacy compared with acetaminophen [23]. In addition, there are findings to demonstrate that the various NSAIDs are, on average, equally efficacious [24]. In individual patients, one NSAID may be more effective than another, and a therapeutic benefit may be obtained by switching to an alternative one [25]. Gastrointestinal, renal, and potential cardiac toxicities must be considered with long-term NSAID use [19].

The category of muscle relaxants includes a heterogeneous group of medications, and is sometimes subdivided into benzodiazepine and non-benzodiazepine muscle relaxants. There is strong evidence to demonstrate that tetrazepam, a benzodiazepine, is more effective than placebo at improving short-term pain and moderate evidence to indicate that it improves muscle spasms; there is a lack of good data for long-term outcomes [19]. The data on non-benzodiazepine muscle relaxants are not as strong; however, there is moderate evidence for short-term overall improvements, although there is no clear improvement in specific pain outcomes [23]. The common side effects are drowsiness and dizziness and must be weighed against the potential benefits.

Table 1. Summary of the evidence for efficacy of medications in chronic low back pain.

Medication	Short-term outcomes		Long-term outcomes	
	Pain	Function	Pain	Function
Acetaminophen	+	?	?	?
NSAIDs	++	+	?	?
Muscle relaxants				
Benzodiazepine	++	?	?	?
Non-benzodiazepine	+/–	?	?	?
Antidepressants				
Tri/tetracyclics	+	+/–	?	?
SSRIs	–	–	?	?
Opioids	+	+/–	?	?

++: good evidence of efficacy; +: some evidence of efficacy; +/–: mixed or inconclusive evidence; ?: unknown; –: evidence of ineffectiveness.
NSAID: nonsteroidal anti-inflammatory drug; SSRI: selective serotonin-reuptake inhibitor.

Two systematic reviews found antidepressants improved pain in chronic LBP, but no consistent improvement in functional outcome was seen [19,23]. The efficacy for pain relief appears to be limited to, or at least greater for, tricyclic and tetracyclic antidepressants. Selective serotonin-reuptake inhibitors have not shown a similar efficacy [26].

The long-term use of opioids for chronic LBP remains a highly controversial topic [6,21,27]. Patient use of opioids varies between different studies and can be between 3% and 66% [28]. In a review of six trials that compared opioids with placebo or non-opioid analgesics, all studies reported that opioids were superior to control interventions for pain reduction; however, in a meta-analysis of the four of these studies that could be adequately analyzed, the pooled estimate showed reduction in pain to be non-significant when comparing opioids with control interventions [28]. Overall, conclusions from this systematic review were that opioids may be effective for short-term pain relief, but their long-term efficacy in chronic LBP patients is still unknown; additionally, a review of studies investigating aberrant medication-taking behaviors found that rates varied from 5% to 24% [28].

Non-pharmacological, non-invasive interventions

A variety of non-pharmacological interventions have been used to treat chronic LBP (Table 2). Among the most common of these are: activity modification, exercise, "back schools", cognitive–behavioral therapy, intensive multidisciplinary programs (functional restoration), acupuncture, massage, spinal manipulation, lumbar supports, traction, and transcutaneous electrical nerve stimulation (TENS).

Activity modification in some form nearly always occurs among patients in response to their back pain. In acute LBP sufferers, advice from physicians to stay active has been shown to be better than both bed-rest and prescribed exercise [6,19]. Clearly, bed-rest is not a viable strategy in patients with chronic LBP and encouraging individuals to remain active is a logical strategy [6]; however, there is no direct evidence for the effectiveness of such advice to stay active to aid chronic LBP [19].

Exercise therapy is commonly used to treat chronic LBP; however, the specific interventions are often heterogeneous and there is little evidence to suggest one particular exercise approach is superior over another. In a pooled meta-analysis of a variety of exercise interventions, there was strong evidence that showed fairly sizeable short-term improvements in pain when patients used exercise therapy compared with no treatment. There was also a smaller, but still significant, improvement from exercise compared with other conservative treatments. Improvements were additionally seen in functional outcomes [19].

Swedish-style "back schools" generally consist of education and information about LBP problems, ergonomic instruction, and back exercises. For chronic LBP the evidence is somewhat conflicting, but overall there is some evidence that back schools may be effective in improving short-term pain and functional outcomes, but not long-term outcomes [19].

Cognitive–behavioral therapy is used to modify maladaptive responses to chronic pain and there is a variety of different specific approaches used [27]. There is evidence that behavioral therapy can improve short-term pain and functional outcomes compared with receiving no treatment [23]. Behavioral treatment seemed to have similar outcomes to using an exercise approach when they were directly compared [19]. The use of EMG biofeedback has not been shown to be effective [19].

Multidisciplinary treatment with a functional restoration approach has been well studied in chronic LBP patients. Intensive programs include >100 h of therapy and there is

Table 2. Summary of the evidence for efficacy of non-pharmacological, non-invasive treatments in chronic low back pain.

Treatment	Short-term outcomes		Long-term outcomes	
	Pain	Function	Pain	Function
Advice to stay active	?	?	?	?
Exercise	++	++	?	?
Back schools	+	+	–	–
Behavioral therapy	+	+	?	?
Intensive multidisciplinary rehabilitation	++	++	+/–	+
Acupuncture	+	–	?	?
Massage	+	++	+/–	+/–
Spinal manipulation	+	+	–	–
Lumbar supports	?	?	?	?
Traction	–	–	?	?
Transcutaneous electrical nerve stimulation	+/–	+/–	?	?

++: good evidence of efficacy; +: some evidence of efficacy; +/–: mixed or inconclusive evidence; ?: unknown; –: evidence of ineffectiveness.

moderate evidence to suggest that these programs improve pain and strong evidence to indicate that they improve function when compared with routine rehabilitation or usual care methods [19]. These are one of the few types of intervention in which good evidence exists regarding long-term outcomes. A systematic review of long-term outcomes (lasting ≤5 years) showed strong evidence for the long-term efficacy of multidisciplinary treatment on quality of life and work participation, although the evidence relating to specific measures of pain and self-reported functional status was more mixed [29]. However, this review used a cut-off time of only 30 h to identify intensive programs, rather than the 100 h usually used. Programs that were less intensive than 100 h have not shown significant efficacy [23].

Acupuncture has been studied extensively as a treatment for chronic LBP with >10 randomized controlled trials (RCTs) published; however, methodological issues in many of these studies limit the ability to draw firm conclusions [30]. A recent systematic review suggests that acupuncture improves short-term pain compared with a sham procedure or no treatment, but there appears to be no significant difference in patients' physical function compared with sham [31]. Acupuncture appears to be similarly efficacious to other treatments such as NSAIDs or TENS, but not as effective as massage therapy [30]. Massage therapy has been studied in at least three recent RCTs and has consistently shown efficacy in treating pain and improving physical function compared with control interventions [30]. In one study, the effects seemed to last to 1 year [32] and functional outcomes were more consistently positive than for pain. When massage is combined with exercise and education, it may prove to be better than massage alone [31].

Spinal manipulation for chronic LBP has been extensively studied and extensively meta-analyzed. A recent systematic review concluded that there is good evidence of a real, but modest, effect of spinal manipulation on chronic LBP when compared with sham or control interventions (judged to have no efficacy); however, this effect is no greater than when therapies such as analgesics, exercise, or usual care are used [33]. The effects of spinal manipulation compared with sham were significant for relieving pain and improving physical function in the short-term, but it was not found to improve long-term outcomes [30]. A recent study in acute LBP patients was able to identify subgroups of patients who were more likely to respond to manipulation treatment [14]. Whether the same is true for chronic LBP remains to be seen.

There is a lack of studies that have specifically evaluated the use of lumbar supports in chronic LBP [23]. In a mixed population of patients with back pain of varying or unknown duration, groups receiving lumbar supports fared no better than control groups receiving other types of treatment [19]. Evidence for traction is also limited; a recent review did not show improvement in pain or function for subjects receiving traction compared with control patients [19].

TENS is a controversial treatment for chronic LBP. A Cochrane review found conflicting evidence regarding the efficacy of TENS in two randomized trials [34]. Thus, the effectiveness of TENS in chronic LBP remains unknown [23].

Invasive interventions

A variety of invasive interventions has been used to treat chronic LBP and includes lumbar epidural steroid injections, intra-articular facet injections, median branch blockade, radiofrequency neurotomy, intradiscal electrothermal therapy (IDET), spinal cord stimulation, and spinal fusion (Table 3).

Table 3. Summary of the evidence for efficacy of invasive treatments for chronic low back pain.

Treatment	Short-term outcomes		Long-term outcomes	
	Pain	Function	Pain	Function
Epidural steroids	?	?	?	?
Intra-articular facet injections	+/–	+/–	?	?
Median branch blocks/radiofrequency neurotomy	+	+	–	–
Intradiscal electrothermal therapy	+/–	+/–	?	?
Spinal cord stimulation	?	?	?	?
Spinal arthrodesis	Likely to be better than unstructured physical therapy, but similar to intensive multidisciplinary rehabilitation			

++: good evidence of efficacy; +: some evidence of efficacy; +/–: mixed or inconclusive evidence; ?: unknown; –: evidence of ineffectiveness.

Lumbar epidural steroid injections are often used in the type of back pain that is accompanied by radiculopathy – for which there is some evidence of efficacy [6]. Evidence for the effectiveness of epidural steroids in chronic LBP without the presence of radiculopathy is scarce [23]. One recent review concluded that there was moderate evidence that caudal epidural steroids improved chronic LBP [35]; however, a review of the trials cited for this conclusion shows that efficacy was based on a comparison of the outcomes before and after treatment, and not on direct comparisons of intervention and control parameters [36,37]. As a result, these studies function as a case-series and do not provide significant evidence of efficacy. Thus, the evidence base for assessing the potential efficacy of epidural steroids in chronic LBP is lacking.

Facet joint intra-articular injections are a controversial treatment for the management of chronic LBP [6]. The one major randomized study to evaluate this lead to somewhat confusing results [38]. Injecting methylprednisolone acetate into the facet joints of patients who had experienced previous transient relief of pain from an intra-articular local anesthetic resulted in similar outcomes at months 1 and 3 compared with control subjects given a saline injection. At 6 months, the methylprednisolone acetate group had better pain and functional outcomes; however, the steroid group received more co-interventions and controlling for these co-interventions decreased the apparent benefit at 6 months. Only 22% of subjects from the steroid group and 10% of individuals from the placebo group improved at all three time points, and these improvements were not statistically significantly different.

Radiofrequency denervation appears to improve short-term pain outcomes in patients thought to have facet joint pain, defined by successful median branch injections with local anesthetic [6]. These improvements appeared to be present for up to 2 months, although a study lasting 12 weeks did not show any long-term difference compared with control subjects [39].

IDET is another controversial treatment for chronic LBP. A Cochrane review found conflicting evidence of efficacy, with some trials yielding positive results and others giving negative results [39]. The largest RCT to show improvement in pain and function was in a highly selected population. If IDET is effective, it is likely this will only be observable in a very carefully chosen subset of patients [40].

A systematic review of spinal cord stimulation in patients with failed back surgery syndrome or complex regional pain syndrome concluded that the literature was inadequate to draw any strong conclusions regarding the efficacy of this technique [41]. The authors did find some evidence for efficacy in complex regional pain syndrome, but there were no high quality controlled studies for patients with failed back surgery syndrome; one randomized trial comparing spinal cord stimulation to re-operation in patients with failed back surgery syndrome did not report pain or functional outcomes and another had only 38% follow-up [41]. Thus, the efficacy of spinal cord stimulation for patients with chronic LBP remains unknown.

Spinal arthrodesis for chronic LBP is another highly controversial topic. A recent systematic review found four randomized trials that compared spinal fusion with non-operative control subjects [42]. All of the trials had some methodological concerns; however, all the studies showed fairly modest improvements overall, but they all differed in their conclusions regarding the relative improvement compared with control subjects. The major differences between these trials were in the outcomes of the control groups, which were better for the studies in which patients received more intensive rehab and not as good for those who underwent less intensive rehab. A reasonable conclusion from the available data is that spinal fusion surgery is probably more efficacious in carefully selected patients with chronic LBP than those who received either no treatment or unstructured low intensity rehabilitation, but it may not be any more effective than intensive multi-disciplinary rehabilitation [42].

Conclusion

Chronic LBP is a heterogeneous condition that is challenging to treat. While there is a vast amount of literature evaluating different treatment options, there are substantial methodological challenges that greatly limit evidence-based conclusions in many situations. The accurate identification of specific subgroups who are likely to respond to specific interventions remains an important research need. With current evidence, limited conclusions can be drawn. NSAIDs, muscle relaxants (particularly the benzodiazepines), and tri- and/or tetracyclic antidepressants appear to have some efficacy for providing pain relief in chronic LBP sufferers and represent a reasonable starting point for therapy. In addition, judicious and careful use of opioids may have a role in the appropriate setting. Massage, spinal manipulation, and perhaps acupuncture are potential options with reasonable expectations for pain reduction. Exercise and cognitive–behavioral therapy can improve pain and functional outcomes. Intensive, multi-disciplinary rehabilitation programs have the strongest support in the literature for improving both short- and long-term outcomes. Spinal fusion surgery is an option in properly selected patients and there is a reasonable expectation of improved pain and function, but the outcomes are likely to be similar to an intensive multidisciplinary rehabilitation program. Injections and other non-surgical invasive interventions may have a limited role in highly selected patients, but these methods cannot, in general, be recommended. The optimal management of chronic LBP will vary from individual to individual. Patients' expectations of benefit and preferences for treatment have been shown to significantly affect their recovery; an effect that can be as big or bigger than the effect of the intervention itself [43]; therefore, both the specific characteristics of each patient's back pain, as well as their personal goals and values, need to be incorporated into the choice of treatment.

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Opioid-Induced Constipation

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LEADING ARTICLE

Opioids are a common and popular choice for chronic pain management. Although they provide adequate pain relief in most patients, a major disadvantage to opioid use is their associated side-effect profile. One of the most debilitating adverse events to affect patients' quality of life is constipation. A proactive bowel regimen including laxatives when starting opioids can be helpful, but in many individuals, constipation remains a problem. This review discusses some of the presently used agents and new treatment options being investigated to relieve opioid-induced constipation.
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Opioids are the mainstay for the treatment of pain. This was emphasized in 1998 when the US Federation of State Medical Boards established pain treatment recommendations and many states have adopted these recommendations in the form of intractable pain treatment acts. Despite recent controversy concerning increasing abuse of this class of drug, most patients derive meaningful pain relief with opioids even when used for long periods of time; however, a major disadvantage is their side-effect profile. No permanent end-organ damage has been found with persistent use, but adverse events are common. In clinical trials, >25% of patients drop out due to side effects, a percentage that is substantially higher than that for subjects who are given placebo [1]. Common adverse effects are dry mouth, nausea, and constipation.

Pathophysiology of opioid-induced constipation

Opioids have a central and peripheral effect on μ, δ, and κ opioid receptors. One of their peripheral effects has been seen in intestinal preparations from several animal species [2]. Muscarinic M2 receptors in the spine and gastrointestinal system have been implicated in opioid-induced constipation. The role of the δ and κ receptors is less well known. The gastrointestinal tract is innervated by the autonomic nervous system and opioids can have an effect on both sympathetic (T4–L2) and parasympathetic (vagus nerve and S2–4) nerves. Opioid receptors are present on the periphery of submucosal and myenteric plexus, and on intestinal smooth muscles. The submucosal plexus controls secretory and absorption function; the myenteric plexus controls motor activity, including the intensity and rhythm of contractions and conduction velocity. Both are innervated with sympathetic and parasympathetic nerves. These effects, along with opioid-induced changes in neurotransmitters, result in decreased intestinal motility, delayed transit, and increased fluid absorption [3,4].

Opioids have multiple effects on the gastrointestinal tract; they can cause a condition referred to as opioid bowel dysfunction, which consists of symptoms of bloating, intestinal gas, abdominal pain, a decreased appetite, gastroesophageal reflux, and nausea. In addition, despite the use of laxatives, opioid-induced constipation can result in, and cause, fewer bowel movements, more straining, hard stools, and incomplete evacuation [5]. Constipation is seen in 14–70% of patients on opioid treatment [6]. Tolerance, occurring with the first dose or continued use, can occur to many of the side effects of opioids, but rarely to constipation. Laxative therapy, while commonly prescribed, is often inadequate [7].

Current laxative therapies

The most common regimen for treating opioid-induced constipation is the combination of a stimulant laxative (senna) with a stool softener (docusate sodium) [8]. Bulking agents or fiber (such as Metamucil®, Procter & Gamble, Cincinnati, OH, USA; Fiberchoice®, GlaxoSmithKline, London, UK; and Phillips' Fiber Caps®, Bayer, Leverkusen, Germany) contain indigestible psyllium or methylcellulose. The bulk stimulates propulsive muscles and attracts fluid into the colon, but should not be used for treating opioid-induced constipation. Opioid therapy decreases bowel motility and secretions, and bulking agents can increase the risk of bowel obstruction for patients particularly when they have an inadequate fluid intake [8].

Lubricant laxatives (for example fleet mineral oil and fleet enema) coat the gastrointestinal tract with an oil film.

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Emulsified mineral oil penetrates into the stool to soften it and allows ease of passage. The lubricant laxatives are commonly used when straining should be avoided (for example, in postoperative and post-injury patients, and in individuals suffering from hemorrhoids and anal fissures). Fat-soluble vitamins may be malabsorbed with prolonged use of such lubricant laxatives.

A stool softener such as docusate requires intestinal motility and may not be effective when administered as a single treatment in patients with opioid-induced constipation [9]. Docusate sodium at doses of >400 mg/day can promote peristalsis. Osmotic agents, on the other hand, create a hypertonic environment and draw extraluminal water into the colon. Examples of osmotic laxatives include saline (magnesium hydroxide and sodium phosphate), sugar alcohols (lactulose, mannitol, and sorbitol), and polyethylene glycol (Miralax® Schering-Plough, Kenilworth, NJ, USA). Osmotic agents are particularly useful when constipation is resistant to stimulants and stool softeners. Some patients on saline laxatives can experience electrolyte disturbances and so they should be avoided if the individual suffers from renal insufficiency, congestive heart failure, or cirrhosis [10].

Senna is the most commonly used laxative for opioid-induced constipation and is often combined with docusate sodium. Senna administration has been associated with melanosis coli, a dark pigmentation of the colon that is reversible upon discontinuation of the agent. Senna and bisacodyl are prokinetic agents and appear to be safe for long-term use. The starting dose of senna is 17.2 mg (taken as two 8.6 mg tablets at bedtime) and is 5–10 mg for bisacodyl. The onset of action can occur between 10 min and 12 h after administration [10].

New agents for opioid-induced constipation

Several opioid receptor antagonists have been evaluated in opioid-induced constipation, the most cited being naloxone. At doses of 4–18 mg/day, constipation improves but there can be systemic absorption that may precipitate withdrawal symptoms and reduced analgesia. This narrow therapeutic window limits the usefulness of naloxone [11]. Naltrexone, an orally active opioid receptor antagonist, has no utility in constipation. Readily absorbed from the gastrointestinal tract, it reverses analgesia and has a systemically active metabolite with a long half-life.

Two medications currently being studied, alvimopan and methylnaltrexone, are peripherally acting opioid receptor antagonists that have no central effects. Oral alvimopan is a potent peripheral μ receptor antagonist with activity that is localized to the gastrointestinal tract. Its systemic bioavailability is <6%. Alvimopan is five-times more potent than naloxone as a μ opioid receptor antagonist and does not cross the blood–brain barrier [12,13]. Methylnaltrexone, has an additional methyl group on the naltrexone molecule, resulting in it becoming peripherally acting without central effects [14].

Alvimopan was evaluated in patients taking >30 mg oral morphine and reporting less than three spontaneous bowel movements per week. An improvement in spontaneous bowel movements was noted within 1 week, sustained throughout the 6-week treatment period, and returned to baseline at discontinuation [15]. Subjects taking alvimopan showed improvements in straining, stool consistency, completeness of evacuation, abdominal pain, and bloating, compared with placebo. There was no evidence of opioid analgesia antagonism based on pain intensity scores, opioid consumption, or systemic withdrawal assessment [16].

Subcutaneous administration of methylnaltrexone has been studied in Phase 2 trials in advance opioid bowel dysfunction [14]. Subjects receiving 0.15–0.30 mg/kg of methylnaltrexone had bowel movements at ≤70 mins compared with >24 h intervals for placebo, without changes in pain scores or withdrawal symptoms. Abdominal cramping, flatulence, and nausea were noted side effects. Studies are being conducted on the effectiveness of orally administered methylnaltrexone [17].

Conclusion

Side effects often limit the usefulness of medication, a factor that is particularly applicable in the administration of opioids for chronic pain. Opioid bowel dysfunction describes a constellation of side effects from opioid therapy that are related to the gastrointestinal tract, including nausea, vomiting, bloating, and reflux; the most prominent of these symptoms is opioid-induced constipation. Astute practitioners anticipate this side effect following the initiation of opioids by prescribing pre-emptive laxatives. In general, this therapy does not prevent much of the constipation, especially in an older population where polypharmacy is common – many of these drugs, in addition to the opioid – cause constipation. Combined with the underlying age-related loss of bowel function, even laxative therapy fails to relieve constipation and thus patients opt for more pain rather than deal with the bowel dysfunction. A new approach to this problem utilizes drugs that locally antagonize the gastrointestinal effects of the opioids without clinically significant central opioid receptor antagonism. Using these novel agents, the critically important analgesia is not reversed. When available, this new class of drugs should prove very effective in allowing clinicians to provide pain control without the opioid-induced constipation that continues to plague so many chronic pain sufferers.

Disclosure

The author has served on speakers bureau for Alpharma, Cephalon, Eli Lilly, King Pharmaceuticals, Merck, Pfizer, Pricara, and Purdue.

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CASE STUDY

Satisfactory Pain Relief and Improved Function in the Management of Complex Regional Pain Syndrome/Reflex Sympathetic Dystrophy with Intravenous Ibandronate: A Case Report

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This report is a case study of a patient diagnosed with complex regional pain syndrome/reflex sympathetic dystrophy (CRPS/RSD) who was successfully treated with intravenous ibandronate, a third-generation bisphosphonate. Multiple lines of evidence suggest that a subgroup of patients who suffer from CRPS/RSD may have neuropathic bone pain mechanisms responsive to bisphosphonate-type compounds. This case also suggests that some patients may only respond to specific bisphosphonates; however, safety concerns about the long-term use of these drugs and the potential complication of osteonecrosis of the jaw remain. *Adv Pain Manage* 2008;**1**(4):150–2.

The classical description by Silas Weir Mitchell of "patients who complain of very acute pains, which they themselves compare to a burn, or to the action of a very hot mustard plaster, or to the effect of a red-hot file abrading their skin" [1] resonates with the description of the pain experienced by the patient discussed in the current case report. The mechanisms of this post-traumatic neuropathic pain syndrome known as complex regional pain syndrome/reflex sympathetic dystrophy (CRPS/RSD) are still poorly understood and multiple subsets of this syndrome are likely to occur. The exact analgesic mechanism of intravenous bisphosphonates in the management of cancer bone pain and pain from Paget's disease, inflammatory spondylo-arthopaties, and CRPS/RSD are also undetermined [2–8]. Here, the authors report a case that explores the off-label analgesic use of an intravenous bisphosphonate in the management of CRPS/RSD.

Case study

The patient was a 36-year-old female who presented with a history of severe left lower extremity pain. After a fall sustained while horseriding, she underwent multiple orthopedic surgical procedures that were complicated by poor bone fusion of her left femur. She described her chief complaint thus, "my leg was bright red from my knee to my ankle. I mean *flaming* red. I couldn't touch it. I couldn't put clothes on it." She was diagnosed with CRPS/RSD and her pain failed to respond to a multitude of oral therapies including acetaminophen with codeine, duloxetine, gabapentin, morphine, oxycodone, pregabalin, and transdermal fentanyl. Her pain was also unresponsive to topical agents such as doxepin 5% cream or lidocaine patches. Neither lumbar sympathetic nor epidural blocks were able to diminish her pain substantially or allow for increased activity levels. She was offered a spinal cord stimulator trial, but refused this mode of therapy.

In early 2006, she was enrolled in an investigational pilot trial of intravenous bisphosphonate ibandronate 6 mg/day for 3 days [14]. Due to a potential adverse event, known as osteonecrosis of the jaw (ONJ), related to the use of high dose intravenous bisphosphonates, all enrolled patients were required to have excellent dental health, be cleared for any ongoing endodontic disease, and have no dental implants. Within the first week of starting intravenous infusions of ibandronate, the patient began to experience >50% pain relief; a benefit that lasted for approximately 1.5 months, at which time her pain slowly began to re-emerge. After pain had resurfaced, use of high doses of oxycodone and

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oxymorphone provided the patient with only modest relief and no improvement in function (she was unable to carry out her daily activities).

In late 2006, the patient underwent an off-label trial of intravenous pamidronate, which not only had no effect on her pain, but also caused side effects that she described as "unacceptable", as well as "flu-like" symptoms. On a compassionate basis, and after involving her dentist in her follow-up care, an off-label dose of intravenous ibandronate (3 mg over 2 h) was given. The patient again reported significant benefit from the treatment with a decrease from 10/10 to 6/10 on a pain intensity scale within the first week of therapy. After two additional courses of intravenous ibandronate, she reported a three- to four-fold decrease in her opioid requirements and a stable pain intensity score of 3/10. Moreover, the patient was able to return to her daily activities, including 45 min of aerobic exercise on an elliptical machine, three times a week.

Discussion

A number of controlled clinical trials of bisphosphonates for the treatment of CRPS/RSD have been published that report significant pain reduction and improved physical function [5–13]. Some lines of evidence suggest that a subgroup of patients who suffer from CRPS/RSD may have neuropathic bone pain mechanisms responsive to bisphosphonate-type compounds [2]. Bisphosphonates are a class of drugs that act via various intracellular mechanisms to suppress osteoclast-mediated bone resorption. Bisphosphonates are known to decrease the life span of osteoclasts and inhibit their activity. Other potential relevant mechanisms are discussed below. One safety concern with bisphosphonates is ONJ. This condition has been observed in a subgroup of cancer patients treated with chronic bisphosphonate therapy for multiple myeloma and bone metastases from breast, prostate, or lung malignancies. The risk of developing ONJ seems to be far greater in oncological patients who receive monthly intravenous bisphosphonate therapy for >1–2 years, have poor oral hygiene, and a history of recent dental implant or extraction [2].

In the past, regional skeletal changes known to occur in CRPS/RSD patients have been used as a diagnostic index. A three-phase technetium bone scan is still used in the evaluation of this disorder, although it is no longer used to establish a CRPS/RSD diagnosis [2]. Of note, the three-phase bone scan uses a bisposphonate marker – the technetium-99 radiolabeled bisphosphonate. Three-phase bone scintigraphy has historically been regarded as having high specificity (>90%) in the diagnosis of reflex sympathetic dystrophy, especially in patients with symptoms of <6-month duration [15,16].

The anatomy of bone innervation, revealed by immunohistochemical studies, consists of a network of nerve fibers throughout the bone marrow, cortical and trabecular bone, and periosteum [17]. The bone microenvironment surrounding small nerve fibers may be influenced by multiple algogenic factors such as an increase in local proton concentration from activated osteoclasts, local synthesis of nerve growth factor (NGF), and an increased concentration of proteases and inflammatory substances such as cytokines and prostaglandins [2].

Activated osteoclasts produce an acidic microenvironment (pH <4) via the release of protons through vacuolar H^+ATPase [18,19]. A potential mechanism of bone pain may be the activation of two main groups of acid-sensing nociceptors [20]: acid-sensing ion channels (ASICs) and the capsaicin receptor transient receptor potential vanilloid subtype 1 (TRPV1), which are involved in proton transduction mechanisms and pain signal transmission [21–23]. ASIC-expressing nociceptors may additionally be involved in the transduction and transmission of mechanical pain [24]. It follows that some of the anti-nociceptive properties of the bisphosphonates may be attributed to inhibition of ostoclast activity and, in turn, to a decrease in proton concentration in the bone microenvironment.

NGF-expressing cells and nociceptors with high affinity tyrosine kinase receptors for NGF are found in bone [25,26]. NGF acts on small nerve fibers and upregulates the transcription of gene-encoding receptors such as capsaicin receptor TRPV1 and neuropeptides such as calcitonin gene-related peptide and substance P [2].

In vitro and *in vivo* studies suggest the hypothesis that direct exposure to bisphosphonates may result in bisphosphonate-induced toxic effects on NGF-expressing cells, for example, osteocytes, resident mast cells, activated macrophages, endothelial cells, and bone marrow stromal cells [26]. It is conceivable that a contribution to the analgesic action of bisphosphonates for bone pain might occur via inhibition of NGF-producing cells.

Conclusion

This case study supports previous reports and clinical trials suggesting that some patients who suffer from CRPS/RSD may benefit from intravenous bisphosphonate treatment. This case also indicates that some patients may only respond to specific bisphosphonates (e.g. third-generation bisphosphonates such as ibandronate) and not to others. However, concerns remain about the long-term use of these drugs and the potential complication of ONJ.

Disclosure

Dr Pappagallo is a member of the scientific advisory boards for Anesiva, Elan, and GlaxoSmithKline. He has received research support from Endo Pharmaceuticals, GlaxoSmithKline, and Roche. Dr Ghandehari has no relevant financial interests to disclose.

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CLINICAL REVIEWS

Commentary and Analysis on Recent Key Papers

Clinical reviews were prepared by Lara Dhingra, PhD and Helena Knotkova, PhD

OPIOIDS

Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain

Edlund MJ, Steffick D, Hudson T et al.
Pain 2007;**129**:355–62.

Identifying potential risk factors for drug abuse and addiction among chronic pain patients prescribed opioid therapy is a priority. This large epidemiological study identified potential risk factors for opioid abuse or dependence in veterans with chronic pain. Although non-opioid substance abuse disorders were the strongest risk factor for opioid abuse/dependence (OA/D), their prevalence was low; mental health disorders had more predictive value as a risk factor. Being male, a younger adult, and using higher doses of opioids, predicted a greater likelihood of developing OA/D. Candidates for opioid therapy need to be screened for substance abuse and mental health disorders to ensure appropriate treatment.

Opioid therapy may be associated with a higher risk of abuse in specific subgroups of patients. The main purpose of this study was to identify independent risk factors for the development of opioid abuse/dependence (OA/D) in chronic pain patients. A large longitudinal dataset (n=15 160) was analyzed, with comprehensive information from patients treated in the South Central Veterans Affairs Health Care Network. Potential risk factors identified in 2002 were used to predict a new diagnosis of OA/D in 2003, 2004, or 2005. The potential risk factors for OA/D evaluated in the study were:

- Non-opioid substance abuse disorders.
- Chronic pain disorders.
- Mental health disorders.
- Ociodemographic variables.

To control for nuisance variables, patients who were on methadone maintenance therapy (potentially for opioid substance abuse disorders), diagnosed with cancer, or diagnosed with opioid substance abuse disorders, were excluded from the analyses. The results show that rates of mental health disorders (45.3%) were much higher than those of opioid substance abuse disorders (7.6%), and that 2% of patients without a prior history of OA/D between 2000 and 2002 received a new diagnosis of OA/D between 2003 and 2005. Using multivariate analyses, multiple risk factors were shown to be significant predictors of OA/D. The strongest predictor of patients having OA/D between 2003 and 2005 was the presence of a non-opioid substance abuse disorder in 2002 (odds ratio [OR]=2.34). Mental health disorders were also found to be moderately strong predictors of OA/D (OR=1.46). African Americans had lower rates of OA/D compared with Caucasians, and patients who received a >211-day supply of opioids had higher rates of OA/D than those receiving a 91–120-day supply. Other predictors of OA/D included a younger age, a greater number of health care visits, male sex, and a single, divorced, or separated family status.

These findings are significant in several regards. First, it was found that non-opioid substance abuse was the strongest predictor of OA/D in chronic pain patients; however, it should be noted that relatively few patients in this study had non-opioid substance abuse disorders (7.6%) compared with the large number of patients experiencing mental health disorders (45.3%). Second, this rigorous study identified a comprehensive set of covariates of OA/D while controlling for confounding variables. One potential methodological issue is the quality of the diagnostic data from an archival dataset. Furthermore, the study did not specify which mental health disorders were associated with higher rates of OA/D. Nonetheless, these longitudinal data may have promising implications for identifying subgroups of patients at high risk for opioid abuse.

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Development and validation of the current opioid misuse measure

Butler SF, Budman SH, Fernandez KC et al.
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Rates of long-term opioid use for treating chronic pain are increasing, and ongoing assessment to minimize the potential risk of abuse and addiction in patients is essential. The current study describes the development and initial validation of a new measurement tool, known as the Current Opioid Misuse Measure, designed specifically for repeatedly assessing problematic drug use behaviors in patients during the course of long-term opioid therapy. Preliminary results suggest that the tool is reliable and valid, and holds promise in improving risk monitoring efforts.

Long-term opioid therapy may be linked to a higher risk of drug abuse in certain populations. Therefore, safe and effective administration of opioid therapy requires ongoing assessment of the risks related to abuse and addiction. This was the first known study to develop and preliminarily validate a measurement tool – the Current Opioid Misuse Measure (COMM) – to allow repeated assessments of "problematic drug-related behaviors" (PDRBs) in patients receiving opioids for extensive time periods. PDRBs refer to the nonadherence behaviors of patients who are using opioid therapy, and who are suggestive of misuse, abuse, or addiction [1].

In the first phase of the COMM design, 177 items indicative of PDRBs were generated and ranked in order of importance. Cluster analysis revealed six underlying constructs:

- Medication misuse/noncompliance.
- Evidence of lying and illicit drug use.
- Emotional problems/psychiatric issues.
- Inconsistent appointment patterns.
- Signs and symptoms of drug misuse.
- Poor response to medications.

Forty items were retained, and 277 patients completed the COMM to refine item selection. Seventeen items were retained based on high intra-class correlations (ICC) and other properties. Additional results (n=60) showed that test-retest reliability (ICC=0.86) and internal reliability (Cronbach's α=0.86) were high. A receiver operating characteristic (ROC) curve analysis showed that sensitivity and specificity were good when compared with the Aberrant Drug Behavior Index, a subscale of the Prescription Drug Use Questionnaire. A cut-off score of >9 on the ROC curve produced a sensitivity >0.94 and specificity >0.73, suggesting an optimal cut-off.

To determine whether the COMM identified changes in PDRBs, the researchers conducted an assessment at 3-month follow-up on 86 patients. Results showed that 15.4% (n=4) of subjects who initially exhibited PDRBs no longer displayed these behaviors, and 15% (n=9) with no prior PDRBs went on to demonstrate PDRBs. These scores show that the COMM can identify changes in PDRBs over the course of opioid therapy.

These encouraging findings suggest that the COMM has good face and convergent validity and excellent reliability. Strengths of this study include the rigorous design, the multiple approaches used to measure PDRBs, and the focus on assessing current PDRBs. However, the study design could not establish the COMM's reliability in patients receiving opioid therapy for >3 months or whether the items accurately identified PDRBs among different pain populations. Future studies may determine if these results can be applied to other populations and settings, and whether the COMM can help clinicians to structure pain treatment.

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CANCER PAIN

Transcutaneous electrical nerve stimulation vs. transcutaneous spinal electroanalgesia for chronic pain associated with breast cancer treatments

Robb KA, Newham DJ, Williams JE.
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Forty-one women with chronic pain due to breast cancer treatment participated in this randomized, placebo-controlled trial. Subjects received either transcutaneous electrical nerve stimulation,
transcutaneous spinal electroanalgesia (TSE), or a placebo (sham TSE). Outcome measures included: pain report, pain relief, pain interference with activities, anxiety and depression, arm mobility, and analgesic consumption. The results showed that all three interventions (including placebo) had beneficial effects on both pain report and quality of life.

Transcutaneous electrical nerve stimulation (TENS) has been widely used for many years to manage a range of acute and chronic pain syndromes. However, when examining the use of TENS in the management of cancer pain, the evidence is inconclusive and is based on only a few studies.

Recently, some attention has been directed to another stimulation technique, transcutaneous spinal electroanalgesia (TSE). This method uses electrodes placed over the spine and operates at a higher frequency than the traditional TENS. With TSE, there is no sensory stimulation, so it is easier to perform blind assessments in clinical trials. In the current study, the authors examined the effects of both TENS and TSE compared with placebo (sham TSE) in women with pain associated with breast cancer treatment. The study had a double-blind, randomized, cross-over design, and involved 41 subjects. The outcome measures were pain report, pain relief, pain interference with activities, anxiety and depression, arm mobility, and analgesic consumption. The results showed no significant differences between the three study treatments (TENS, TSE, and sham TSE). All three interventions led to an improvement in pain scores for worst and average pain compared with baseline, and analgesic consumption did not differ significantly between the three types of treatment. The authors suggest that the improvement reflected either a placebo effect or a psychophysical improvement due to a personal interaction involved in the treatment. As noted in the article, it was difficult to analyze improvements in psychological status as the baseline scores were low; however, the results showed that after using TENS and placebo, patients had lower anxiety scores. This study has some potentially significant implications for clinical practice. The research performed by this multidisciplinary team has an important role in the future management of chronic pain associated with breast cancer treatments.

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An open-label, multi-dose efficacy and safety study of intramuscular tetrodotoxin in patients with severe cancer-related pain

Hagen NA, Fisher KM, Lapointe B et al.
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This multicenter, dose-escalation study was conducted in patients with unrelieved cancer pain to determine the safety and efficacy of intramuscular tetrodotoxin, a highly selective sodium channel blocker. A total of 24 patients underwent 31 courses of treatment at doses ranging 15–90 μg/day, administered in divided doses during a 4-day period. The results showed a substantial reduction in pain intensity in the majority of patients and pain relief persisted for up to 2 weeks.

Results from studies in animal models suggest that voltage-gated sodium channels (VGSCs) are key regulators of neuronal excitability. VGSCs play a role in persistent pain, and it has been shown that the accumulation of VGSCs in injured primary afferent neurons of peripheral nerves contributes to the development of neuropathic pain [1,2]. Previous research indicated that tetrodotoxin, a selective blocker of the VGSCs, had an adequate safety profile and may have a potential role in pain relief [3]. The objective of this Phase IIa, multicenter clinical trial of intramuscular tetrodoxin was to determine the following parameters: the efficacy and safety of tetrodoxin, the duration of its analgesic effect, the minimal effective dose and dosing frequency, and to identify differential responses to treatment based on the inferred pathophysiology. The authors hypothesized that some types of pain might respond better to tetrodotoxin treatment than others. Twenty-four patients with severe cancer pain participated in the study and received a total of 31 courses of treatment. The dose-escalation study design included up to six dose levels of intramuscular tetrodotoxin administered over a 4-day treatment period. Initially, six patients were planned to be enrolled into six dose-levels successively until complete pain relief was achieved or until the dose was poorly tolerated; however, only five dose levels were administered (7.5 μg twice daily, 15 μg twice daily, 22.5 μg twice daily, 30 μg twice daily, and 30 μg three-times daily) due to the level of toxicity experienced by subjects in the 30 μg three-times daily group. All subjects who were enrolled in the first four dose groups completed the study and did not display any specific safety concerns. The results showed a significant variability in the magnitude and duration of the analgesic response between the dose level groups. The findings also suggest that the response to intramuscular tetrodotoxin may be better in patients with pain of a somatic or visceral origin (nine responders of 11 patients) compared with patients with neuropathic pain (eight responders of 20 subjects). The analgesic response to treatment was typically detectable on the second day of treatment, reaching a maximum response on days 5 or 6. A total of 17 patients reported clinically meaningful pain relief and nine of these reported a substantial pain relief beyond the treatment period. The overall findings show that intramuscular tetrodotoxin in doses from 15 μg/day to 60 μg/day was safe and effective in treating severe treatment-resistant cancer pain.

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NEUROPATHIC PAIN

Spontaneous pain and brain activity in neuropathic pain: functional MRI and pharmacologic functional MRI studies

Baliki M, Geha PY, Apkarian AV.
Curr Pain Headache Rep 2007;**11**:171–7.

This article discusses a novel approach for studying brain activity in patients with chronic neuropathic pain and its modulation by pharmacological manipulation. The authors review the differences in brain activity between acute pain and chronic neuropathic conditions, as well as differences in brain activity across various neuropathic diseases. The study findings demonstrate that functional magnetic resonance imaging (fMRI) and fMRI with pharmacological intervention provide a solid methodology for determining neuropathic pain in clinical conditions in various patient populations.

The volume of literature written about brain circuitry for acute or experimental pain suggests that the topic is now well established. However, only limited data exist on brain activity in clinical neuropathic pain conditions. This article highlights the differences between acute or experimental and clinical neuropathic pain from the point of view of brain activity and the neuronal circuits involved. The authors point out that recent results indicate cognitive or sensory processing changes during chronic pain, and that an anatomical reorganization may develop as a result of chronic pain. In fact, sensory or cognitive and anatomical findings suggest that chronic pain could have a distinct underlying brain activity pattern. The standard approach for studying brain activity during acute pain is to induce pain by a mechanical or thermal stimulus and determine the brain regions that have been modulated by the stimulus. Thus, it seems natural to use the same technology and methodology in patients with spontaneous pain. This standard approach has been extensively used in the past, despite the fact that many researchers were aware of its shortcomings. The issue that was often ignored was the effect of the presence of spontaneous pain on brain activity in general. To overcome this limitation, the authors improved the standard functional magnetic resonance imaging (fMRI) methodology and used a pharmacological fMRI approach when studying spontaneous pain in clinical conditions. In a previously reported study, brain activity in patients with post-herpetic neuralgia was imaged before and at several timepoints after treatment with lidocaine [1]. Patients were scanned while they rated their ongoing pain or while they were rating a visual bar that varied in time with a pattern that mimicked ratings of pain. This design made it possible for investigators to distinguish between brain activity unrelated to pain and brain activity related to particular levels of pain during the analgesic effect of lidocaine. The authors discuss the findings of this study in the context of current knowledge of the brain circuits involved in chronic versus acute pain states, and across a spectrum of pain syndromes involving neuropathic pain. They conclude that the pharmacological fMRI approach provides a useful and solid methodology for studying spontaneous pain in clinical conditions.

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Repetitive transcranial magnetic stimulation (rTMS) in experimentally induced and chronic neuropathic pain: a review

Leo RJ, Latif T.
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The authors of this article assess a potential role for repetitive transcranial magnetic stimulation (rTMS) in the treatment of pain. A review of the literature shows that rTMS can produce pain relief, but such an effect is transient and highly dependent on parameters of stimulation, type of pain, as well as other determinants. However, rTMS may be clinically useful for pain management in selected patient populations.

Transcranial magnetic stimulation (TMS) has been demonstrated to be useful in treating various medical conditions, such as depression or seizures [1,2]. In addition, recent studies have indicated that TMS may have potential in the treatment of neuropathic pain [3]. The core of TMS technology is based on an electric current passing through an insulated circular or figure-eight coil to produce a magnetic pulse that is capable of penetrating through the skin and skull to the brain. It has been shown that a repeated series of pulses, known as repetitive TMS (rTMS), can modify neuronal activity both locally in the cortex and at subcortical sites. A review of the recent literature suggests that a high-frequency rTMS induces cortical excitability, while a low-frequency rTMS results in neural inhibition. Although the mechanisms underlying pain relief induced by rTMS are not yet fully understood, research data suggest that rTMS over the motor cortex produces changes in activity at local cortical sites and in the thalamic nuclei, which ultimately modulate pain-relaying activity. It is believed that corticothalamic tracts may exert an inhibitory action on thalamic pain processing; thus, when such tracts are stimulated with high-frequency rTMS, nociceptive

signals transmitted over spinothalamic tracts and the ipsilateral thalamic nuclei can become suppressed.

A limitation of the potential use of rTMS in clinical pain practice is that its effect is transient and highly dependent on parameters of stimulation, type of pain, and other factors. The authors conclude that, despite these limitations, rTMS may be a useful tool for managing pain in patients who are awaiting surgical interventions for pain relief or in patients whose pain does not respond to conventional treatment. Moreover, aside from its potential clinical utility, rTMS plays an important role as an investigative tool, which could facilitate a better understanding of supraspinal mechanisms of pain transmission.

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Chemotherapy-evoked neuropathic pain: abnormal spontaneous discharge in A-fiber and C-fiber primary afferent neurons and its suppression by acetyl-L-carnitine

Xiao WH, Bennett GJ.
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The current authors studied afferent axonal activity in rats with pain syndrome induced by the antimitotic drugs, paclitaxel and vincristine. The results showed a significant increase in the rate of spontaneously discharging A and C fibers compared with that in placebo-injected control rats. Furthermore, prophylactic treatment with acetyl-L-carnitine resulted in a considerable reduction of spontaneous discharge. The results of this study suggest that abnormal, spontaneous afferent discharge may be a factor in the pathogenesis of chemotherapy-induced, painful peripheral neuropathy as it occurs in some patients treated with drugs from the taxane and vinca alkaloid classes.

Clinical observations show that cancer patients who receive treatment with antimitotic drugs from the taxane and vinca alkaloid classes often develop chronic, painful peripheral neuropathy. Neurotoxicity is the main dose-limiting side effect experienced by patients taking such drugs. In many patients receiving chemotherapy, nerve damage can lead to the development of peripheral neuropathy; however, mechanisms underlying this phenomenon have not yet been determined. The authors of this study used a rat model of paclitaxel- and vincristine-evoked pain syndromes to investigate primary afferent axonal activity and spontaneous discharges of A and C afferent fibers in the sural nerve. The authors hypothesized that the mechanism of paclitaxel-induced neuropathic pain may be linked to a toxic effect of paclitaxel on axonal mitochondria. Impaired mitochondrial function might be associated with an energy deficit in the afferent terminals, which may compromise the ability of the neuron to operate ion transporters. This could subsequently cause depolarization of the neuronal membrane and the generation of spontaneous action potentials.

The findings from this research group showed that animals treated with paclitaxel and vincristine had an increase in spontaneously discharging fibers compared with control rats that received placebo. The results additionally demonstrated that prophylactic treatment with acetyl-L-carnitine, which blocks paclitaxel-evoked pain, caused a considerable reduction in abnormal spontaneous afferent discharge. The authors concluded that abnormal, spontaneous afferent discharge could be a factor involved in the development of chemotherapy-induced, painful peripheral neuropathy, and that the therapeutic effect of acetyl-L-carnitine may be a result of a reduction in the discharge rate.

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On the repeatability of brush-evoked allodynia using a novel semi-quantitative method in patients with peripheral neuropathic pain

Samuelsson M, Leffler AS, Johansson B et al.
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The present study examined the repeatability of brush-evoked allodynia and spontaneous pain in patients with peripheral neuropathy. The results revealed very good repeatability for brush-evoked pain intensity, and a significant positive correlation was demonstrated between spontaneous ongoing pain and the mean total brush-evoked pain intensity.

Patients with neuropathic pain across different etiological diagnostic entities frequently suffer from dynamic mechanical allodynia, which is sometimes as troublesome as the ongoing pain. When assessing mechanical allodynia, a valid and reliable stimulation technique is needed. The present study aimed to evaluate the repeatability of brush-evoked allodynia in nine patients with spontaneous ongoing pain and dynamic allodynia due to peripheral neuropathy. In addition, the study addressed the relationship between the intensity of spontaneous ongoing pain and the total brush-evoked pain intensity.

A brush stimulus was applied by lightly stroking 60 mm of the skin four times repeatedly with an inter-stimulus interval of 10 min; the patients continuously rated the intensity and duration of brush-evoked allodynia. The procedure was repeated on four days during 1 month – on day 1, 3, 28, and 30. The authors evaluated the variation between repeated assessments on each day and between the four assessments. Results showed an excellent repeatabilty for both parameters (i.e. the variation within days and the variation between days). In addition, the mean intensity of spontaneous ongoing neuropathic pain and the mean brush-evoked intensity had a significant positive correlation. The findings demonstrated that the semiquantitative technique used for evaluation of brush-evoked allodynia in this study is a tool with good repeatability and can be used as the method of choice for short- and long-term evaluation of dynamic mechanical allodynia in future treatment studies.

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Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: a randomized open trial

Keskinbora K, Pekel AF, Aydinli I.
J Pain Symptom Manage 2007;**34**:183–9.

Patients with cancer pain receiving opioid therapy were randomized to one of following two protocols for the treatment of neuropathic pain: gabapentin titrated according to pain response while keeping the opioid dose constant or continuation of opioid monotherapy according to the treatment ladder approach. The results of this analysis suggest that the combination of gabapentin with opioids provides better pain relief than opioid monotherapy. Moreover, the incidence of side effects was lower in the gabapentin combination group than in the group receiving opioid monotherapy.

In cancer patients, neuroactive or neuromodulatory non-opioid adjuvant drugs are often required to complement opioid therapy for the management of neuropathic pain. Anticonvulsants are commonly used as adjuvant analgesics. There are several reports on the use of gabapentin as an adjuvant analgesic with opioid therapy for the treatment of neuropathic cancer pain. Previous data indicate that the combination of gabapentin and an opioid may result in additive effects [1]. The purpose of this randomized, single center, open study was to compare the efficacy and safety of a combination of gabapentin and an opioid with opioid monotherapy for the treatment of patients with neuropathic cancer pain. A total of 75 patients participated in the study; the subjects were randomly allocated to one of two groups: gabapentin as an adjuvant to ongoing opioid treatment (GO group), or opioid treatment alone (OO group). In the GO group, the initial gabapentin dose was 100 mg three-times daily for patients aged ≥60 years and 300 mg three-times daily for patients aged <60 years. Gabapentin was titrated to 3600 mg/day according to the pain response, while the opioid dose was kept constant. In the OO group, opioid doses were increased incrementally according to the World Health Organization ladder until sufficient pain relief was obtained. Side effects in both groups were monitored. Assessments of pain and other symptoms were performed on days 4 and 13. The results showed that, at baseline, mean pain intensity for burning and shooting pain was similar in both groups. These decreased in both groups; however, in the GO group, the mean burning and shooting pain scores at day 4 and 13 were substantially lower than in the OO group. Moreover, the rate of allodynia in the GO group significantly decreased at day 4 and day 13, while in the OO group the decrease in allodynia reached a statistical significance at day 13 but not at day 4. The incidence of side effects in the GO group was significantly lower than in the OO group. These results suggest that the combination of gabapentin with opioids provide better pain relief than opioid monotherapy.

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RHEUMATOID ARTHRITIS

Beneficial action of statins in patients with rheumatoid arthritis in a large observational cohort

Okamoto H, Koizumi K, Kamitsuji S et al.
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This epidemiological study examined the association between statins and rheumatoid arthritis in a large cohort of patients. At 6-month follow-up, patients who used statins had significantly lower disease activity compared with those who did not use statins, with decreased C-reactive protein levels, tender and swollen joint count, pain intensity, and physician-rated disease severity. These findings suggest that stains may have promising effects in rheumatoid arthritis treatment. Future studies on the anti-inflammatory mechanisms of statins may be warranted.

Rheumatoid arthritis is a progressive and degenerative disease that causes inflammation of the synovial tissue and

joint destruction, leading to disability and pain. While statins are currently a first-line drug for hyperlipidemia, they have received recent attention for their potential benefits in treating rheumatoid arthritis [1–4]. Atorvastatin use is correlated with lower C-reactive protein (CRP) levels [1], potentially through the inhibition of proinflammatory cytokines [2–4]. These preliminary data suggest that statins may alleviate rheumatoid arthritis-associated inflammation. The main goal of the present observational study was to examine the relationship between statins and rheumatoid arthritis disease activity (DA).

A large database of 7512 patients enrolled in a single-site observational study in Tokyo, Japan was analyzed to evaluate the effects of statins in rheumatoid arthritis patients. Participants completed clinical and laboratory measurements of demographical, medical, and disease-, treatment-, pain-, and disability-related variables. Data was extracted at two time points (April and October 2003) from 4152 rheumatoid arthritis patients. In the sample, 83.3% of participants were female (mean age 58.4 years), and 6.7% (n=279) were using statins. It was found that 49% of patients were using pravastatin (mean daily dose 6.4 mg), 23% atorvastatin (mean daily dose 17.3 mg), 18% simvastatin (mean daily dose 7.2 mg), and 10% fluvastatin (mean daily dose 12.5 mg. Nonparametric tests showed that statin use was strongly associated with lower DA, including lower CRP levels, pain ratings, and physician global assessment of DA. In addition, statin use was positively associated with older age, longer disease duration, and higher rate and dosage of corticosteroids – corticosteroid use in patients using statins was 62.0% versus 52.5% in those not using statins. When the effects of corticosteroid dose were controlled, statin use significantly correlated with a lower DA P value and a dose–response relationship between corticosteroid use and serum cholesterol levels was observed.

This observational study concluded that patients with rheumatoid arthritis who used statins had lower DA than those who were not taking this drug. Study strengths included the large sample size and the novel nature of this research topic. The investigation may have benefited from a greater elaboration on the methods used in the study, in particular, why the relationship between corticosteroid dose and cholesterol levels was evaluated. In addition, more details on the study measures and rationale for their use would have been helpful. These findings indicate that the role of statin use in rheumatoid arthritis is an area for additional research.

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MISCELLANEOUS

A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain

Goldberg RJ, Katz J.
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The authors of this article summarized a meta-analysis of 17 randomized, controlled trials that investigated the efficacy of polyunsaturated fatty acids (PUFAs) to relieve pain in patients with inflammatory joint pain. The investigators assessed results of six separate outcomes: patient- and physician-assessed pain, duration of morning stiffness, number of painful or tender joints, Ritchie articular index, and consumption of nonsteroidal anti-inflammatory drugs. The results showed that PUFA supplements represent an attractive adjunctive treatment for joint pain.

Dietary constituents and supplements that can be used as potential therapeutic agents in the treatment of pain include dietary soy, sucrose, anthocyanins, and polyunsaturated fatty acids (PUFAs). Dietary supplementation with long chain PUFAs, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) may be an effective adjunct to nonsteroidal anti-inflammatory drug (NSAID) therapy. In humans, supplementation with EPA/DHA increases the incorporation of PUFAs into phospholipids, and mediates an anti-inflammatory effect. Recent findings indicate that this anti-inflammatory response is due to EPA/DHA-derived novel anti-inflammatory lipids, such as resolvins and protectins.

The purpose of this study was to conduct a meta-analysis to address the pain-relieving effects of EPA/DHA in patients with rheumatoid arthritis or joint pain secondary to inflammatory bowel disease or dysmenorrhea. Using a search of relevant databases, the authors identified 60 potentially usable articles; however, 43 studies were excluded for various reasons, which left 17 articles that reported randomized, controlled trials available for the meta-analysis. The results show that EPA/DHA supplementation substantially reduces scores of patient-assessed pain, duration of morning stiffness, number of painful or tender joints, and consumption of NSAIDs. The analysis does not

reveal considerable differences in physician-assessed pain or Ritchie articular index. Overall, the findings indicate that PUFA supplementation represents an attractive adjunctive treatment for joint pain; however, the authors point out that further studies are required to optimize the analgesic effects of EPA/DHA in patients with such pain as well as other types of chronic inflammatory pain.

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Chronic intrathecal infusion of minocycline prevents the development of spinal-nerve ligation-induced pain in rats

Lin CS, Tsaur ML, Chen CC et al.
Reg Anesth Pain Med 2007;**32**:209–16.

This study examined the effect of a continuous intrathecal infusion of minocycline – a second-generation tetracycline – on neuropathic pain and on the activation of microglia in spinal nerve ligated rats. Recently, it was shown that microglial activation is a component of the mechanisms underlying the development of neuropathic pain in a spinal nerve ligation model. Results of the current study demostrated a preventive effect of minocycline on the development of neuropathic pain induced by spinal nerve ligation, as well as on microglial activation associated with nerve ligation.

Recent studies have shown that spinal glial cells are activated in various animal models of pain [1]. Glial cells are likely to become activated by various substances linked to the transmission of nociceptive impulses in the organism. The activation of spinal glial cells is causally related to pathological pain states, and it has been shown that pharmacological inhibition of glial activation prevents the development of neuropathic pain.

The purpose of this study was to examine the effects of continuous intrathecal minocycline, a second-generation tetracycline, on microglial activation and the development of neuropathic pain after spinal nerve ligation in rats. The authors performed spinal nerve ligation in two groups of adult male rats under general anesthesia, while one group received a sham operation. A continuous intrathecal infusion, which consisted of an osmotic infusion pump filled with either saline or minocycline, was connected to the intrathecal catheter for 7 days after surgery. The rat hind paw withdrawal threshold to von Frey filament stimuli and withdrawal latency to heat stimuli were determined before and on days 1–7 after surgery. Spinal microglial activation was assessed via immunoreactive methods on day 7 after the surgery. The results indicated that continuous intrathecal infusion of minocycline can prevent the development of mechanical allodynia and thermal hyperalgesia induced by spinal-nerve ligation in rats. The infusion of minocycline additionally inhibited nerve-ligation-induced activation of spinal microglia.

These findings support the newly emerging role of microglial activation as a contributing factor to the development of neuropathic pain, and may be considered as a potential strategy for prevention of neuropathic pain in clinical settings in the future. However, further studies are needed to examine the safety and efficacy of minocycline.

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Highlights from the 26th Annual Congress of the European Society of Regional Anaesthesia and Pain Therapy 2007

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The 26th Annual Scientific Congress of the European Society of Regional Anaesthesia and Pain Therapy was held at the brand new Convention Center in Valencia, Spain from September 12–15, 2007. A diverse array of programs, symposia, and lectures featured at this meeting. The main themes were focused on postoperative pain outcome, the advantages of continuous nerve blocks, the roles of an acute pain service and a labor pain service, targeted neuromodulation and pulsed radiofrequency in neuropathic pain treatment, and interventional pain management techniques. This meeting report presents a summary of a number of these presentations that the current author found to be among the most interesting in the ongoing field of pain therapy.

Postoperative outcome – does the choice of analgesic technique matter?

A significant number of patients continue to experience unacceptable levels of pain after surgery. This pain may result in several deleterious effects on neuroendocrine function, respiration, gastrointestinal function, circulation, and autonomic activity. Patients who undergo major thoracic and abdominal surgery are particularly affected. Severe postoperative pain is a risk factor for the development of chronic pain after surgery. The increased costs of newer analgesic techniques are justified because of better outcomes, including reduced morbidity and shorter periods of hospitalization.

Narinder Rawal (Örebro University Hospital, Örebro, Sweden) discussed the results of various trials of postoperative outcome. A summary of his talk is presented here. A meta-analysis of 15 randomized controlled trials (RCTs), with a total of 787 patients, found greater analgesic efficacy and patient satisfaction with patient-controlled analgesia (PCA; intravenous opioid therapy) compared with conventional analgesia, without an increase in side effects [1]. Another meta-analysis of 32 RCTs consisting of 2072 patients reported that PCA was associated with improved analgesia, reduced risk of pulmonary complications, and greater patient satisfaction scores, compared with conventional opioid therapy; however, the length of hospital stay was not reduced [2].

The role of perioperative epidural anesthesia and analgesia has been evaluated in a meta-analysis of 141 trials and 10 000 patients. The overall mortality rate was reduced by 30% and the risk of deep venous thrombosis, pulmonary embolism, and pneumonia reduced by 40–55% [3]. Dr Rawal discussed how postoperative myocardial infarct is an important predictor of poor outcome after major surgery and can be found in 40% of high-risk patients. A thoracic epidural decreases the severity of myocardial infarction, blocks sympathetically mediated coronary vasoconstriction, and improves coronary flow to the subendocardial areas. A meta-analysis by Beattie et al. has shown that the use of thoracic, but not lumbar, epidural analgesia significantly decreases the incidence of postoperative myocardial infarction [4]. Pulmonary complications (hypoxemia, pneumonia, atelectasis, and respiratory failure) are important causes of postoperative morbidity and mortality, and may contribute to a prolonged stay in hospital. A meta-analysis by Ballantyne and colleagues showed a decrease in the incidence of atelectasis and respiratory complications [5]. In addition, delays in postoperative gastrointestinal function can contribute to increased postoperative pain, pulmonary dysfunction, and delayed wound healing. In a meta-analysis of nine trials, Park et al. found that when the epidural catheter tip is located to the dermatomes of surgical incision, an earlier return to normal gastrointestinal function is seen [6]. Even patients who underwent abdominal surgery displayed reduced gastrointestinal paralysis when epidural local

anesthetics were used in comparison with that observed when systemic or epidural opioids were employed. There is overwhelming evidence to suggest superior analgesic efficacy of epidural local anesthetics; however, the advantages of epidural analgesics have to be balanced against their risks and costs. Patients undergoing lower-extremity orthopedic surgery can be treated equally as effectively, but with fewer potential severe complications, by the less invasive and less expensive perineural techniques. Indeed, upper- and lower-extremity plexus blocks of the distal nerve are very successful and their analgesic duration can easily be extended by the use of catheters.

Incisional catheters allow the perfusion of local anesthetic to the desired area, resulting in patients having substantially reduced pain scores and/or opioid consumption. In the future, the success of peripheral blocks and incisional catheters may reduce the need for epidural catheters.

Multimodal analgesia (i.e. the use of nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, or paracetamol in combination with intravenous opioid PCA) provides additive or synergistic effects and reduces the required dose of individual analgesics, thus decreasing the potential for adverse effects from each drug.

Advantages of continuous nerve blocks

Patrick Narchi (Hôpital Purpan, Toulouse cedex 9, France) discussed how modern techniques of analgesia, such as a perineural catheter, allow for intense physiotherapy to treat painful exacerbations. Pain control during patient mobilization is one of the principal goals after orthopedic surgery, and brachial and lumbar plexus blocks are highly effective for managing intense postoperative pain after upper- and lower-extremity surgery. Several approaches were discussed, including various techniques, drugs, and delivery systems. Logistical problems related to pain relief at home using continuous regional anesthesia catheters for long-lasting pain relief can be easily solved. Superior analgesia and a less frequent incidence of opioid-related side effects are possible with continuous perineural infusions.

Role of acute pain service

Dr Rawal also stressed that acute pain services play a role in the development of cost-effective, evidence-based pain treatment strategies for different surgical procedures. Postoperative patients should receive the pain treatment they are entitled to, without any delay. It is necessary that the hospital management realizes that good postoperative pain relief not only results in less experience of pain, and hence more satisfied patients, but also in less complications (and thus reduced costs), and less impact on claims. Overall, a good degree of acute postoperative pain relief results in a significant cost saving. However, above all, there is clear evidence to suggest that intense postoperative pain relief prevents patients' surgical pain becoming chronic pain after surgery [7]. Pain relief by anesthesiologists is only one aspect of acute pain care in these patients. Multimodal postoperative rehabilitation and fast-track surgery depend on surgical issues such as the early removal of drains and tubes (in particular, nasogastric tubes should be removed as early as possible in the immediate postoperative period), and early mobilization. Intravenous fluids should be restricted, while enteral nutrition should be started early. Other factors, such as the extent of tissue trauma, duration of surgery, intraoperative complications, and the skills of the surgeon, have to be evaluated as they all may be a risk factor for the postoperative outcome of the patient.

Role of a labor pain service

Alex Sia (KK Women's and Children's Hospital, Singapore) gave an overview of the use of pain relief techniques in obstetrics. Labor pain can be severe with potential negative consequences to both the mother and baby and a maternal request should be sufficient justification for pain relief during labor. Several international colleges of obstetrics and gynecology believe that, of all the various pharmacological methods used for pain relief during labor and delivery, the lumbar epidural block is the most effective and least depressing method, allowing for an alert, participating mother. Dr Sia discussed the initiation of labor analgesia (combined spinal epidural [CSE] vs. epidural), the advantages of low versus high doses of local anesthetic epidural block solutions, and various modes of delivery, such as patient-controlled epidural analgesia (PCEA) – in automated intermittent bolus doses – and computer integrated-patient-controlled epidural analgesia (CI-PCEA) techniques. She concluded that a CSE provides a faster onset of effective pain relief, decreases the requirement for supplementary analgesics, and increases maternal satisfaction without increasing maternal or fetal side effects, or affecting obstetric outcomes. Maintenance of epidural pain relief should consist of low doses of motor blockade that provide a local anesthetic effect and allow adequate pain relief without clinically significant effects on motor function. Individualizing treatment with PCEA or CI-PCEA according to a woman's pain level and stage of labor can improve obstetrical outcomes and maternal satisfaction.

Targeted neuromodulation

Peripheral neuromodulation (and also spinal cord stimulation) has been practiced since the early 1960s, mainly for the treatment of neuropathic pain with mononeural distribution. Since that time, many modifications have been

described that can simplify the technique. Theodor Goroszeniuk (Guy's & St. Thomas' NHS Foundation Trust, London, UK) discussed the application of single-shot, direct stimulation at single nerves and plexuses in the diagnosis and treatment of chronic, mainly neuropathic, pain. Targeted stimulation comprehensively covers all components of subcutaneous stimulation, as well as the stimulation aimed at deeper non-dermatomal areas by other modalities such as needle and external stimulation. The principle of targeted neuromodulation is to deliver an electrical field at the epicenter of the painful area with the aim to cover the whole, or nearly all, of the effected terminal receptors by placing a quad or octo lead – subcutaneously targeted – at the site of pain.

The use of a simple stimulating monoelectrode has opened up a very inexpensive, but effective, modality for neuromodulation tests in patients with chronic pain conditions. Several modifications since then have been realized. The stimulating electrode is very promising due to its effectiveness, simplicity, and low potential complication rate. The indications for the method include neuropathic pain of different etiologies, scars, abdominal pains, angina, nociceptive pain, and low back pain; more indications are likely to follow. Miniaturizing the existing technology will be adopted to further the use of this technique. In the present author's opinion, input from basic sciences is needed to explain the exact mechanism of action, and many theories are currently under investigation. A comparison of the effects of targeted stimulation, peripheral nerve stimlation, and spinal cord stimulation is clearly required.

Pulsed radiofrequency in neuropathic pain

Jan van Zundert (University Medical Center Maastricht, Maastricht, The Netherlands) discussed the evidence for pulsed radiofrequency (PRF) therapy in neuropathic pain that may result in changes to the neuronal structure, to target the etiology of neuropathic pain. The less neurodestructive nature of PRF is a great advantage over conventional radiofrequency treatment. The use of RF therapy – using a high frequency electrical current applied adjacent to the causative nerve structure – is based on the assumption that thermocoagulation of the nerve fibers will interfere with conduction of nociceptive stimuli.

The most common neuropathic pain syndrome is trigeminal neuralgia and is the most frequently described indication for radiofrequency treatment. The development of PRF treatment, in which a high frequency current is applied in short bursts followed by a silent period that allows the generated heat to be washed out (the output is set for the electrode tip temperature not to exceed the neurodestructive level of 42°C), created interest in this treatment option. Cervical and lumbar radicular pain are well-known indications for PRF therapy. In this presentation, the role of the dorsal root ganglion in radicular pain was discussed, with biological and histological changes and practical issues also highlighted.

Interventional pain management techniques – are they evidence based?

According to Dr van Zundert, in low back pain patients, a specific cause (e.g. herniated disc, spondylolisthesis, discitis, or Bechterew disease) can be identified only 5–10%. The origin of non-specific low back pain can be mechanical (originating from the facet or zygapophyseal joints), discogenic, or from the sacroiliac joint. Treatment usually involves epidural corticosteroid administration and although success rates vary substantially, meta-analysis has shown a reduction in lumbosacral radicular pain. Transforaminal (periadicular/sleeve) infiltration, observed under fluoroscopy, allows for the precise application of corticosteroids into the vicinity of the irritated nerve root, resulting in a massive concentration of the agent at the required site. Success is generally achieved, but complications are frequently reported and consist of sudden-onset paraplegia or parapareses after a nerve root block. The latter might be attributed to the inadvertent penetration and direct intra-arterial injection into small arterial branches that directly supply the spinal cord.

Interventional pain management techniques for cervical zygapophyseal joint pain are efficient for treating patients with chronic pain of the lower cervical facet joints after whiplash. Facet pain was confirmed with double-blind, placebo-controlled local anesthetic blocks, and it was further revealed that multiple lesions of target nerves could provide long lasting pain relief, which was not realized after placebo therapy.

Cervical radicular pain can be treated with corticosteroids and/or RF therapy. A clinical audit showed a positive outcome in 72% of the patients after 2 months and in 33% of subjects after 1 year. The need for pain medication was significantly reduced in the PRF group after 6 months.

Conclusion

Freedom from postoperative pain is a central concern of patients undergoing surgery and alleviation of pain may contribute to improved clinical outcomes. Over the course of the meeting several methods were discussed, but the cornerstone to pain relief is good management, recognition of the problem, early treatment of any pain, and alleviation of any side effects following the operation. Good organization of such an acute pain service needs to include a pain nurse-based model where the role of ward

nurses is upgraded, the maximum acceptable pain scores (measured regularly) need to be defined, and education and audit are required in order to continuously improve the acute pain service. In addition, chronic pain deserves special attention and should be treated in pain clinics as they have many treatment opportunities to offer these kind of patients. Patients deserve pain relief, whether their pain is acute or chronic, due to operations, labor, or chronic pain problems, or whether as a result of inadequate therapy or other conditions, such as malignancies. The number of hospitals offering both acute and chronic pain relief services is increasing – a great benefit to our patients.

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