Pain 3

Treatment of cancer pain

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This is the third in a **Series** of three papers about pain

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In patients with active cancer, the management of chronic pain is an essential element in a comprehensive strategy for palliative care. This strategy emphasises multidimensional assessment and the coordinated use of treatments that together mitigate suffering and provide support to the patient and family. This review describes this framework, an approach to pain assessment, and widely accepted techniques to optimise the safety and effectiveness of opioid drugs and other treatments. The advances of recent decades suggest a future that includes increased evidence-based targeting of specific analgesic interventions within an individualised plan of care that is appropriate throughout the course of illness.

Introduction

Cancer subsumes many diseases, varied illness trajectories, and a rapidly changing therapeutic landscape. The burden of cancer-related illness is high for both patients and families, and symptom distress contributes substantially to this burden. Chronic pain is among the most important of symptoms in terms of prevalence and potential consequences, and integration of best practices for pain management into humane, effective, and affordable cancer care is a key challenge for health-care systems worldwide.

Key messages

- The assessment and management of pain in populations with cancer is best considered as an essential component of the broad therapeutic approach known as palliative care
- Pain assessment should characterise the pain complaint; take into account the status of the underlying disease; clarify the pain in terms of its cause, syndrome, and pathophysiology; and obtain details about other factors that contribute to illness burden
- Pain can be addressed with primary disease-modifying treatment, most often radiotherapy, if this approach is available, feasible, and consistent with the goals of care
- The mainstay symptomatic treatment for cancer pain is opioid-based pharmacotherapy, and all clinicians who provide care to patients with cancer should aim to optimise the positive outcomes from these drugs and minimise the risks associated with both side-effects and outcomes related to chemical dependency (misuse, addiction, and diversion)
- Effective opioid treatment depends on appropriate selection of a drug and route, individualisation of the dose, consideration of so-called rescue dosing for breakthrough pain, and treatment of common opioid side-effects
- The addition of a non-steroidal anti-inflammatory drug to opioid treatment can be helpful, especially in some painful conditions, but the gastrointestinal, cardiovascular, and renal risks of these drugs should be weighed against their benefits on a case-by-case basis
- Adjuvant analgesic drugs, such as glucocorticoids, antidepressants, and anticonvulsants, have many uses as adjuvant analgesics when opioid treatment is not sufficient; clinicians should familiarise themselves with the common indications and agents
- Many non-pharmacological treatments can be used to improve pain control, coping, adaptation, and self-efficacy; mind–body strategies have established benefit and can be used in a restricted but potentially useful manner by non-specialists
- Interventions, including neural blockade and implanted therapies, play a small but important part in the management of refractory pain

In populations with solid tumours, the overall prevalence of clinically significant chronic pain ranges from 15% to more than 75%, depending on the type and extent of disease and many other factors.[1] Many treatment guidelines have been published during the past quarter of a century,[2–10] and few data and an extensive clinical experience suggest that adherence to these guidelines yields satisfactory relief for most patients.[11] Unfortunately, as a result of many barriers to effective treatment, outcomes are not optimum.[12] A review suggested that an average of 43% of cancer patients receive inappropriate care for pain.[13] These data affirm the continuing need for professional education in this area.

This review discusses the management of chronic pain in populations with active cancer. Pain in cancer survivors—patients cured of cancer or living with cancer as a chronic illness—is poorly characterised, and there is no consensus about the therapeutic framework and best practices in this heterogeneous group.

Framework for care

Background

In patients who are medically ill, chronic pain is seldom an isolated problem. Most patients have several ailments, many symptoms, and other concerns.[14] Distress can be worsened by psychological or social factors, or be heightened by spiritual or existential challenges.

Search strategy and selection criteria

This review emphasises assessment and analgesic pharmacotherapy. Each topic was mainly assessed with systematic reviews or selected primary references from within the past 5 years. These references were largely accessed via a search of Medline (1966–2010). Several historically relevant narrative reviews also were included when appropriate and were obtained from Medline or from primary references. Keywords used to search included "cancer pain", "pain assessment", "opioid therapy", "opioid toxicity", "NSAIDs", "adjuvant analgesics", "neural blockade", "neuraxial analgesia", and "mind–body therapy".

Communication between the patient, family, and health professionals can be limited, inaccurate, or constrained by cultural expectations, and this situation can lead to uncertainty about the goals of care, absence of advance care planning, problems in care coordination, or high caregiver burden. Efforts to relieve pain are welcome, but might not adequately improve quality of life or reduce suffering if they unfold separately from the so-called whole-person concerns associated with a serious or life-threatening illness. A broad clinical framework is needed to address these complex needs. This framework, sometimes termed supportive care in oncology settings, is more usefully regarded as part of the emerging international framework for palliative care.

Palliative care is an interdisciplinary therapeutic approach that focuses on comprehensive management of the physical, psychological, social, and spiritual needs of patients with serious or life-threatening illnesses and their families. The model applies throughout the course of the illness and includes interventions that are intended to maintain quality of life, mitigate suffering, and improve coping and adaptation by reducing the burden of illness and supporting communication, autonomy, and choice. Although palliative care practised by specialist teams historically has focused on end-of-life care, the broader framework encompasses care from the time of diagnosis onward. Both generalist palliative care overseen by the primary treatment team and specialist care provided by an interdisciplinary palliative care team should be integrated with other best practices in oncology.[15]

Evidence supporting the effectiveness of palliative care is steadily growing. For example, a recent randomised controlled trial[16] that compared the usual care provided to patients with advanced non-small-cell lung cancer with usual care plus access to a specialist palliative care team found that patients with access to the team had reduced depression and improved quality of life and, remarkably, a 3-month survival advantage despite receiving less aggressive and less costly treatments at the end of life.

Pain assessment

Recognition of the nexus between pain management and palliative care has many important implications. Pain assessment should be regarded as a standard of care[8] and broadened to include other concerns (panel 1). The assessment should clarify both the need for additional evaluation and a rational plan of care. Laboratory testing or imaging might be needed to define the cause or pathophysiology of the pain, clarify the extent of disease, or assess comorbidities. The treatment strategy can include disease-modifying therapy, any of a range of treatments for symptom control, and plans to address the need for improved communication, goal setting, care coordination, concrete services, or family support. Over time, reassessment of pain might revisit these varied recommendations repeatedly.

***Panel 1:* Key objectives of pain assessment in populations with active cancer**

1 To characterise the multiple dimensions of the pain
   - Intensity
   - Temporal features: onset, course, daily fluctuation, and breakthrough pains
   - Location and radiation
   - Quality
   - Provocative or relieving factors
2 To formulate an understanding of the nature of the pain
   - Cause
   - Inferred pathophysiology
   - Pain syndrome
3 To characterise the effect of the pain on quality-of-life domains
   - Effect on physical function and wellbeing
   - Effect on mood, coping, and related aspects of psychological wellbeing
   - Effect on role functioning and social and familial relationships
   - Effect on sleep, mood, vitality, and sexual function
4 To clarify the extent of neoplastic disease, planned treatment, and prognosis
5 To clarify the nature and quality of previous testing and past treatments
6 To elucidate medical comorbidities
7 To elucidate psychiatric comorbidities
   - Substance-use history
   - Depression and anxiety disorders
   - Personality disorders
8 To identify other needs for palliative care interventions
   - Other symptoms
   - Distress related to psychosocial or spiritual concerns
   - Caregiver burden and concrete needs
   - Problems in communication, care coordination, and goal setting

Cause, inferred pain pathophysiology, and syndromes

The analgesic plan of care can be informed by an understanding of the pain's cause, pathophysiology, or syndrome. Although there is no universally accepted classification system for cancer pain,[17] these constructs are clinically meaningful and widely applied. The cause of the pain is a verifiable lesion or disorder that is likely to be sustaining pain through direct tissue injury or a related process, such as inflammation. Once identified, the cause might suggest disease-modifying treatment for analgesic purposes, such as radiation to a bony metastasis, or might redefine the extent of disease.

Inferences about pathophysiology reflect a clinical consensus about the broad types of neural processes that are likely to be sustaining the pain. The basic research that has begun to clarify the pathogenesis of bone pain[18] and pain due to nerve injury[19] demonstrates the complexity of the processes involved and confirms that the clinical classification by inferred pathophysiology is a gross oversimplification. Nonetheless, this classification has become conventionally accepted and is used to rationalise treatment. Pain is termed nociceptive if it seems to be sustained by ongoing tissue injury, either somatic or visceral, or neuropathic if sustained by damage or dysfunction in the nervous

Panel 2: **Chronic cancer pain syndromes**

Related to tumour

Neuropathic syndromes

- Leptomeningeal metastases
- Painful cranial neuralgias
  - Glossopharyngeal neuralgia
  - Trigeminal neuralgia
- Malignant painful radiculopathy
- Plexopathies
  - Cervical plexopathy
  - Malignant brachial plexopathy
  - Malignant lumbosacral plexopathy
  - Sacral plexopathy
  - Coccygeal plexopathy
- Painful peripheral mononeuropathies
- Paraneoplastic sensory neuropathy

Visceral nociceptive syndromes

- Hepatic distension syndrome
- Midline retroperitoneal syndrome
- Chronic intestinal obstruction
- Peritoneal carcinomatosis
- Malignant perineal pain
- Adrenal pain syndrome
- Ureteric obstruction

Somatic nociceptive syndromes

- Tumour-related bone pain
  - Multifocal bone pain: bone metastases, bone marrow expansion (haematological malignancies)
  - Vertebral syndromes: atlantoaxial destruction and odontoid fracture; C7–T1 syndrome; T12–L1 syndrome; sacral syndrome (back pain secondary to spinal-cord compression)
  - Pain syndromes related to pelvis and hip: pelvic metastases; hip joint syndrome
  - Base of skull metastases: orbital syndrome; parasellar syndrome; middle cranial fossa syndrome; jugular foramen syndrome; occipital condyle syndrome; clivus syndrome; sphenoid sinus syndrome
- Tumour-related soft tissue pain
  - Headache and facial pain
  - Ear and eye pain syndromes
  - Pleural pain
- Paraneoplastic pain syndromes
  - Muscle cramps
  - Oncogenic osteomalacia
  - Hypertrophic pulmonary osteoarthropathy
  - Tumour-related gynaecomastia
  - Paraneoplastic pemphigus
  - Paraneoplastic Raynaud's phenomenon

Related to treatment

Chemotherapy

- Painful peripheral neuropathy
- Raynaud's syndrome
- Bony complications of long-term steroids
  - Avascular (aseptic) necrosis of femoral or humeral head
  - Vertebral compression fractures

Radiation

- Radiation-induced brachial plexopathy
- Chronic radiation myelopathy
- Chronic radiation enteritis and proctitis
- Lymphoedema pain
- Burning perineum syndrome
- Osteoradionecrosis

Surgery

- Postmastectomy pain syndrome
- Post radical neck dissection pain
- Post-thoracotomy pain syndrome
- Post-thoracotomy frozen shoulder
- Postsurgery pelvic floor pain
- Stump pain
- Phantom pain

system. Although psychological processes profoundly affect pain expression and consequences, the label psychogenic pain, which refers to a syndrome that is attributed mainly to psychological factors and identified as a psychiatric disorder, is rarely applied in patients with active cancer.

Roughly three-quarters of patients with chronic pain have syndromes that are directly related to the neoplasm; most of the remainder have syndromes caused by an antineoplastic treatment[20] (panel 2). Syndrome recognition can guide additional clinical assessment and treatment, clarify prognosis, allow preventive care, or offer reassurance to the patient who has interpreted the pain as a certain indication of cancer progression.

Management of cancer pain

Treatment of chronic cancer-related pain should be individualised and balance benefits and burdens in relation to the broader goals of care. If the health system includes access to specialist palliative care teams, referral usually is considered when pain is difficult to control, is accompanied by other complex concerns, or occurs in the setting of very advanced illness and short prognosis.[15] Some systems also support access to pain specialists, and patients with refractory pain might be able to access their help as well.

The feasibility, appropriateness, and potential effects of primary disease-modifying treatment should be considered in development of a strategy for pain. If pain is focal and related to mass effect or local destruction by a tumour, radiotherapy can be highly effective, particularly

in bone lesions.[21] Published studies into the potential pain-relieving effects of chemotherapy are complicated by methodological issues, the large number of regimens used, the restricted availability of comparative trials, and other concerns.[22] If clinical observation has supported the conclusion that a partial tumour response can have analgesic consequences, the benefit from which outweighs expected toxic effects, then the desire to palliate pain could be a factor to consider in the decision to offer chemotherapy.

Whether or not primary disease-modifying therapy is possible, a large proportion of patients with pain due to active disease need symptomatic treatments. There are many options (panel 3). Opioid-based pharmacotherapy has been viewed as the most important of these options since WHO posited the so-called analgesic ladder approach more than 25 years ago.[2]

Opioid treatment for chronic cancer pain

Risk management

Although evidence-based clinical guidelines have expanded on the expert opinion originally described in the WHO approach,[3–7,10] much of conventionally accepted practice remains supported by clinical observations only. Existing guidelines need to be continually updated as new information emerges and clinical consensus shifts. An important example is the emerging emphasis on risk management in some countries.

In many countries, access to opioid treatment is limited by governmental regulation intended to prevent misuse. A recent study in Europe identified serious regulatory barriers in some countries[23] and the situation is far more challenging in much of the developing world.[24] The clinical community should continue to advocate strongly for improved access to opioids for legitimate medical purposes, thereby ensuring an adequate supply within a regulatory system that does not discourage or impede appropriate clinical use. At the same time, clinicians have to acknowledge the serious nature of drug misuse and addiction, and the obligation to minimise these outcomes if possible.[25,26] This obligation has taken on great importance in some countries, including the USA, and has been spurred by a troubling increase in prescription drug misuse during recent decades.

The assessment of risk necessitates an understanding of key characteristics.[27] Addiction is a disease with a strong genetic basis that is characterised by craving, loss of control, compulsive use, and continued use despite harm. Addiction might or might not be accompanied by the potential for an abstinence syndrome that defines physical dependence or the loss of drug effect over time that defines tolerance. Addiction is distinct from drug abuse or misuse, which refers to the use of any drug outside of medical or social norms. In the medical setting, misuse behaviours can also be characterised by other descriptors, such as aberrant drug-related behaviour or non-adherence behaviour.[26]

***Panel 3:* Categories of treatments for pain in cancer populations**

Pharmacological
- Opioid analgesics
- Non-opioid analgesics
- Non-traditional analgesics (adjuvant analgesics)

Interventional
- Injection therapies
- Neural blockade
- Implant therapy

Rehabilitative
- Modalities
- Therapeutic exercise
- Occupational therapy
- Hydrotherapy
- Treatment for specific disorders (eg, lymphoedema)

Psychological
- Psychoeducational interventions
- Cognitive behavioural therapy
- Relaxation therapy, guided imagery, other types of stress management
- Other forms of psychotherapy

Neurostimulation
- Transcutaneous
- Transcranial
- Implanted

Integrative (complementary or alternative)
- Acupuncture
- Massage
- Physical or movement
- Others

Universal risk assessment and management is within the purview of all prescribers (table 1) and has the goals of reduction of both individual harm and potential harm to public health. The ability to manage risk also improves expertise in prescription to diverse populations, including those characterised by comorbid substance-use disorder.

Principles of prescribing

The goal of long-term opioid treatment is to provide sustained, clinically meaningful relief of pain with side-effects that are tolerable and an overall benefit to quality of life. Guidelines based on limited evidence and expert review[2–7,10] provide a rationale for the selection of drug and route of administration, dosing, and side-effect management.

Drug selection

The so-called pure μ-agonist opioids are conventionally selected for cancer pain (table 2). Important exceptions are pethidine and dextropropoxyphene, which are not recommended because of their potential for adverse effects.

	Goals	Strategies	Comments
Stratification of risk	To clarify the likelihood of future aberrant drug-related behaviour	Regard as high risk if: history of alcohol or drug misuse; family history of alcohol or drug misuse; or major psychiatric disorder. Other factors that suggest risk: cancer associated with heavy alcohol use or smoking; current heavy smoking; young age; history of automobile accidents, chronic unemployment, poor support system Factors that can mitigate risk: poor performance status; restricted prognosis; active recovery programme	All patients should undergo risk assessment and stratification; although many questionnaires have been developed to predict aberrant behaviour or addiction, the clinical assessment is generally used in practice
Structuring of treatment commensurate with risk	Practices to match monitoring with risk, and when needed to help patients maintain control	Strategies include: use of drug monitoring (eg, urine drug testing); small amounts prescribed; no use of short-acting drugs; use of one pharmacy; pill counts at time of visit; compulsory consultations	The decision to implement one or more of these strategies is a matter of clinical judgment
Assessment of drug-related behaviours over time	Track drug-use in tandem with all relevant outcomes	Monitor: drug-related behaviour—eg, need for early refills, obtaining several prescriptions, etc; pain relief; adverse drug effects; effect of drug on other outcomes	Broad monitoring of outcomes is consistent with integration of pain management into a palliative care model
Response to aberrant drug-related behaviours	Clinician compliance with laws and regulations; identification of patients needing additional management	If the patient engages in aberrant drug-related behaviour: reassess and diagnose (addiction, other psychiatric disorder, pseudoaddiction, family issues, criminal intent) If diversion into the illicit marketplace is discovered, stop prescribing Otherwise, restructure treatment to improve control and obtain consultative help as needed	Even advanced illness does not free the clinician from the requirement of compliance with laws and regulations
Documentation and communication	Risk assessment and management should be viewed as integral to safe and effective prescribing	Document: plan for monitoring and education of patient and family; monitoring of drug-related behaviour on a regular basis; response should aberrant behaviour occur	Open discussion of the need for universal risk management with other clinicians is valuable to reduce the risk of stigmatising patients

Table 1: **Principles of risk management during opioid treatment for pain**

Although buprenorphine, a partial μ-receptor agonist and κ-receptor antagonist, and centrally acting drugs with mixed mechanisms, such as tramadol and tapentadol, can be used, the pure μ-agonist drugs are more familiar and offer greater dosing flexibility.

Codeine and morphine were selected for the original WHO analgesic ladder, but there is no pharmacological rationale for this preference, especially in view of the genetically established variation in the effects of codeine[28] and the potential effect of morphine metabolites in patients with renal impairment.[29] Much experience with sequential opioid trials, or opioid rotation, emphasises the importance of individual differences in the response to the various opioid drugs[30,31] and suggests that the most favourable opioid in an individual cannot be predicted. The important principle is that treatment can be initiated with any of the commonly used pure μ-agonist drugs and the clinician should be prepared to switch, if necessary, to identify the drug that provides the best outcomes.

The WHO analgesic ladder approach selects different opioids on the basis of moderate (eg, codeine) or severe (eg, morphine) pain intensity.[2] Although common practice is still to follow this recommendation, any of the single-entity, pure μ-agonist drugs, such as morphine or oxycodone, can be prescribed at doses low enough to be safe for the management of moderate pain—effectively eliminating the second rung of the analgesic ladder.[32]

In some countries, methadone has been used increasingly for pain. This drug has a unique pharmacology that has to be understood to encourage appropriate use and reduce risk.[33] Several properties might be highly favourable. Methadone has a fairly long half-life, which allows effective dosing at a 6–8 h interval in most patients, and its cost relative to other opioids is low. It lacks active metabolites, which suggests the potential for more reliable effects in the setting of renal failure compared with other drugs, and its accepted effectiveness in mitigation of craving in those with addiction encourages its use when patients with substance-use disorders develop cancer pain. When administered after treatment with another opioid, its potency increases,[30] and observational studies suggest that most patients benefit when an unsatisfactory regimen is rotated to methadone.[34] Although controlled trials have not been able to confirm that methadone has benefits in cancer pain that exceed those of other opioids,[35,36] favourable clinical observations by experienced clinicians,[34] and low cost, have encouraged increased use.

With rising use has come increasing concerns about toxic effects of methadone, particularly in populations with chronic non-cancer pain.[37] These concerns suggest the need for increased education of clinicians and caution in the use of this drug for cancer pain. Although the half-life of methadone averages about 24 h, it is highly variable, ranging from half a day to almost a week. With steady-state concentrations in blood approached after five to six half-lives, effects should be monitored for a fairly long period after the dose is changed to anticipate delayed toxic effects with unintentional overdose. The increased potency after a

	Equianalgesic doses	Half-life	Duration	Comments
Codeine	200 mg PO	2–4 h	4–6 h	Sometimes used for moderate pain
Hydrocodone	30 mg PO	3–4 h	4–8 h	Used for moderate pain in a combination product containing a non-opioid
Morphine	10 mg IM/IV/SQ; 20–30 mg PO	2–3 h; 2–3 h	3–4 h; 3–6 h	Standard for comparison for opioids; several routes available
Modified-release morphine	20–30 mg PO	2–3 h	8–12 h	..
Sustained-release morphine	20–30 mg PO	2–3 h	12–24 h	..
Hydromorphone	1·5 mg IM/IV/SQ; 7·5 mg PO	2–3 h; 2–3 h	3–4 h; 3–6 h	Potency and high solubility can be beneficial for patients needing high opioid doses and for subcutaneous administration
Modified-release hydromorphone	7·5 mg PO	2–3 h	24 h	..
Oxycodone	20–30 mg PO	2–3 h	3–6 h	Available as a single entity or combined with aspirin or paracetamol
Modified-release oxycodone	20–30 mg PO	NA	8–12 h	..
Oxymorphone	1 mg IM/IV/SQ; 10 mg PR, 15 mg PO	..	3–6 h; 4–6 h	..
Modified-release oxymorphone	15 mg PO	NA	12 h	..
Levorphanol	2 mg IM/IV/SQ; 4 mg PO	12–15 h; 12–15 h	3–6 h; 3–6 h	With long half-life, accumulation possible after beginning or increasing dose
Methadone	10 mg IM/IV/SQ, 20 mg PO	12–150 h	6–8 h	Can be far more potent than indicated here, presumably because potency of available racemate attributable in part to the d-isomer, a NMDA antagonist that can reverse tolerance and augment analgesia; with highly variable half-life, patients need increased vigilance for weeks, until steady state has definitely occurred; can prolong the QTc interval, and ECG should be checked at doses higher than 100 mg per day
Fentanyl	50–100 µg IV/SQ	7–12 h	1–2 h	Can be administered as a continuous IV or SQ infusion
Fentanyl transdermal system	..	NA	48–72 h per patch	Refer to package insert for equianalgesic dosing guidelines for oral and parenteral medication; not usually recommended for opioid-naive patients in currently available doses; not recommended for acute pain
Transmucosal fentanyl citrate formulations	..	7–12 h	1–2 h	New formulations indicated for the treatment of breakthrough pain; available in various forms, including intraoral, buccal tablet, buccal patch, sublingual, and intranasal formulations; not recommended for opioid-naive patients; starting dose for breakthrough pain should always be one of the lowest doses available, even if the patient is receiving a high dose of a scheduled opioid

PO=by mouth. IM=intramuscular. IV=intravenous. SQ=subcutaneous. NA=not applicable. PR=by rectum. NMDA=N-Methyl-D-aspartate. ECG=electrocardiogram.

Table 2: **Selected opioid analgesic drugs**

switch from another opioid poses another risk of unintentional overdose;[30] this concern has justified the recommendation that rotation to methadone be accompanied by a large reduction in the calculated equianalgesic dose.[31] Finally, methadone prolongs the QTc interval,[38] and in appropriate settings, QTc monitoring is warranted.

Regular administration of an opioid to prevent or minimise chronic pain can be accomplished with a short-acting or a long-acting opioid. In developed countries, long-acting drugs are generally viewed as advantageous, and the options include the modified-release oral formulations, transdermal fentanyl, or methadone. In the USA, new modified-release formulations, such as long-acting oxycodone and morphine, now include so-called abuse-deterrent technology.[39] These formulations incorporate either a mechanical or a chemical strategy to reduce the likelihood that a tablet can be converted into an immediate-release opioid by crushing or dissolving. The objective is to benefit public health by reducing the likelihood of unintentional overdose, and possibly depressing street value sufficiently to mitigate diversion. These benefits have not been established empirically and their effect on management of cancer pain remains unknown.

Drugs for breakthrough pain

With growing recognition of the prevalence and potential negative consequences of breakthrough pain,[40] a short-acting drug is usually offered as needed during regular opioid treatment. Depending on the dose needed and other factors, this drug can be a single-entity oral formulation, such as morphine, oxycodone, hydromorphone or oxymorphone, or an opioid–non-opioid combination product.

Alternatively, breakthrough pain can be treated with one of the new, rapid-onset, transmucosal fentanyl formulations. These drugs are specifically indicated for cancer-related breakthrough pain, were designed to allow rapid absorption through mucosa, and were developed in an effort to address the observed mismatch between the time course of a typical breakthrough pain and the time-action relation of an oral drug. Available fentanyl formulations include an oral transmucosal lozenge, an effervescent buccal tablet, a buccal patch, a sublingual tablet, and nasal sprays; products that use other routes or other lipophilic drugs are in development. Clinical observations and a few comparative trials[41] suggest that the rapid-onset formulations yield faster pain relief and better outcomes compared with traditional formulations, at least for some patients. Although further study will be

needed to assess the safety of these drugs and optimally position them relative to oral agents, consideration of their use is reasonable for patients with severe breakthrough pains that peak quickly and those who do not respond well to oral drugs.

Route of administration

The oral and transdermal routes are used conventionally for chronic pain and alternative routes are considered for specific reasons. The intramuscular route is not used because it is painful and provides no pharmacological advantage, and the rectal route is considered rarely when the oral route is unavailable and treatment duration will be short. Intravenous or subcutaneous infusion is often used in the setting of advanced illness. Continuous subcutaneous infusion can be accomplished with a butterfly catheter inserted under the skin for a week or more and can deliver any drug, or combination of drugs, available in injectable formulations;[42] methadone can produce painful subcutaneous nodules and is not preferred by this route. The addition of hyaluronidase to the infusate can allow high-volume subcutaneous infusion for hydration or delivery of fairly high drug doses. If available, pumps that have a patient-controlled analgesia option can be used to allow treatment of breakthrough pain by this route. If subcutaneous infusion is problematic, long-term intravenous therapy can be accomplished with a peripherally inserted central catheter or an implanted central venous access device, or extended use of intermittent subcutaneous injection.

Properly selected patients can benefit from intraspinal therapy, known generically as neuraxial infusion.[43] A randomised trial comparing conventional analgesic treatment and neuraxial infusion via an implanted programmable pump in patients with cancer found that neuraxial infusion yielded improved analgesia and reduced side-effects.[44] If this option exists, patients with pain refractory to routine systemic treatment should be considered for referral.

Practical considerations in dosing

Individualisation of the dose is the key to optimisation of the outcomes of opioid treatment. The regularly scheduled opioid should be titrated after treatment is initiated and whenever readjustment of the dose is necessitated by worsening pain. Conventionally, dose titration involves an increase in the fixed scheduled dose by 30–100%, or by an amount equal to the average daily consumption of supplemental doses for breakthrough pain during the previous few days. These methods of dose escalation ensure safety as the dose rises. The need for fairly high doses (for example, >200 mg per day of morphine or equivalent) is uncommon, and when this occurs, reassessment of subtle toxic effects, drug-related behaviours, and the burdens associated with the number of tablets or patches should be assessed. If problems in these domains are not evident, dose escalation should continue until there is a favourable balance between analgesia and side-effects, irrespective of dose, or interruption by treatment-limiting side-effects.

Ideally, the interval between dose escalations should be long enough to allow a steady state to be approached. This interval is 2–3 days for the modified-release oral formulations and 3–6 days for the transdermal patch; as noted, it is usually 5–6 days for methadone, but can be much longer. When pain is severe, however, more rapid dose escalation is needed. Indeed, very severe pain can be treated by intravenous bolus injections at very short intervals to eliminate the delay that occurs with absorption after each dose. Although aggressive dosing achieves analgesic blood concentrations quickly, it carries the risk of delayed toxic effects as concentrations continue to rise toward steady state after the dose stabilises. To avoid toxic effects related to this overshooting, monitoring is needed after rapid dose adjustments until steady state is approached; if delayed somnolence or other adverse effects occur, the dose should be adjusted downward.

The dose of the short-acting drug for breakthrough pain should also be adjusted over time to maintain effects. Clinical experience suggests that the dose should remain in the range of 5–15% of the total daily dose. The exceptions are the rapid-onset fentanyl formulations, which have effects at doses that might not be proportional to the fixed schedule dose.[40] A prudent strategy is to begin treatment with these drugs at one of the lowest available doses and then titrate the dose on the basis of clinical response.

Patients who develop treatment-limiting opioid side-effects are poorly responsive to the specific regimen. Some clinical characteristics, such as neuropathic pain, breakthrough pain, addiction, and others predict poor responsiveness.[45] These patients are usually considered for an alternative analgesic strategy (table 3), including opioid rotation.[30] Specific guidelines for opioid switching emphasise safety by incorporating a two-step process to select the starting dose of the new drug[31] (panel 4). The first step involves calculation of the equianalgesic dose from widely accepted tables (table 2), followed by a standard reduction of the calculated dose to account for incomplete cross-tolerance and individual variation; the second step involves additional dose adjustment based on clinical factors.

	Options
Identify a more effective opioid	Opioid rotation
Open the therapeutic window	Increase aggressiveness of side-effect management
Add a systemic or spinal co-analgesic to reduce the opioid requirement	Coadministered NSAID or non-traditional analgesic, or a trial of neuraxial analgesia
Add a non-pharmacological approach to reduce the opioid requirement	Neural blockade, a neurostimulatory approach, or a psychological or rehabilitative treatment

NSAID=non-steroidal anti-inflammatory drug.

Table 3: **Clinical strategies to address poor opioid responsiveness**

Management of side-effects

Effective treatment of side-effects increases the likelihood of a favourable opioid response and is consistent with the goals of a broad strategy for palliative care. Opioid-induced constipation is common and presumably worsened by old age, immobility, poor diet, intra-abdominal pathology, neuropathy, hypercalcaemia, or the use of other constipating drugs.[46] Contributing causes should be minimised, if possible, and symptomatic treatments should be pursued; prophylactic treatment is appropriate in patients with predisposing factors. Management can involve diet changes if appropriate (increased fibre and hydration) and a simple oral regimen using a surfactant, such as docusate, and either an osmotic agent (eg, a poorly absorbed sugar such as lactulose or sorbitol, or polyethylene glycol) or a stimulant cathartic (eg, senna or bisacodyl). Novel treatments with peripherally acting opioid antagonists, such as methylnaltrexone or naloxone, are available in many countries[46,47] and should be considered in challenging cases.

Opioid treatment can cause somnolence or mental clouding, which typically wanes over a period of days or weeks, but is persistent in some patients. Although supporting data are very scarce,[48] some patients have symptoms that can be ameliorated through co-administration of a psychostimulant such as methylphenidate or modafinil. Other opioid-related adverse effects are less common, but are well recognised; the occurrence of nausea or pyrosis, dry mouth, itch, urinary retention, or myoclonus can present other targets for concurrent treatment. Other adverse effects are less well recognised. Opioid-induced hypogonadism is common[49] and raises concerns about the potential for sexual dysfunction, fatigue, accelerated bone loss, and mood disturbance. There is no evidence to guide treatment in cancer populations, but carefully selected patients are considered for hormone replacement.

Long-term opioid treatment also is associated with a syndrome of sleep-disordered breathing, characterised in some cases by a subtype of central sleep apnoea.[50] The prevalence and effect in the cancer population is not known. Assessment should be considered when the clinical scenario suggests that interventions to address disturbed sleep or the risks associated with sleep apnoea would be appropriate.

Opioid-induced hyperalgesia (OIH) has been clearly shown in animal models and has been invoked to account for the anecdotal occurrence of escalating pain in the absence of worsening pathology during opioid treatment.[51] Little is known about its clinical relevance or the extent to which it can be distinguished from other causes of escalating pain.[52] Although clinical observations support the view that OIH is rarely the driving force behind clinical pain, the possibility should be considered when pain worsens in the absence of clearly progressive pathology during aggressive opioid titration, and particularly when tremulousness, confusion, or skin sensitivity occurs simultaneously. When suspected, opioid rotation or the use of a non-opioid strategy for pain control are reasonable to consider.

***Panel 4:* Guidelines for opioid rotation**

Step 1

- Select the new drug on the basis of previous experience, availability, cost, and other factors
- Calculate the equianalgesic dose from the equianalgesic dose table
- If switching to any opioid other than methadone or fentanyl, identify an automatic dose reduction window of 25–50% lower than the calculated equianalgesic dose
  - If switching to methadone, the automatic dose reduction window is 75–90%; rarely converting to methadone at a dose higher than 100 mg per day
  - If switching to transdermal fentanyl, do not do an automatic dose reduction; use the calculated equianalgesic dose included in the package insert
- Select a dose closer to the lower bound (25% reduction) or the upper bound (50% reduction) of the automatic dose reduction window on the basis of how applicable the equianalgesic dose table is to the characteristics of the regimen or patient
  - Select a dose closer to the upper bound if the patient is receiving a fairly high dose of the opioid, is not white, or is elderly or medically frail
  - Select a dose closer to the lower bound otherwise and particularly if switching to a different route using the same drug

Step 2

- On the basis of assessment of pain severity and other medical or psychosocial characteristics, increase or decrease the calculated dose by 15–30% to increase the likelihood that the initial dose will be effective or, conversely, unlikely to cause withdrawal or side-effects
- Assess response and titrate the dose of the new opioid regimen to optimise outcomes

If a supplemental dose as-needed is used, calculate this dose at 5–15% of the total daily opioid dose and administer at an appropriate interval; transmucosal fentanyl formulations are exceptions and always should be initiated at one of the lower doses

Non-opioid and non-traditional analgesic drugs

For patients with active cancer, paracetamol or a non-steroidal anti-inflammatory drug (NSAID) is conventionally used for mild or moderate pain; NSAIDs are usually preferred for bone pain. A recent systematic review concluded that paracetamol and the NSAIDs are efficacious, but there is only equivocal evidence that the combination of the non-opioid and opioid is more effective than an opioid alone.[53]

The decision to administer an NSAID for chronic cancer pain is strongly affected by safety concerns. Most clinicians are aware of the potential for renal, haematological, gastrointestinal, and cardiovascular toxic effects. Research pertaining to gastrointestinal and cardiovascular safety has grown exponentially, is inconsistent,[54,55] and has not focused on patients with cancer. Most of these patients are likely to be at fairly high risk of adverse gastrointestinal outcomes, and baseline cardiovascular risk varies with comorbid conditions. A study that assessed the treatment preferences of experts suggested that high gastrointestinal risk should be

	Examples	Comment
Multipurpose analgesics		
Glucocorticoids	Dexamethasone, prednisone	Bone pain, neuropathic pain, lymphoedema pain, headache, bowel obstruction
Antidepressants		
Tricyclics	Desipramine, amitriptyline	Used for opioid-refractory neuropathic pain, first if comorbid depression; secondary amine compounds (eg, desipramine) have fewer side-effects and might be preferred
SNRIs	Duloxetine, milnacipran	Good evidence in some conditions, but overall less than for tricyclics; better side-effect profile than tricyclics, however, and often tried first
SSRIs	Paroxetine, citalopram	Very scarce evidence, and if pain is the target, other subclasses are preferred
Other	Bupropion	Little evidence for effectiveness, but less sedating than other antidepressants, and often tried early when fatigue or somnolence is a problem
α_2 adrenergic agonists	Tizanidine, clonidine	Seldom used systemically because of side-effects, but tizanidine is preferred for a trial; clonidine is used in neuraxial analgesia
Cannabinoid	THC/cannabidiol, nabilone, THC	Good evidence in cancer pain for THC/cannabidiol; scarce evidence for other commercially available compounds
Topical agents		
Anaesthetic	Lidocaine patch, local anaesthetic creams	..
Capsaicin	8% patch; 0·25%, 0·75% creams	High concentration patch indicated for postherpetic neuralgia
NSAIDs	Diclofenac and others	Evidence in focal musculoskeletal pains
Tricyclics	Doxepin cream	Used in itch; can be tried for pain
Others	..	Compounded creams with varied drugs tried empirically, but no evidence
Used for neuropathic pain		
Multipurpose drugs	As above	As above
Anticonvulsants		
Gabapentinoids	Gabapentin, pregabalin	Used first for opioid-refractory neuropathic pain unless comorbid depression; may be multipurpose in view of evidence in postsurgical pain; both drugs act at N-type calcium channel in CNS, but individuals vary in response to one or the other
Others	Oxcarbazepine, lamotrigine, topiramate, lacosamide, valproate, carbamazepine, phenytoin	Little evidence for all drugs listed; newer drugs preferred because of reduced side-effect liability, but individual variation is great; all drugs considered for opioid-refractory neuropathic pain if antidepressants and gabapentinoids are ineffective
Sodium-channel drugs		
Sodium-channel blockers	Mexiletine, intravenous lidocaine	Good evidence for intravenous lidocaine
Sodium-channel modulator	Lacosamide	New anticonvulsant with very scarce evidence of analgesic effects
GABA agonists		
$GABA_A$ agonist	Clonazepam	Very scarce evidence, but used for neuropathic pain with anxiety
$GABA_B$ agonist	Baclofen	Evidence in trigeminal neuralgia is the basis for trials in other types of neuropathic pain
N-methyl-D-aspartate inhibitors	Ketamine, memantine, others	Evidence scarce for ketamine, but positive experience with intravenous use in advanced illness or pain crisis; little evidence for oral drugs
Used for bone pain		
Bisphosphonates	Pamidronate, ibandronate, clodronate	Good evidence; like the NSAIDs or glucocorticoids, usually considered first-line treatment; also reduces other adverse skeletal-related events; concern about osteonecrosis of the jaw and renal insufficiency might restrict use
Calcitonin	..	Scarce evidence, but usually well tolerated
Radiopharmaceuticals	Strontium-89, samarium-153	Good evidence, but restricted use because of bone-marrow effects and need for expertise
Used for bowel obstruction		
Anticholinergic drugs	Hyoscine compounds, glycopyrronium	Along with a glucocorticoid, considered first-line adjuvant treatment for non-surgical bowel obstruction
Somatostatin analogue	Octreotide	Along with a glucocorticoid, considered first-line adjuvant treatment for non-surgical bowel obstruction

SSRI=selective serotonin reuptake inhibitor. SNRI=selective noradrenaline reuptake inhibitor. THC=tetrahydrocannabinol. NSAID=non-steroidal anti-inflammatory drug. GABA=γ-aminobutyric acid.

Table 4: **Adjuvant analgesic agents in management of cancer pain, by conventional use category**

addressed by use of a selective cyclo-oxygenase-2 inhibitor, such as celecoxib, or a non-selective inhibitor plus a proton-pump inhibitor, and high cardiovascular risk should suggest a role for naproxen; NSAIDs should not be used in the presence of both high gastrointestinal and cardiovascular risk.[56] In view of the medical frailty of many patients with cancer pain, a prudent approach is to view high baseline risk related to renal, gastrointestinal, or cardiovascular disease as a strong relative contra-indication to NSAID administration. Further study in the cancer population will be necessary to confirm these conclusions.

A poor response to an opioid regimen can be managed in some cases by co-administration of a non-traditional

analgesic agent (table 3). These so-called adjuvant analgesics or co-analgesics include many drugs in diverse classes. On the basis of conventional use, the non-traditional analgesic agents can be categorised into multipurpose drugs, drugs specifically used for neuropathic pain, drugs used for metastatic bone pain, and drugs used to relieve the pain and other symptoms of malignant bowel obstruction[57] (table 4). The glucocorticoids, such as dexamethasone or prednisone, are often used in the setting of pain in advanced illness, largely on the basis of favourable clinical observations. First-line treatments for neuropathic pain typically include the gabapentinoids (gabapentin or pregabalin), the analgesic antidepressants (tricyclics or serotonin-noradrenaline reuptake inhibitors), and topical lidocaine; many other drugs are options for refractory pain of this type.[57,58] Multifocal bone pain often is addressed with a glucocorticoid combined with a bisphosphonate,[8,59] and conventional treatment for pain related to inoperable bowel obstruction includes a glucocorticoid, an anticholinergic drug, and the somatostatin analogue, octreotide.[60]

Other treatments for chronic cancer pain

Although most patients with cancer experience substantial benefit when pain and other symptoms are aggressively managed with systemic drug treatments, there is an important role for other modalities (panel 3). Some approaches are considered specifically for refractory pain. Among these are many interventional approaches, which consist of a large and varied group of injections, neural blockade approaches, and implant therapies.[43,61] Coeliac plexus block for pain due to upper abdominal malignancy and neuraxial analgesia techniques for potentially any type of pain are the most widely accepted interventions.

Other strategies—psychological, integrative and rehabilitative—are used by experienced clinicians when available, feasible, desired by the patient, and consistent with the goals of care. Each of these strategies includes an array of specific interventions that vary in complexity and supporting research. Among the most useful are the so-called mind-body approaches, which are classified as both psychological and integrative interventions. Some of these treatments can be offered by the physicians or nurses who provide cancer care if access to a specially trained health professional is restricted, and should be regarded as mainstream adjunctive treatments intended to reduce pain and anxiety, improve coping, and increase self-efficacy. Included among the individual therapies are relaxation training, guided imagery, hypnosis, and biofeedback. Relaxation therapy, for example, trains the patient to engage a so-called relaxation response by repetitive focus on a word, sound, phrase, or body sensation, accompanied by mental focus, and guided imagery trains the patient to recall specific sights, smells, sounds, tastes, or somatic sensations to engender a positive cognitive and emotional state. There is evidence that these strategies can ameliorate pain[62,63] and they hold promise of positive effects on other symptoms and broader quality of life domains.[64] Their efficacy emphasises the importance of cognitions and emotions as mediators of symptom distress and quality of life, and draws attention to the continuing need for empathic communication and compassionate care by all professional staff. Little research has been done into the effects of other psychological, rehabilitative, and integrative therapies. Nonetheless, cancer centres that offer comprehensive care can provide access to these treatments, when available and appropriate, to address these broader concerns and improve self-efficacy.

Conclusion

Although several decades of experience and research have not changed the consensus that opioid-based pharmacotherapy is the mainstay approach for the long-term treatment of chronic pain in populations with active cancer, there have been striking changes in the clinical approach to this problem. With analgesic strategies integrated into a palliative plan of care, there is increasing hope that patients can experience cancer with a minimum of suffering. Nonetheless, the treatments used have very little supporting evidence and there continues to be a pressing need for more research to provide comparative and long-term data pertinent to current treatments and novel treatment strategies for refractory conditions. Efforts to bring cost-effective strategies to resource-poor areas of the world should have equal priority.

Contributors

I was the sole contributor to this paper.

Conflicts of interest

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