The MASCC Textbook of Cancer Supportive Care and Survivorship

Ian N. Olver
Editor

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Preface

The Multinational Association of Supportive Care in Cancer (MASCC) has as its underlying principle that "Supportive Care Makes Excellent Cancer Care Possible." This international group attracts a multidisciplinary group of support care practitioners and researchers to its annual symposia. Over the years it has expanded to having 17 study groups led by key professionals in their fields. More recent developments have seen a focus on survivorship. The groups have not only provided education, networking and the promotion of research but have produced guidelines and research and teaching tools.

With all of that expertise across the world, what better organisation could there be to produce a book on supportive care and survivorship, which spans the management of symptoms and the control of the side effects of treatment? The result is a textbook with authorship by experts from 17 countries. The authors are MASCC members and their colleagues, all of whom have volunteered their time and expertise to produce this comprehensive text.

The topics range from management of broad general symptoms such as pain and fatigue to the very specific details of toxicities affecting the eye. Special consideration is given to children and the elderly, to rehabilitation and to palliative care. The ongoing issues of survivorship embrace the physical, the psychosocial and the spiritual. As such this book will be a resource for people from a broad range of disciplines.

I am most grateful to the Board of MASCC for giving me the opportunity of participating in this exciting project and to work with so many talented experts across the world.

Surry Hills NSW, Australia — Ian N. Olver

Contents

Preface v

Contributors xi

Part I: Introduction

1. **Cancer Symptoms and Side Effects of Treatment** 3
   Ian N. Olver

Part II: General Symptoms

2. **Cancer Pain** 11
   Mellar P. Davis

3. **Cancer-Related Fatigue** 23
   Barbara F. Piper, Karin Olson, and Carina Lundh Hagelin

4. **Palliative Care: End-of-Life Symptoms** 33
   Paul Glare, Tanya Nikolova, and Nessa Coyle

5. **Supportive Care in Elderly Cancer Patients** 45
   Matti S. Aapro

6. **Supportive Care in Paediatric Oncology** 49
   Marianne D. van de Wetering and Wim J. E. Tissing

7. **Quality-of-Life Assessment: The Challenge of Incorporating Quality-of-Life and Patient-Reported Outcomes into Investigative Trials and Clinical Practice** 63
   Richard J. Gralla and Patricia J. Hollen

Part III: Cardiovascular

8. **Cardiac Toxicities of Cancer Therapies: Challenges for Patients and Survivors of Cancer** 73
   Winson Y. Cheung

9. **Malignant Pericardial Effusion and Cardiac Tamponade (Cardiac and Pericardial Symptoms)** 83
   Marek Svoboda

10. **The Vena Cava Syndrome** 93
    Mario Dicato and Vincent Lens

Part IV: Respiratory

11. Pulmonary Toxicity of Therapy 99
Andriani G. Charpidou and Kostas K. Syrigos

12. Management of Respiratory Symptoms in People with Cancer 107
David C. Currow and Amy P. Abernethy

Part V: Endocrine and Metabolic

13. Endocrine and Metabolic Symptoms of Cancer and Its Treatment 117
Rony Dev

Part VI: Reproductive

14. Sexual Problems in Patients with Cancer 127
Andreas Meißner, Charalampos Mamoulakis, Grada J. Veldink, and Jean J. M. C. H. de la Rosette

15. Sterility, Infertility, and Teratogenicity 133
Hele Everaus

16. Menopause Symptoms 145
Debra L. Barton and Sherry L. Wolf

Part VII: Hematological and Cardiac

17. Preserving Cardiac Health in the Breast Cancer Patient Treated with Anthracyclines 161
Neville Davidson

18. Thrombosis and Bleeding in Cancer Patients 171
Wolfgang Korte

19. Lymphedema Care 179
Andrea M. Steely and Patricia O'Brien

Part VIII: Infections in Cancer

20. Infections and Cancer 195
Bernardo L. Rapoport and Ronald Feld

Part IX: Gastrointestinal

21. Cancer Cachexia and Anorexia 205
Neil MacDonald and Vickie Baracos

22. Xerostomia and Dental Problems in the Head and Neck Radiation Patient 213
Arjan Vissink, Fred K. L. Spijkervert, and Michael T. Brennan

23. Dysphagia, Reflux, and Hiccups 223
Amy A. Shorthouse and Rebecca K. S. Wong

24. Nausea and Vomiting 231
Ian N. Olver

25. Mucositis (Oral and Gastrointestinal) 241
Rajesh V. Lalla and Dorothy M. K. Keefe

26. Diarrhea, Constipation, and Obstruction in Cancer Management 249
Lowell B. Anthony

27. Ascites 261
Rohit Joshi

28. Hepatotoxicity and Hepatic Dysfunction 267
Ahmet Taner Sümbül and Özgür Özyilkan

Part X: Urogenital
29. Urological Symptoms and Side Effects of Treatment 281
Ehtesham Abdi

30. Gynecological Symptoms 301
Stefan Starup Jeppesen and Jørn Herrstedt

Part XI: Neurologic and Muscular
31. Central Nervous System Symptoms: Headache, Seizures, Encephalopathy, and Memory Impairment 313
Roxana S. Dronca, Charles L. Loprinzi, and Daniel H. Lachance

32. Neuromuscular Disease and Spinal Cord Compression 321
Roxana S. Dronca, Charles L. Loprinzi, and Daniel H. Lachance

33. Eye Symptoms and Toxicities of Systemic Chemotherapy 333
April Teitelbaum

Part XII: Skin
34. Extravasation 351
Lisa Schulmeister

35. Dermatologic Toxicities 361
Eugene Balagula and Mario E. Lacouture

36. Chemotherapy-Induced Alopecia: Overview and Methodology for Characterizing Hair Changes and Regrowth 381
Elise A. Olsen

Part XIII: Rehabilitation
37. Rehabilitation in Cancer 389
Martin R. Chasen and Paul B. Jacobsen

Part XIV: Survivorship
38. Oral Health and Survivorship: Late Effects of Cancer and Cancer Therapy 399
Joel B. Epstein and Barbara E. Murphy

39. Survivorship: Psychosocial, Physical Issues, and Insomnia 407
Melissa Y. Carpentier, Tammy Weitzmann, Ziv Amir, Grace E. Dean, and Ian N. Olver

40. Spiritual Issues in Supportive Cancer Care 419
Antonella Surbone, Tatsuya Konishi, and Lea Baider

Index 427

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Part I
Introduction

Chapter 1
Cancer Symptoms and Side Effects of Treatment

Ian N. Olver

This is a book to cover the management of the symptoms of cancer and side effects of cancer treatment. The symptoms discussed range from general symptoms to organ-specific symptoms and cover all stages of cancer from the presenting symptoms of the cancer to symptoms that arise in the terminal phase of the illness which require palliation, or symptoms and late effects of treatment which persist post-treatment into the survivorship phase. The authors discuss the management of symptoms which apply to both adults and children.

One unique aspect of this handbook is that it covers the whole patient journey including survivorship. This includes both the late effects of treatment and the psychosocial issues to be managed post-treatment. There is also specifically a section on rehabilitation and another on palliative care.

The authors are members of MASCC (Multinational Association for Supportive Care in Cancer), a multidisciplinary international organisation whose focus is on supportive care and whose membership includes many of the world leaders in that field. The organisation regularly publishes guidelines in symptom control in order to encourage evidence-based practice.

The target audience is the health professional who manages cancer. This includes those from the primary specialties of surgery, radiation oncology, medical oncology, palliative care and rehabilitation medicine as well as from allied disciplines of psychology, social work, physiotherapy, occupational therapy and pharmacy as well as specialist and general nurses. General practitioners who manage many of the symptoms and side effects after treatment will find it a useful reference. The book will also be a helpful resource for medical and allied health students. Finally, with the increasing sophistication of consumers, some will benefit from the greater detail provided in this book if they wish to research beyond traditional resources for patients and carers.

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The Symptoms of Cancer

It is important to become familiar with the symptoms of cancer when it presents and when it recurs, to aid in prompt diagnosis, but also to know when the symptoms are not typical of cancer and other diagnoses must be considered (Table 1.1). The differential diagnosis of the symptoms of cancer includes the side effects of treatment, which can occur at the time of treatment or later, other drugs given to patients including those for symptom control and unrelated illnesses. Symptoms also have both a physical and psychological dimension and so cannot be isolated from the other experiences of the patient with a diagnosis of cancer.

A common feature of cancer-related symptoms is persistence [1]. In the absence of treatment, a cancer-related symptom will persist and often worsen as the cancer progresses. For example, a pain due to an acute back injury or a cough due to an infection would be expected to improve over time because the underlying problem may improve, but that is not the pattern expected if the same symptoms are due to cancer.

Some of the physical symptoms of cancer are general and so this book contains chapters which describe symptoms such as fatigue, insomnia, anorexia, cachexia, delirium, fever and pruritus. Some common symptoms such as pain can be associated with multiple organ systems. There are many symptoms specific to organ systems when the cancer directly affects them either as the site of the primary or due to secondary spread. All the major organ systems, cardiovascular, respiratory, gastrointestinal, urogenital and neurological are associated with specific symptoms. For example, the headache associated with primary or secondary cerebral malignancy is usually due to raised intracranial pressure and so is worst in the morning and progresses over several weeks [2].

Paraneoplastic symptoms are distant effects associated with cancer but not directly due to local pressure from the primary or from metastatic disease. They can be associated with any organ system but are commonly endocrine, neurological, haematological, renal or dermatological. Sometimes a rash, for example, may be the initial manifestation of an

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Table 1.1 How cancers present

Found by screening or incidentally when asymptomatic
Local presentations
Lump
Bleeding
Organ specific, e.g. pain, cough
Systemic symptoms
Weight loss
Fatigue
Fever and sweats
Medical emergency
Spinal cord compression
Superior vena caval obstruction
Bowel obstruction
Hypercalcaemia

internal malignancy [3]. Unfortunately, the paraneoplastic symptom may not resolve with successful treatment of the underlying malignancy.

More generally, the symptoms due to the damage done by a tumour, for example nerve compression, may not reverse if the cancer is treated because the cancer may have caused irreversible cell death. Rehabilitation of the patient with cancer then parallels that which would be employed following other causes of the symptoms in the above example, that is vascular accidents or trauma [4].

Cancers often have predictable patterns of spread which will direct where to look for secondary spread, but will also predict from where symptoms are likely to arise. For example, breast cancer spreads first to the liver, lung, bones and brain [5]. Lung cancer spreads to the liver, brain and bones while colorectal cancer secondaries are most likely to be found in the liver and lungs [6, 7]. Prostate cancer will often cause most of its metastatic symptoms by spreading to the bones, but a subset of prostate cancers spread to soft tissues, often initially to lymph nodes [8]. Conversely, symptoms presenting because of secondaries can provide clues as to the primary sites of the cancer. For example, secondaries in the bone are most likely from prostate, breast, lung, thyroid, adrenal, and renal cancers or myeloma.

The Side Effects of Treatment

It is perhaps easiest to group the side effects of cancer treatment depending on their temporal relationship to the treatment. With surgery, chemotherapy and radiotherapy side effects can be acute at the time of the treatment or late, coming sometimes years after the therapy. This can be illustrated by considering chemotherapy toxicities.

The immediate toxicities of chemotherapy would include extravasation injury as it is being administered or an acute hypersensitivity reaction [9, 10]. A few hours later side effects like emesis can occur, but even that has an acute phase spanning the first 24 h and a delayed phase which starts at the end of the first day and can continue for a week [11]. Furthermore, uncontrolled emesis following chemotherapy can establish a learned response where anticipatory emesis can occur prior to subsequent cycles of therapy. In 10–15 days after chemotherapy, in tissues with constant turnover such as the bone marrow, the mucosa or the hair follicles, the dividing cells that were meant to replace mature cells which had completed their life cycle in those tissues do not do so, because they had been destroyed by the chemotherapy, and so myelosuppression, mucositis and alopecia results [12–14]. The stem cells will be stimulated to produce replacements eventually, but the patient needs the symptoms managed in the interim.

Next come symptoms that are often delayed by weeks or months, and these are the organ toxicities. Often these are due to cumulative damage from each cycle of chemotherapy. These include cardiotoxicity, pulmonary toxicity, neurotoxicity, nephrotoxicity and hepatic toxicity [15–18]. A good example is the cardiotoxicity associated with the anthracylines [19]. Every dose damages the myocardium until finally sufficient damage is done to manifest itself as a reduction in the ejection fraction. This becomes more likely with cumulative doses in excess of 500 mg/m^2, but this varies between patients and depends on factors such as whether there is underlying cardiac disease or whether other cardiotoxic drugs are being administered, including other anticancer agents such as the targeted therapy, trastuzumab. Toxicities such as this are detailed in the chapters on the side effects associated with various organs.

Months to years after the chemotherapy come the late effects. These include organ damage such as encephalopathy, sterility, or the most unfortunate late effect of the treatment, a second cancer [20–22].

Similar temporal relationships between the treatment and side effects are described for radiation therapy. Here the acute effects within the radiation field are most often due to direct cell death which leaves depleted stem cells and progenitor cells and results in denuded tissue, which recovers over time [23]. More general effects such as somnolence and fatigue are due to the release of cytokines by radiation. Subacute effects, are exemplified by pneumonitis when the lung is irradiated, or L'Hermitte's syndrome following radiation to the spine, and occur between 6 weeks and 3 months. Their aetiology is uncertain, but they recover [24]. Late effects which occur months or years after treatment in tissues such as the brain, do not recover. Stem cells are depleted and the microvasculature is damaged, but also collagen is deposited secondary to activation by the radiation of a series of cytokines, ultimately resulting in fibrosis [25].

With the increasing use of multimodality treatment the propensity for different treatments to interact and worsen the

side effects in tissues, must be considered. Including the heart in a radiation field may increase the propensity for later cardiotoxic drugs to exacerbate the damage done. Some drugs, such as gemcitabine will also cause recall reactions of the radiation reaction in a previous field [26].

Differential Diagnoses

The importance of knowing the symptoms of cancers and the side effects of therapy has a practical significance because they form part of the differential diagnosis of a symptom cluster in a patient. Consider, for example, a patient receiving chemotherapy for a metastatic cancer who develops a non-specific symptom, such as somnolence, and on examination is dehydrated. This could be due to progressive disease, perhaps with the development of cerebral secondaries or worsening hepatic disease where nausea may decrease the oral intake. Alternately a patient who becomes neutropenic on treatment may develop sepsis with a fever causing somnolence and dehydration. This requires immediate treatment with broad spectrum antibiotics to avoid septic shock. Other medication which a patient is taking should be scrutinised. The same symptoms of somnolence and dry mouth would fit with the side effects of morphine. Paraneoplastic syndromes may also need to be considered with particular malignancies. For example non-small cell lung cancer or squamous cell carcinoma of the head and neck may be associated with secretion of a parathyroid-like hormone causing hypercalcaemia which could manifest itself with both of these symptoms. Note also that the hypercalcaemia could be from progression of bone metastases. The importance of considering hypercalcaemia, for example, is that even if the underlying cause is difficult to treat, the symptoms may respond quickly to rehydration and bisphosphonates.

It is also important that not every symptom reported by a patient with cancer is automatically considered as due to the cancer or its treatment. Patients may be more susceptible to infections spreading through a community, or can develop common conditions like acute appendicitis. Also, given that the majority of cancers occur in older people, underlying heart or renal problems may be the problem. Separate consideration is given to managing cancers in the elderly where the goals of treatment may be modified by the prognosis of an underlying illness. However, symptom control will always be foremost.

Parallel Care

Cancer is increasingly being treated by multidisciplinary teams because of the need for multimodality treatment. Often, anti-cancer treatment is very good for palliating symptoms. When treated with full doses with curative intent, a partial response to radiotherapy or chemotherapy may not translate into a survival advantage but will often shrink a tumour enough to relieve symptoms by taking the pressure off a nerve root, or relieving the obstruction of a hollow viscus or duct. The use of anti-cancer treatment for palliation requires a balance between the likely efficacy and toxicity of the treatment and the possible duration of each.

Reducing the toxicity of a therapy may mean reducing the dose or duration of therapy, to treat with palliative intent. Often, a single fraction of radiation can provide excellent relief from the pain of bone metastases, for example [27]. Substituting drug regimens can also alleviate side effects. An early example was the decrease in secondary leukaemia after the successful treatment of Hodgkin disease when ABVD (Doxorubicin, Bleomycin, Vinblastine, dacarbazine) was substituted for MOPP (Nitrogen Mustard, Vincristine, Procarbazine, Prednisone) [28]. More recently, the targeted therapies such as Trastuzumab, used in breast cancer, have a much improved toxicity profile as compared to conventional cytotoxic drugs because they spare normal tissues and therefore are better candidates for palliation [29].

The specialty of palliative care uses supportive care drugs to relieve symptoms. Near the end of life, for example, it is said that just four drugs, morphine, midazolam, haloperidol and atropine can alleviate the majority of symptoms. However, symptom control is also required during times when patients are being treated with anti-cancer therapy often since the effects of treatment may take weeks to manifest themselves.

My ideal model of multidisciplinary care for symptom control is parallel care, where the palliative care physicians join oncologists on rounds to help with symptom control and also learn when anti-cancer therapies are best used to alleviate symptoms (Fig. 1.1). The other advantage of this model is that as anti-cancer treatment becomes less relevant, a gradual transition can be made to palliative care without an abrupt change. Patients will have been used to seeing the palliative care team during the time when the treatment was primarily directed at shrinking the cancer and the palliative care team will just become progressively more involved with the patients' management as symptom control becomes the major focus of care.

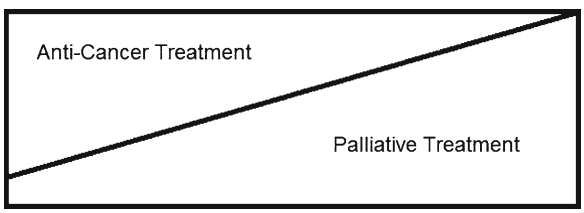

Fig. 1.1 Parallel care

Quality of Life and Spiritual Well-Being

To achieve the optimum quality of life the balance between the efficacy and toxicity of a drug must be optimised, whether it is an anti-cancer or supportive care drug. Scales of measurement of quality of life can range from simple measures of performance status, which equates to the ability to perform the tasks of daily living, to validated scales which measure many domains of life's quality [30]. Often in deciding the balance, physical symptoms predominate but psychosocial issues are being increasingly recognised as having a major impact on well-being [31].

Spiritual well-being has also shown to impact independently on quality of life. In one study which compared spiritual well-being as measured by the FACIT-Sp scale to quality of life, a hierarchical multiple regression showed spiritual well-being to be a significant, unique contributor to quality of life beyond the core domains of physical, social/family, and emotional well-being [32].

Survivorship

Survivorship has several definitions ranging from surviving from the time of diagnosis to survivorship beginning at the time that a complete remission has been achieved [33]. It encompasses issues of adjusting to life with the experience of cancer and its treatment. There may be physical sequelae of the cancer, or late effects of treatment, or distress with anxiety and depression. There may be constant underlying concerns about recurrence of the cancer, particularly after the cessation of active treatment and less frequent monitoring. This is a time of change and relationships can be under stress and previous employment not as satisfying as the patients' priorities have changed. It is recognised that survivorship issues may require management by a multidisciplinary team of health professionals. Recognising the problems and providing ongoing information and support as well as managing physical symptoms and treating psychological problems may all be required.

Conclusions

After the diagnosis of cancer, supportive care is an ongoing need. Symptoms will arise from the cancer or its recurrence and side effects will occur in relation to the treatments offered. Supportive care encompasses managing the physical, psychosocial and spiritual needs of patients at the time of diagnosis, through treatment and once the patients have survived the cancer, or at the time when the end of life is approaching. Children and the elderly have special supportive care needs. The carers and families of patients will also be impacted by a relative or close friend's diagnosis of cancer and will require support as well.

Symptoms can arise from a number of causes which constitute a differential diagnosis. Once the cause of symptoms has been identified a multidisciplinary team of oncologists, allied health practitioners and palliative care specialists will all work together within a patients' social support structure to maximise the patient's quality of life for as long as possible. This book encompasses the many facets of that support.

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Part II
General Symptoms

Chapter 2
Cancer Pain

Mellar P. Davis

Introduction

Cancer pain is a subjective sensation of tissue damage, which has an adverse influence on multiple domains in an individual's life. Severe pain is associated with decreased function, increased interference with daily activities, depression, and anxiety. Pain is a major problem in 25–30% of individuals with newly diagnosed cancer and 70–80% with advanced cancer. Over 500,000 Americans die of cancer each year corresponding to 1,500 deaths per day [1]; therefore, cancer pain is a major problem that cancer specialists face. The lifetime probability of invasive cancer is 45% for men and 38% for women. Among men, prostate, lung, colon, and rectal cancers account for 50% of newly diagnosed cancers. Breast, lung, and colorectal cancers account for 50% of cancers in women. [1] As a result, bone and visceral pain are major pain subtypes clinicians need to manage.

Over 20% of individuals who have cancer pain also have pains related to treatment [2]. Over 60% with chronic pain have breakthrough pain. Most chronic pain is moderate to severe (>7 on a numerical rating scale where 0=no pain, 10=severe pain). Many suffer pain for months. There are 22 commonly classified cancer pain syndromes. These syndromes involve bone and/or joint lesions in 41%, visceral metastases in 28%, soft tissue in 28%, and pain from peripheral nerve injury in 28% [2]. Individuals frequently experience two or more distinct cancer pain syndromes. Nociceptive pain accounts for 72%, visceral pain 35%, and neuropathic pain (mixed or purely neuropathic) is experienced by 48% of individuals [2]. Factors associated with the greatest chronic pain intensity are the presence of breakthrough pain, bone, and neuropathic pain. Individuals less than 60 years and those with poor performance score will experience severe pain more frequently [2].

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Pain and Nociception

Rene Descartes in the 1600s articulated the theory that pain is conveyed by special nerves to the brain [3]. Nerves carry information about tissue damage to the central nervous system (CNS). This is termed nociception, which involves transduction of the electrical signals to the dorsal horn of the spinal cord, transmission through the superficial layers of the dorsal horn, through the contralateral spinothalamic tract or the ipsilateral dorsal column (in case of visceral pain) to the cerebral pain matrix. Nociception is modulated or gated through the spinal cord, brainstem, and supraspinal sites. Individual genetic makeup, prior experiences, physiological status, appraisal of the meaning of pain, mood, and social cultural environment modulate the conversion of nociception to pain [4]. Nociceptive stimuli are capable of eliciting pain but are not equated with pain. Pain is defined as "sensory and emotional experience associated with actual or potential tissue damage" and not tissue damage per se. There is a poor correlation between the degree of tissue damage and pain severity [4]. Acute pain is of short duration and is associated with a high level of physical pathology. Chronic pain (by definition >3–6 months) has low physical pathology because chronic pain tends to be perpetuated by factors that are both pathogenetically and physically remote for the original cause [4]. The degree of tissue injury does not correlate well with the pain severity for two reasons: (1) persistent pain alters the CNS, resulting in facilitatory pain transmission and modulation (neuroplasticity) [5, 6]; (2) affective and cognitive factors associated with unrelieved pain interact with tissue damage and contribute to persistent pain and illness behaviors [4]. Prolonged uncontrolled pain kills [7]. It is therefore important that clinicians manage cancer pain aggressively.

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The Anatomy of Pain

Vanilloid, Sodium Channels, Acid-Sensing Channels

Both A-delta (lightly myelinated) and C nerve fibers (unmyelinated) are "pain fibers," which slowly conduct impulses; they have high thresholds and are often "silent" except with noxious stimuli (Fig. 2.1). Transient receptor potential vanilloid receptor-1 (TRPV-1) respond to heat and capsaicin (found in peppers) (Fig. 2.1) [8]. TPRV-1 receptors are activated by various kinases (protein kinase A, protein kinase C, phosphatidylinositol-3-kinase). These kinases are, in turn, activated by inflammation [9]. Certain sodium channels are also activated or modulated by nerve injury (Na1.3, Na 1.8, Na 1.9), which facilitates nociception. Neuropathic injury increases certain sodium channel expression, channel trafficking in axons, and channel phosphorylation. As a result, surviving sensory nerves develop increasing responsiveness. Certain adjuvants (lidocaine, bupivicaine, tricylic antidepressants, topiramate, lamotrigine, and carbamazepine) block sodium channels and reduce neuropathic pain [10, 11]. Metastases are frequently hypoxic in the center, resulting in an acidic environment. Osteoclasts stimulated by metastatic cells within the bone trabeculae require an acidic environment (pH 4–5) for osteolysis. Both stimulate acid-sensing ion channels (ASIC), which increase sensory afferent depolarization [12].

Bone Pain

Bone pain has a unique spinal cord "signature," which is a combination of neuropathic and inflammatory pain. Continuous pain in addition to activation of ASIC involves local production of prostaglandin and endothelin, which stimulates pre- and postsynaptic afferent nociceptors in marrow spaces. As tumor grows within marrow, it destroys medullary sensory afferents. TPRV-1 receptors are also activated. Bone destruction leads to mechanical instability and periosteum nerve impingement. In the dorsal horn, sensory neurons produce and express C-fos, and astrocytes around secondary sensory neurons are activated and multiple in numbers [12–14]. For this reason, nonsteroidal anti-inflammatory drugs (NSAIDS) and gabapentin (an anticonvulsant commonly used for neuropathic pain) reduce bone pain [15].

Other Allergic Medications

Neurokinins such as substance P are released by peripheral and central sensory neurons and bind to NK-1 receptors. Substance P causes neurogenic inflammation, hyperalgesia, vascular changes (increased permeability and dilatation), and increases prostaglandin production. Bradykinin and certain cytokines (interleukin-1 and tumor necrosis factor alpha) induce hyperalgesia through production of

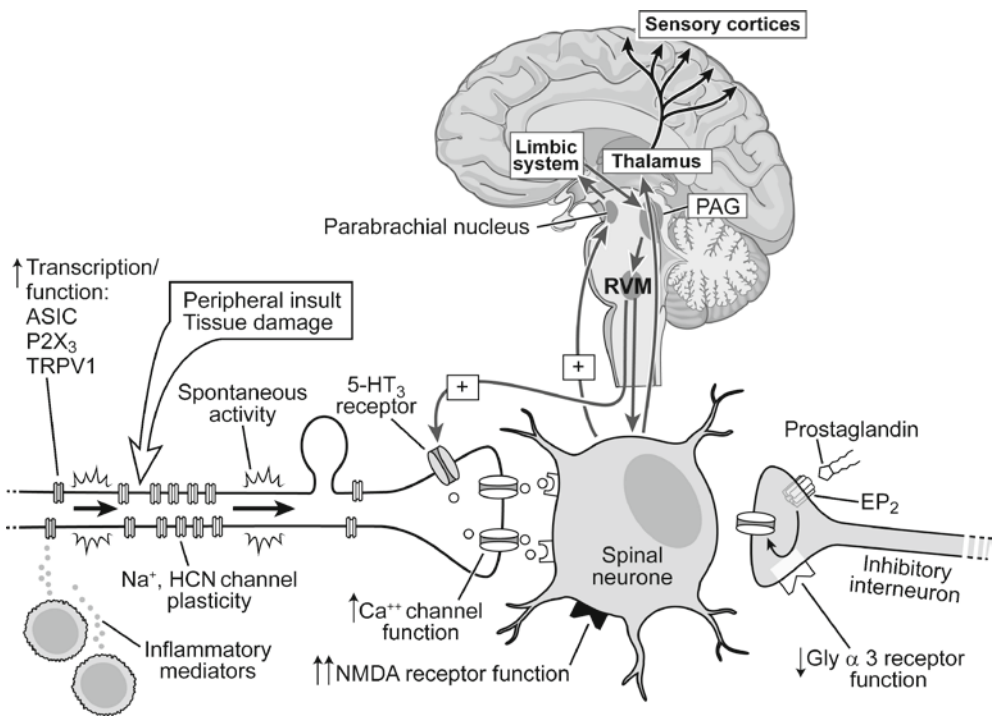

Fig. 2.1 Anatomy of pain

prostaglandins [16]. Nerve growth factors maintain and stimulate sensory nerve regeneration and are avidly taken up by membrane receptors. It also stimulates production of substance P [16].

Calcium Channels, NMDA Receptors

Several types of calcium channels are present in sensory afferents, which facilitate conduction, transmission, and modulation of pain. N-type calcium channels contain alpha$_2$ delta subunits that are targeted by gabapentinoids. *N*-methyl-D-asparate (NMDA) receptors require glutamate (released presynaptically) and glycine to be activated. Activation results in removal of magnesium from the center of the channel, which then allows calcium to enter. NMDA receptors are largely responsible for maintaining pain through "wind up" from repetitive stimulation of wide dynamic range neurons by primary afferents [16]. Increasing intracellular calcium leads to depolarization. NMDA receptors are noncompetitively blocked by ketamine.

A common pathway to pain is by way of prostaglandin (PGE_2) production. PGE_2 binds to multiple receptors (EP_1–EP_4) to activate neurons. PGE_2 alone does not produce pain but is necessary for induction of pain by other mediators, such as histamine and bradykinin. PGE_2 amplifies pain. Prostaglandins are not stored (which differs from other mediators of pain) but are synthesized at the time of depolarization by membrane-bound prostaglandin synthase and cyclooxygenase [17]. Prostaglandin synthesis uses arachidonic acid mobilized from membranes. PGE_2 is released and binds to multiple EP receptors both pre- and postsynaptic. Cyclooxygenase 1 and 2 are the important enzymes in PGE_2 production and are amplified peripherally and centrally within neurons and glia with inflammatory and neuropathic pain. Both NK-1 receptors and NMDA receptors increase cyclooxygenase transcription in the spinal cord [17]. Central nervous system cyclooxygenase is much more responsive than peripheral mechanisms to NSAIDS [17]. NSAID levels are measurable in the CNS within 15–30 min of administration. Certain NSAIDS (ibuprofen, indomethacin, and ketoprofen) have CNS levels that exceed plasma levels [17]. CNS nociceptive transmission inhibition is one of the more important components to NSAID analgesia [18]. Cyclooxygenase 2 is not the only enzyme to be targeted by NSAIDS. Cyclooxygenase 1 in the brainstem (periaqueductal gray) controls A-delta and C fiber-evoked spinal nociception. Cyclooxygenase 1 blockade within the periaqueductal gray (PAG) is important to analgesia [19]. Hence, broad, nonselective NSAIDs should be used to treat cancer pain as there are no trials of cyclooxygenase 2 selective inhibitors in cancer pain.

Central Excitatory Mechanism

Primary sensory afferents synapse on superficial laminae of the dorsal horn (lamina I and II). Secondary afferents cross over to the contralateral lateral funiculus and ascend as the spinothalamic tract. The spinothalamic tract projects to the brainstem, PAG, rostral ventromedial medullary (RVM), thalamus, nucleus tractus solitarius, and medullary reticular formation. These fibers contain substance P and NK-1 receptors [8]. In the deeper laminae of the dorsal horn reside wide dynamic range neurons that respond to a wide variety of painful stimuli. These secondary neurons are activated by repetitive release of substance P and glutamate from primary afferents. These neurons produce a prolonged amplified signal (wind-up) and increase synaptic transmission efficiency [8, 20]. Wide dynamic range neurons are blocked by inhibitory interneurons and monoamines (mainly norepinephrine) [9]. Wide dynamic range neurons also project to the thalamus by way of the spinothalamic tract.

The gate control theory proposed by Melzack and Wall in 1965 involved a descending modulatory/facilitatory system that gated nociceptive transmission through the dorsal horn [21]. The descending limb of the spinobulbospinal loop arises from the PAG, and RVM modulate spinal cord neurotransmission. The locus coeruleus, which contains norepinephrine, is also involved in modulation along with the PAG and RVM. The descending limb facilitates or inhibits nociceptive traffic at the level of dorsal horn, and descends through the dorsal funiculus [9]. Descending facilitation leads to central hypersensitivity (allodynia) and hyperalgesia. This facilitation is mediated by a particular serotonin receptor ($5HT_3$). This receptor is blocked by ondansetron. This may explain why selective serotonin reuptake inhibitors (SSRI's) are less effective than tricyclic antidepressants (TCAs) and selective norepinephrine serotonin reuptake inhibitors (SNRIs) in treating central sensitization and neuropathic pain [9]. Paradoxically, $5HT_3$ receptors are needed for gabapentin to work optimally as an analgesic [5].

Cerebral Pain Matrix

The cerebral cortex "pain matrix" consists of a cerebral cortex medial and lateral pain matrix system. The medial system (prefrontal cortex, insular cortex, cingulate gyrus, and amygdala) is involved in the affective and motivational response to pain. The lateral sensory cortex locates the site of pain. The medial system receives projections from the medial thalamus as well as ascending projections from the brain stem. The sensory cortex receives input from the ventrioposteriolateral thalamus. The spinothalamic tract

projections are devoid of motor neuron projections, which can be interrupted by anterolateral cordotomy without producing motor deficits [16].

Visceral Pain

Visceral sensory afferents travel with abdominal sympathetic afferents arising from internal organs and converge on the celiac plexus within the abdomen or thoracic paravertebral sympathetics in the chest. In the pelvis, the sensory afferents ascend with parasympathetics. Visceral afferents converge with somatic sensory afferent neurons on the dorsal horn. For this reason, somatic referral pain frequently occurs with severe visceral pain. Pain from pancreatic cancer, as an example, is referred to the abdomen, back, or shoulder. Lung cancer will refer pain to the ear, mediastinum, or back [16]. Visceral afferents terminate in lamina I, IV, and ventral horn. Secondary visceral sensory afferents ascend in the dorsal column of the spinal cord rather than the lateral funiculus. Celiac, hypogastric, or splanchnic blocks effectively reduce visceral pain, as does medial myelotomy at the level of the cervical cord (where the dorsal column projections cross over to the contralateral side) [16].

Opioid Receptors

In 1973, morphine was found to bind to particular sites within the brain called "morphine receptors" [22, 23]. Two years later, endogenous opiate peptides were discovered. Three major receptors have been described and are located on peripheral afferents, within the dorsal horn, visceral afferents, within the brain stem, and cerebral pain matrix [22]. Mu receptors are divided into high affinity (mu_1) and low affinity (mu_2) receptors. Mu_2 receptors produce respiratory depression, pruritus, prolactin release, physical dependence, anorexia, and sedation, whereas mu_1 receptors produce analgesia, euphoria, and serenity. Kappa receptors produce analgesia sedation, dyspnea, dysphoria, and respiratory depression. Both mu and kappa produce constipation by binding to receptors on enteral neurons [23]. The actions of delta receptors are not well known but are upregulated when mu receptors are activated and may facilitate pain control. Separate genes are responsible for each of the major opioid receptors; receptor subtypes are produced by mRNA splicing. Opioid receptors are found on pre- and postsynaptic A-delta and C fibers [22]. Activation results in inhibition of calcium channels, reduction in adenyl cyclase, and stimulation of inward rectifying potassium channels [23]. These three mechanisms prevent neuron depolarization and release of substance P and glutamate. Opioids inhibit gamma aminobutyric acid release by interneurons and increase dopaminergic neurotramission and prolactin release. Opioids reduce gonadotropin release from the hypothalamus. This leads to reduced libido and impotence. The rewarding effects of opioids. Are due to release of dopamine in the nucleus accumbens.

There are three majors types of opioids used to treat cancer pain: phenanthrenes (represented by morphine), phenylpiperidines (represented by fentanyl), and diphenyl heptanes (represented by methadone). Tramadol resembles venlafaxine; however, the metabolite, 0-desmethyl tramadol, is a mu agonist. Each opioid binds to receptors with different affinity, producing a different conformation, resulting in a different set of G protein interactions. Some opioids internalize receptors. Morphine causes receptor inactivation without internalization [24]. Opioid receptor affinity and opioid receptor activation are two different properties of opioid ligands. A ligand may poorly activate the receptor (low intrinsic efficacy) but have a high affinity for the receptor [22]. Differences in opioid responses between individuals are determined mainly by differences in opioid receptor pharmacodynamics rather than individual differences in opioid metabolism and clearance (pharmacokinetics) [25]. Low intrinsic efficacy opioids require more opioid receptors to be bound for the same degree of analgesia relative to high intrinsic efficacy opioids. As a result, a "ceiling effect" to analgesia occurs with low intrinsic efficacy opioids at high doses or high pain intensities, which alter equianalgesic ratios. This is one reason why morphine–methadone equivalents change with morphine doses [22]. Opioids have a log linear response with dose; doses are generally limited by side effects, not analgesia [22].

Opioid Tolerance

Chronic opioid exposure leads to an "antiopioid" response, which lasts longer than analgesia. This antiopioid response causes a withdrawal syndrome when opioids are suddenly stopped. Opioid receptors activate various kinases, which in turn phosphorylate NMDA receptors rendering them active. Opioid receptor phosphorylation leads to receptor inactivation and internalization [24]. Go/i proteins switch to G_z proteins with analgesic tolerance causing activation of neurons. Receptor activation is curtailed through phosphorylation of certain regulatory proteins (RGS) [24, 26]. A change in opioids (opioid rotation) may reverse opioid tolerance and enhance pain control. In rare cases, opioid ligands facilitate pain that becomes neuropathic in character. Opioid dose titration will cause increasing pain. Dose reduction in this situation paradoxically reduces pain. The use of certain adjuvant drugs such as ketamine blocks opioid tolerance and facilitates pain control [5, 16, 26, 27].

Cancer Pain Assessment

Pain is a multidimensional experience though most experts believe pain intensity is most important [28] (Table 2.1). Multidimensional pain questionnaires most frequently measure pain intensity, location, and relief; temporal pattern is often not included [28]. Paradoxically, temporal pattern is most important to opioid dosing strategies [29, 30]. Worst pain and average pain severity over 24 h correlates with interference with daily activities. Breakthrough pain episodes are also critical to assessment. Numerical rating scales (0 = no pain, 10 = severe pain) are preferred to 10 cm. visual analog scales. Verbal rating scales or even observations for pain behaviors are helpful in assessing the cognitively impaired and in those suffering from dementia [31].

Pain qualities are reported to be helpful in determining pain mechanisms. "Numbness," "pins and needles," and "burning" pain occurring within an area of sensory or motor deficit is usually neuropathic pain. Bone pain has an ache-like quality and is worsened with movement. Hyperalgesia (increased sensitivity to touch) occurs with inflammatory, bone, or neuropathic pain [31]. Pain qualities contribute to pain interference independent of severity. Deep pain, sharp pain, sensitive, or itchiness qualities interfere with daily activity [32].

Multidimensional scales provide a more comprehensive pain assessment. However, certain tools such as the Brief Pain Inventory may not be sensitive to changes in pain over time. Unidimensional pain intensity scales are validated and sensitive to changes in pain [33]. Pain interference may improve before severity. Pain relief may be experienced while pain intensity is still moderate or severe [31]. Asking "do you think your analgesics need to be increased (or decreased)" allows patients to find their personal acceptable relief as they judge benefits and risks of opioids. Recall fades with time; pain diaries, which include intensity and opioid doses, recorded several times during the day are helpful between clinic visits [31] (Table 2.2).

Table 2.1 Dimension of pain

Intensity
Affect
Interference
Temporal Pattern
Location
Referral
Quality
Duration
Beliefs (attitude/coping)
Pain history (diffuse noxious inhibitory control)
Treatment (worsening/relieving factors)

Table 2.2 Five axes for classifying pain into syndromes

I.	Anatomical Region
II.	Organ system that is producing pain
III.	Temporal characteristics
IV.	Pain intensity and pain onset
V.	Proposed pain etiology

Source: Data from refs. [28, 31, 33]

In those with cancer and reduced cognition a questionnaire with 13 or more items in a multidimensional scale will have a significant number of items left blank by individuals [34]. The Brief Pain Inventory is completed by <60%, whereas a 9–10 item scale has a completion rate of 84% [35]. Verbal scales are better for those on palliative wards, but this reduces the possibility of detecting small but perhaps important differences in pain with treatment [34]. Individuals with a Mini Mental State Examination Score of <24 (0–30) have poor completion rates for multidimensional questionnaires [34].

Pain trials use the sum of pain intensity differences over time (SPID), total pain relief (TOTPAR), side effects, and patient global medication performance (satisfaction, preference) as outcomes [36]. Pain intensity differences of 33% are clinically meaningful [36, 37]. Two types of methods have been used to test analgesics. An anchor method uses the percentage of responders (the number with a 33–50% reduction in pain intensity or 2 point decrease in an 11-point numerical scale) and compares responders in terms of numbers needed to treat NNT. The numbers needed to treat and numbers need to harm (NNH) gauge analgesic efficacy [38]. The second method uses changes in mean intensity of the entire group. These trials can be powered to show differences in group mean intensity scores yet have little clinical relevance. Changes in mean intensity scores can reflect a large response in a few individuals or a small, perhaps clinically insignificant response, in a large number of individuals [38].

Imaging Pain

Skeletal Metastases

Plain radiographs of painful bone sites are recommended for screening purposes. Over 50% of bone cortex has to be destroyed before lesions are visualized by plain radiographs [3]. Bone fracture is unlikely if <50% of the cortex is lost, whereas fracture should be anticipated if >75% of the cortex is lost. Surgeons use plain radiographs to determine the need for surgical intervention for this reason. Bone radiographs are preferred in myeloma over bone scans since

osteolytic lesions are poorly visualized on bone scans [39]. One of the first signs of vertebral metastases visualized by plain radiographs is the "winking" owl sign due to the loss of a pedicle arising from tumor extension from the posterior vertebral body [40].

Skeletal metastases almost exclusively arise from hematogenous spread to red marrow. Bone is more frequently a site of metastases than anticipated based on percent of cardiac output and blood supply [3]. The distribution based on bone scans are: 39% vertebral, 38% ribs and sternum, 12% pelvis, and 10% long bones [3]. Pain is experienced in only a minority of bone metastases. Painful symptomatic vertebral metastases and spinal cord compression occur more often with thoracic spine metastases (70%) than lumbar (20%) or cervical spine (10%) [40]. Bone scan positivity is due to reactive osteoblastic activity around metastases, which does not occur with osteolytic metastases. Nearly 25% of positive bone scan uptake is related to nonmalignant causes. Bone scans have a high sensitivity, but low specificity and should not be interpreted without clinically relevant data. Metastases, if present diffusely in the red marrow, will cause the red marrow to expand, resulting in diffuse juxtarticular uptake and absence of the kidney shadows (super scan). This may be mistaken for a normal bone scan [3]. Bone scans will worsen as patients respond to treatment (flare). Osteolytic lesions regress, and osteoblasts fill in with healing bone.

Computer tomography scanning (CT scans) is cumbersome when imaging bone and has limited views of the bone structures relative to magnetic resonance imaging (MRI). However, CT scans are more sensitive in detecting bone metastases than plan radiographs and can clarify bone scan positive painful and suspicious lesions in individuals unable or intolerant of MRI scanning [39]. CT scans will detect marrow metastases before bone destruction by differences of >20 Hounsfield units relative to normal fat containing marrow [39].

MRI skeletal metastases have low signals on T_1 weighted images (marrow has high intensity). Fat suppression T_1 images separate local fatty deposits from metastases. T_2 weighted images demonstrate enhancement relative to marrow signals. This is due to the high water content of metastases. A rim of bright T_2 enhancement can occur around metastases (halo sign) [39]. MRI is particularly suitable for vertebral lesions and, in addition, will image epidural metastases and spinal cord compression. Gadolinium-enhanced images better define epidural spaces and spinal soft tissues but are not needed for imaging bone. T_1 sequences can be used to differentiate benign from malignant vertebral fractures [40]. Malignant rather than benign vertebral compression fractures are evidenced by pedicle, posterior vertebral element involvement, or the presence of epidural or paravertebral masses. MRI is also able to image marrow and has been used to stage malignancies such as multiple myeloma for this reason [39].

Liver and Abdominal Imaging

Liver imaging has size limitations when used to screen for cancer. Metastases less than 1 cm are difficult to visualize or classify. For each metastatic lesion found, one to four cannot or will not be visualized due to size [41]. Edge definition is most important for visualizing liver metastases. Cysts have greater edge definition than metastases and hence are better visualized.

Liver ultrasounds are relatively inexpensive, do not involve radiation, and are portable but are operator-dependent [41]. Ultrasound images are limited by the acoustic window. Intervening gas and obesity limit image capability. High-frequency transducers increase lesion detection. Doppler ultrasounds may detect liver metastases by edge definition and by increased hepatic artery blood flow to metastases.

Iodine contrast is needed for liver CT scans to provide optimal imaging. Manipulation of arterial and portal contrast phase sequences help define metastases. Early enhancement during the arterial phase is common with breast and renal cancer, melanoma, and sarcoma [41]. Hypovascular tumors are better seen in the portal phase. CT portography bypasses the hepatic artery; the liver will be enhanced, while cancer remains unenhanced [41].

T_2 weighted enhancement on an MRI is characteristic of liver metastases. Contrast or dynamic scans using gadolinium are generally not helpful. However, certain agents (Mn-DPDP, Gd-BGPTA) are selectively taken up by hepatocytes or reticuloendothelial cells and will give a better edge definition to liver metastases [41].

Lung Imaging

Contrast enhanced CT scans of the lung should extend to the level of adrenals and liver in order to detect metastases [42]. CT scans better define metastases seen on screening chest radiographs and will detect lesions not seen by a standard anterioposterior chest x-ray. However, lesions less than 1 cm are difficult to define. CT scans have 61% sensitivity and 79% specificity for mediastinal involvement [43]. Positron emission tomography (PET) scanning combined with chest CT scanning better define lung lesions as malignant or benign and mediastinal node involvement. Whole-body PET scanning will detect distant metastases. Because the brain avidly takes up glucose,

either a CT scan or MRI of the brain will be needed to detect brain metastases [44].

Cancer Pain Management

The World Health Organization defined three levels of treatment based on pain severity: for mild pain, a nonopioid analgesic (NSAID or acetaminophen) plus an adjuvant; for moderate pain, a weak opioid (tramadol, codeine) plus adjuvant; and for severe pain, a potent opioid plus adjuvant [45–48]. An adjuvant analgesic is, by definition, a drug whose primary indication is for another reason but is analgesic in certain painful conditions. Tricyclic antidepressants, duloxetine, venlafaxine, and gabapentin are adjuvant analgesics.

There are five essential principles to chronic pain management: (1) oral administration is preferred; (2) drugs should be given proactively around the clock to prevent pain from recurring rather than on an "as needed" basis; (3) drug administration should conform to the 3-step analgesic ladder; (4) administration must be individualized due to wide interindividual variability in opioid requirements; and (5) attention to details is needed in order to sculpt opioid administration to temporal pain pattern and repeat assessment at intervals consistent with opioid half-life and pain characteristics (acute or chronic) should follow the dosing strategy [48]. The treatment strategy should be explained and written down for the patient. Most will experience breakthrough pain and not infrequently experience-opioid side effects. Most individuals will require an around-the-clock opioid plus an immediate release potent opioid for breakthrough pain [30]. The use of two sustained release opioids for chronic pain or two immediate release opioids for breakthrough pain should be avoided [48]. Most individuals with cancer pain require less than 200 mg of oral morphine (or morphine equivalents) per day [49]. The majority of individuals (80%) will experience relief from cancer pain by using the 3-step analgesic ladder and five basic principles [46].

Morphine remains the opioid of choice since no potent opioid is a better analgesic than morphine. Morphine is readily available in many countries, versatile as to its route of administration, relatively inexpensive, and has the greatest published experience [46, 50]. There is no difference in pain relief using sustained release morphine at 12- or 24-h intervals compared to immediate release morphine at 4-h intervals. Initial doses are 15 mg every 12 h of sustained release or 5 mg every 4 h of immediate release morphine in the opioid naïve. Low doses of potent opioids can be substituted for "weak" opioids on step 2 of the analgesic ladder [30, 45, 46]. Doses should be titrated to pain relief. The 4 h morphine requirements can range from 5 to ≥250 mg [45]. In place of morphine, oxycodone 5 mg every 4 h, hydromorphone 1 mg every 4 h, or fentanyl 12 mcg/h transdermal patch replaced every 3 days may be used [30]. Fentanyl patches are best used when chronic pain is well controlled by intravenous or subcutaneous fentanyl. The conversion to a patch is 1 to 1 relative to transdermal fentanyl but with wide differences among individuals in absorption from the transdermal patch.

The around-the-clock dose should not be changed until steady state. Individuals on 4 h morphine should have doses adjusted daily if necessary (the same is true for oxycodone and hydromorphone) [51]. Individuals on sustained release morphine should not have around-the-clock doses adjusted sooner than 48 h – the same is true for transdermal fentanyl. Pain flares and unsatisfactory control should be managed by adjusting rescue doses in the interim.

Breakthough Pain

Breakthrough pain includes several clinically distinct pains. The term "breakthrough" is problematic linguistically since literal translations do not exist in all languages [52]. "Episodic" or "transient" pain may be a better universal term. Episodic pain may be "incident" – or movement-related, which is either voluntary or involuntary (with hiccup or colic). Episodes may be spontaneous or occur at the time when the next opioid dose is due (end of dose failure) [52]. Transient pain is usually rapid in onset and short in duration. The offset of pain (30 min) is the average time to analgesia with oral immediate-release opioids [52]. Hence, oral immediate-release opioids may not be effective for this reason. The standard approach to the management of incident and breakthrough (spontaneous) pain is to give 10–20% of the total daily oral morphine dose as a rescue dose [30, 46, 52]. This may be repeated during a 4 h time period [46]. End of dose failure is due to suboptimal around-the-clock opioid doses and should be managed by increasing the sustained release opioid dose (or immediate release 4 h doses) before considering a shortened interval between doses; 8 h for sustained release morphine, 60–48 h for transdermal fentanyl, 3 h for immediate release morphine [30]. Several opioid preparations are available for incident or breakthrough pain: oral transmucosal fentanyl citrate and fentanyl buccal tablets [52]. Sublingual methadone also has a rapid onset to pain relief and parenteral morphine or hydromorphone using 1/6 of the total daily dose converted to parenteral equivalents have also been effective [52]. Both transmucosal and transbuccal fentanyl will need to be titrated to relief independent of the chronic opioid dose.

Rescue doses should be added to the chronic opioid doses if the transient pain is spontaneous. This should be done at

steady state. If pain remains poorly relieved and the patient is not experiencing dose-limiting toxicity (myoclonus, cognitive failure, nausea and vomiting, hallucinations), the total opioid dose (chronic plus rescue doses) should be increased 30% and rescue doses adjusted [30].

Rescue doses for incident should not be added to chronic doses if the baseline pain is under control [30]. Doses for incident pain should be increased independent of the around-the-clock doses if incident pain is poorly relieved. Doses should be increased 100% if <50% response and 50% if >50% response [30]. Rescue doses should also be increased if pain is relieved but rapidly returns before the next rescue dose [30].

Pain Control with Opioid Side Effects

Mild nausea and sedation from opioids usually improves over several days. Doses usually do not need to be adjusted. However, tolerance does not develop to constipation. All who are started on potent opioids should be started on laxatives and stool softeners [30]. In those with pain control but excessive opioid side effects, the chronic opioid dose should be reduced 30% and the rescue dose maintained. Reducing the chronic opioid dose may lead to resurgence of pain, and the rescue dose will be needed to control pain [51].

Uncontrolled Pain with Opioid Side Effects

Opioid dose titration is limited by side effects (Table 2.3). Strategies for managing pain include opioid rotation, route conversion or the addition of an adjuvant analgesic followed by opioid dose reduction [30, 45, 47–49, 53, 54]. These strategies have not been compared: opioid rotation; route conversion; or the addition of an adjuvant with opioid dose reduction are largely based on clinical experience and circumstances. Route conversion, which may be from oral to parenteral opioids, alters the ratio of morphine to metabolites, and thus reduces side effects. However, most route conversions for poorly controlled pain are to spinal opioids. Parental route conversions are usually done for other reasons: where oral administration is impossible due to nausea, dysphagia, mucositis, or bowel obstruction; for poor drug absorption due to dysfunctional or ischemic bowel, short gut syndrome, or fistula; to reduce the number of tablets; as a means of gaining rapid control of acute pain [29, 48].

Table 2.3 Guidelines for opioid rotations

1. Calculate equianalgesic dose then
   - Reduce 50% if rotation is primarily for side effects in the elderly frail, those experiencing side effects on high opioid doses or in those with compromised organ function
   - Reduce 30% in those who are relatively healthy on low or standard opioid doses and normal organ function who are experiencing side effects
   - Use the equianalgesic dose if rotations is predominantly for pain
2. Adjust doses based on comedications, which interfere or alter with opioid clearance
3. Methadone equianalgesic doses should be reduced 75–90%, or a different dosing strategy should be used, which involves an every 3 h as needed dose using 10% of the total daily morphine equivalents. Alternatively a linear equivalent dose can be given every 8 h based on the following equianalgesic scale (morphine to methadone ratio)

4:1	<90 mg morphine/day
8:1	<300 and >90 mg morphine/day
12:1	>300 and <1,200 mg morphine/day
15:1	>1,200 and <2,000 mg morphine/day
20:1	>2,000 mg morphine/day

   Methadone should be prescribed by those with experience of using methadone
4. Provide a rescue dose preferably using the same opioid. The initial dose should be 10–20% of the total daily opioid dose
5. Do not adjust the chronic around the clock opioid dose until reaching steady state. Opioid rotation before reaching steady state is meaningless and dangerous
6. Frequently assess pain response and toxicity. Opioid toxicity may persist for several days. Rapid opioid rotations on a daily basis are dangerous. Methadone responses may not be seen for 1–2 days and steady state may not be reached for 3 days, so patients may experience pain for 1–2 days while rotating to methadone
7. Conservative equianalgesic ratios in one direction are not conservative when rotating back to the first opioid. There are bidirectional differences in opioid equivalents. Clinicians need to be aware that equivalents may not be "reversible" in direction
8. Add rescue doses to the around the clock dose then increase the total dose by 30–50% if baseline pain is uncontrolled at steady state
9. Add rescue doses (for nonincident pain) to the around the clock dose if pain is controlled at steady state and frequent rescue doses (>4) where needed in the last 24 h
10. Do not add adjuvants and rotate simultaneously. Do one at a time and assess analgesia before altering the strategy

Source: Data from refs. [30, 46, 51]