REVIEW ARTICLE

Pharmacological Treatment of Neuropathic Cancer Pain: A Comprehensive Review of the Current Literature

Athina Vadalouca, MD, PhD, FIPP*; Efklidis Raptis, MD†; Eleni Moka, MD, PhD‡; Panagiotis Zis, MD, MRCPsych§; Panagiota Sykioti, MD¶; Ioanna Siafaka, MD, PhD*

*1st Anaesthesiology Clinic, Pain Relief and Palliative Care Unit, Aretaieion University Hospital, University of Athens, Greece; †Specialty Care, Pfizer Hellas, Athens, Greece; ‡Creta InterClinic Hospital (Private Sector), Heraklion, Crete, Greece; §Department of Neurology, Evangelismos General Hospital, Athens, Greece; ¶Neurology University Clinic, Attikon General Hospital, University of Athens, Greece

■ **Abstract:** Neuropathic cancer pain (NCP), commonly encountered in clinical practice, may be cancer-related, namely resulting from nervous system tumor invasion, surgical nerve damage during tumor removal, radiation-induced nerve damage and chemotherapy-related neuropathy, or may be of benign origin, unrelated to cancer. A neuropathic component is evident in about 1/3 of cancer pain cases. Although from a pathophysiological perspective NCP may differ from chronic neuropathic pain (NP), such as noncancer-related pain, clinical practice, and limited publications have shown that these two pain entities may share some treatment modalities. For example, co-analgesics have been well integrated into cancer pain-management strategies and are often used as First-Line options for the treatment of NCP. These drugs, including antidepressants and anticonvulsants, are recommended by evidence-based guidelines, whereas, others such as lidocaine patch 5%, are supported by randomized, controlled, clinical data and are included in guidelines for restricted conditions treatment. The vast majority of these drugs have already been proven useful in the management of benign NP syndromes. Treatment decisions for patients with NP can be difficult. The intrinsic difficulties in performing randomized controlled trials in cancer pain have traditionally justified the acceptance of drugs already known to be effective in benign NP for the management of malignant NP, despite the lack of relevant high quality data. Interest in NCP mechanisms and pharmacotherapy has increased, resulting in significant mechanism-based treatment advances for the future. In this comprehensive review, we present the latest knowledge regarding NCP pharmacological management. ■

Address correspondence and reprint requests to: Athina Vadalouca, MD, PhD, FIPP, Associate Professor of Anaesthesiology, 1st Anaesthesiology Clinic, Pain Relief and Palliative Care Unit, Aretaieion University Hospital, University of Athens, Lefkon Oreon Street, PC 15344, Gerakas, Greece. E-mail: athinajv@ath.forthnet.gr.

Disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. Dr Athina Vadalouca has been a consultant for, has received honoraria from, and has conducted clinical research supported by the following: Pfizer Inc., and Prostrakan. Dr Efklidis Raptis used to be a Scientific Associate of the Pain Relief and Palliative Care Center of Aretaieion Hospital and is currently employed in Pfizer Hellas.

Submitted: March 6, 2011; Revision accepted: May 19, 2011

DOI. 10.1111/j.1533-2500.2011.00485.x

Key Words: cancer, central nervous system agents, chemotherapy, pain, adjuvants, antidepressive agents, GABA, opioid analgesics

INTRODUCTION

Following EFIC's (European Federation of IASP Chapters) declaration in 2001, pain is not a symptom but a disease in its own right, necessitating appropriate treatment. The word pain usually refers to a discrete sensory experience, triggered by an identifiable set of ''painful'' stimuli, acting on a unique or stable ''pain'' pathway and eliciting an invariant sensation. However, pain, and particularly neuropathic pain (NP) can also exist as a diverse group of complex phenomena of unpleasant and distressing nature. NP encloses numerous complicated neurobiologic constituents and reflects potentially dynamic mechanisms, interacting at multiple neuraxial sites.[1]

Modern neurobiological techniques have led to tremendous progress in the exploration of pain pathogenetic mechanisms.[2–4] Research indicates that pain can be produced in multiple ways, at different locations, co-existing between and across various pathological conditions.[5,6] Novel therapeutic targets have been discovered and are used by the pharmaceutical industry for the construction of highly specific molecules, acting as potential innovative analgesics. Recent targets' application, specific to precise NP mechanisms, will very soon enable treatment to be focused at particular mechanisms, introducing a mechanism-based therapy, instead of the classical signs and symptoms-based treatment.[1]

NP is the pain initiated or caused by a primary lesion/dysfunction in the nervous system and is often difficult to be controlled, posing numerous clinical challenges. Similarly to all intractable pains, it has devastating consequences on the overall quality of life; not only it deranges patients' ability to perform daily functions and their ability to manage their disease, but it also amplifies the anxiety and the distress of the affected patient and family.[7–9]

NP is commonly presented in cancer patients and is considered a well-established entity for more than 20 years. Approximately, 1/3 of cancer patients experience NP, usually mixed with nociceptive components, or, occasionally, as a single, autonomous entity.[10,11] As advances in cancer early diagnosis and management prolong life expectancy, there is increasing effort to ameliorate patients' quality of life. New approaches are desperately required in controlling cancer pain. Neuropathic cancer pain's (NCP) severity follows disease progress, requiring miscellaneous types of analgesics, at different time-points.[12] NCP mechanisms have not yet been elucidated, despite the fact that some of them may share common features with noncancer NP. Animal models have been created to facilitate studies on these mechanisms. In the future, these models will definitely offer better understanding of the main aspects of cancer pain, regarding its variety from patient to patient, tumor to tumor, and even from site to site. However, up to now, results are rather confusing than enlightening.[12–15]

Cancer pain results from mixed mechanisms, since it rarely presents as a pure neuropathic, visceral or somatic pain syndrome, but rather as a complex one, with inflammatory, neuropathic, and/or ischemic components, often at multiple sites.[7,16] Even within pure NCP syndromes, pain presentation, and evolution are affected by pre-existing, noncancer damage, as well as by subsequent interventions, and disease relapse. An absolute distinction between cancer and noncancer-related NP is difficult, and possibly artificial. NCP pathophysiology basically remains similar to noncancer NP, with common cross-referencing between the two conditions.[7,17] Research on NCP showed distinct differences in the signature of neuroreceptors/transmitters' alterations and that neuronal function is disrupted or damaged. NCP has unique characteristics, exhibiting an incomparable molecular signature. However, therapy similarities to noncancer-related neuropathies,[7,18,19] may explain the ability of drugs (eg, gabapentinoids) to treat cancer pain, indicating possible neuropathic components.[7,20]

Despite significant progress in cancer exploitation, NCP basic neurobiology and underlying mechanisms are poorly comprehended. Consequently, treatment is often inadequate and patients suffer needlessly. Understanding of NCP pathophysiology, expertise in assessment techniques, familiarity with the NCP states and focus on new pharmacologic modalities would ideally alleviate pain.[21] Such insights might result in new therapeutic tools, altering the methods of cancer pain control.[12]

NCP remains a complex situation, often refractory to treatment. Current therapeutic strategies depend on pharmacotherapy, mainly with the inclusion of adjuvants. At present, variable agents are used to treat NCP, but despite the advances in pathophysiology

understanding, management is still suboptimal.[21,22] Intractable NCP remains an important epidemiological, clinical and economical burden worldwide, posing significant societal impacts.[23]

The aim of this comprehensive review is to provide the most recent knowledge regarding NCP systemic pharmacological management, focusing on evidence-based data, deriving from simple and randomized controlled trials (RCTs), consensus and expert committee reports, literature recommendations, and published guidelines. Apart from a brief reference of basic knowledge regarding terminology, definitions, epidemiology, classification, etiology, pathophysiological mechanisms and diagnosis, our scope is to present and analyze established, new or future pharmacological approaches that are or may become the mainstay in NCP treatment, mainly targeting at nociceptive inputs reduction, modulation of pain transmission to central nervous system (CNS) or alteration of pain central perception.

Our literature search was systematic and comprehensive, initially including major literature databases, such as Medline, Pubmed, Cochrane Library and other electronic ones. Additionally, it was expanded by checking reference lists published in meta-analysis, review articles, RCTs and clinical reports, supplemented by personal knowledge of the literature as well, in order to identify material relevant to developing treatment recommendations for patients with NCP. The databases and reference lists were searched from January 1st 1980 to April 1st 2011, also including articles electronically published ahead of print. In addition, abstracts from conferences (European Association of Palliative Care—EAPC, International Congress of Neuropathic Pain Interest Group—NeuPSIG, International Symposium of Regional Anaesthesia and Pain Therapy, International Pain Clinic of World Society of Pain Clinicians—WSPC, International Symposium of World Institute of Pain—WIP, ALGOS) were extensively hand-searched between 2004 and 2010.

To identify relevant articles with the most recent available data, our search was performed using the terms Neuropathic Pain, Neuropathic Cancer Pain, Mechanisms, Diagnosis, Pharmacological Management, Pharmacotherapy and Treatment Recommendations. Our principal effort is to outline current pharmacological modalities for NCP relief, generated either empirically by clinicians, or through new insights into NCP mechanisms from cancer pain animal models, all discussing the development, evolution and evaluation of current clinical guidelines. Studies that enrolled patients with NP due to any origin or cancer pain with a neuropathic component were included. Studies of any design, quality or sample size were also included and qualitatively assessed. Only publications in English or with available abstracts in English were taken into account. These criteria were applied to both citations retrieved from databases and hand-searching. The decision for inclusion was initially made using the titles and abstracts of the articles, followed by obtaining full text articles, with those being clearly irrelevant excluded at this stage. A team of reviewers independently determined the eligibility of each publication by applying the inclusion/exclusion criteria. Each publication was reviewed by two reviewers and any discrepancies in the decision for inclusion between these two were resolved by a third reviewer.

DEFINITIONS

Despite lengthy pain research history, it was not until the International Association for the Study of Pain (IASP) was founded in 1973 that attention focused on NP etiology and therapy.[24] IASP published its first list of pain terminology in 1979.[25,26] NP was defined and subsequently included in the list in 1994. Neuropathy results from function disturbance or pathologic change in nerves: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy.[27] According to the IASP definition, NP refers to all pain types initiated or caused by a primary lesion or dysfunction or transitory perturbation in peripheral or CNS, disrupting impulse transmission and sensory input modulation.[25,26] NP is a sub-entity, where transitory perturbation is omitted, and hence it refers to irreversible, long-term conditions. This broad definition acknowledges that nerve damage and subsequent alterations within neuronal pathways lead to chronic pain, despite the absence of continuing stimulus. Although this theory has now gained general acceptance, it was initially revolutionary, renouncing the Cartesian model of nociception and pain.[24]

This definition has been a discussion and controversy subject, mostly because of the term ''dysfunction''. The IASP definition does not specify the kind or nature of lesion and doubts exist about the utility of the term ''dysfunction'', since it is applied to

most, if not all, pain conditions. It is accepted that the lesion should involve the somatosensory pathways, with small fibers derangement in peripheral nerves, or the spino-thalamo-cortical system in CNS.[28] If IASP definition is strictly applied, the clinician needs only to demonstrate nerve damage/dysfunction in a patient suffering from pain to diagnose NP. However, nerve damage and/or dysfunction may present either as negative or/and as positive symptoms (eg, sensory loss and hyperalgesia respectively).

In 2002 and 2004 a new definition arose, according to which NP is defined as the pain caused by a lesion in peripheral or CNS.[28,29] Perhaps it is easier to understand this narrow definition; however, the previous one may be rewarding, being more useful under certain circumstances.[28] Studying the mechanisms, it is obvious that nervous system's hyperexcitability and plasticity are major determinants of chronic pain, and that treatment efficacy depends more on the underlying pathogenesis than on etiology.[1,3,6,28] Testing the validity of a narrow vs. a broad definition might be significant in future studies. Meanwhile, according to the European Federation of Neurological Societies (EFNS) guidelines (European Federation of Neurological Societies) the narrow definition is suggested, with the classification to be retained, due to overestimation risk and as it is more easily understandable.[28]

In 2008, neurology and pain community experts introduced a more precise definition; NP is the pain type arising as direct consequence of a lesion or disease and affecting the somatosensory system.[30] This definition fits into the nosology of neurological disorders and the reference to the somatosensory system is derived from a variety of NP conditions, from painful neuropathy to central poststroke pain.

Regarding NCP definition, it does not differ from that of noncancer NP. Many disease-free cancer survivors live with chronic pain syndromes and neuropathies, induced by treatment or by cancer itself. Sometimes such conditions resolve over time, but irreversible tissue and nerve damage can cause pain persistence, or even progression.[27] Across NCP classifications and studies, some controversies are recognized. For example, herpes zoster pain presenting in cancer patients is classified as cancer pain in one study, since cancer-related immune system impairment may be the cause, and as cancer-unrelated to another study. Among different specialties, a consistent definition is necessary.

EPIDEMIOLOGY

Chronic NP is common in clinical practice causing considerable suffering and deterioration in patients' health-related quality of life.[7–9,31,32] NP, as part of the neurological disease spectrum, is a common disability and expresses serious medical pathology. Apart from traumatic nerve injury, numerous diseases may be accompanied by NP. Patients, with conditions as diverse as diabetic polyneuropathy, human immunodeficiency virus (HIV), sensory neuropathy, poststroke syndromes, herpes zoster, myelopathy, multiple sclerosis or cancer, frequently experience daily pain. NP has complicated disguises and can be mimicked by non-neurological pain conditions.[28,29]

NP true prevalence is undetermined, as comprehensive epidemiological studies have not taken place. It is estimated that 1% to 1.5% of the general population is affected.[33] In the United States 1 and 3 million of people suffer from post herpetic neuralgia (PHN) and painful diabetic neuropathy (PDN) respectively; whereas, in Europe 6% to 7.7% of population refers chronic NP at some point in its lives.[34,35] Five percent of patients with traumatic nerve injury suffer from neuropathy,[36] whereas central NP is reported in patients with multiple sclerosis, syringomyelia, spinal cord injury and stroke in percentages of 28%, 75%, 60–70% and 8% respectively.[37–39]

Additionally, pain experienced by patients with cancer, degenerative diseases, or neurological conditions (eg, Parkinson's disease), could have neuropathic components, which still remain unnoticed. Such states are most prevalent in the elderly; since the aging population size is increasing worldwide, NP, inevitably, will pose a progressively demanding burden on health care resources, necessitating its potential treatment.[24] With advancing age, the nociceptive pathway undergoes degenerative adaptation, which is mainly axonal loss. This potentially contributes in NP development, and probably explains why elderly tend to under-report pain in many medical conditions including myocardial infarction, fractures and arthritis.[40]

Despite the fact that the exact prevalence of NCP remains unknown, available data demonstrate that a neuropathic component is present in about 30% of cancer pain cases. Although as much as 9% of cancer patients have solely NP, many have a mixed pain syndrome, a challenge to treat.[10,11,41] Pain may be the first sign of cancer and 30 to 50% of such patients experience moderate to severe pain,[42–46] occurring in

50% to 70% of those in active treatment.[47] Cancer can cause pain at any time during the disease evolution and at least 15% to 20% of patients are likely to suffer from NCP. An even higher proportion of patients experiences NCP of increased intensity at advanced disease stages.[48] In fact, 75% to 95% of patients with metastatic or advanced-stage disease will experience cancer-induced pain,[42–45] with 2/3 of it because of tumor infiltration and 1/4 as a consequence of cancer treatment.[47,49–51] It is reported that 45% of cancer patients have inadequate and undermanaged pain control, mostly because of treatment-associated side effects.[52,53] It is also suggested that 50% of all difficult to control cases is neuropathic.[10,54] However, various extrapolations can be drawn to underline the problem enormity. For example, up to 20% of patients with herpes zoster (common phenomenon in cancer), will develop PHN, and up to 80% of people with limb amputation will suffer from phantom limb pain.[21,55]

In an epidemiological study, which took place in Spain in 2010, after screening 8.615 cancer patients almost 30% of them suffered from pain. Out of them, 33% and 19% were experiencing NCP, according to investigators and DN4 test respectively. Pain decrease at 1 month was greater in patients with metastases. [56]

The overall incidence of chemotherapy-induced peripheral neuropathy (CIPN) and of associated NP is high (30% to 70%).[23,57] Radiation can present with numerous clinical painful manifestations, ranging between 25 and 47%.[27,58] Following radiotherapy, the prevalence of NP in oncology units is increased, leading to sleepiness, anxiety and depression.[59] Diagnostic or therapeutic surgery may lead to NCP, with incidence reaching high rates (60% to 90%) in some cases, such as after surgery for breast cancer, or after thoracotomy.[23,27] Postmastectomy pain syndrome is reported in about 20% of women,[60] may be particularly troublesome and could consequently affect patients' quality of life.[27]

Metastatic cancer-induced bone pain (CIBP) is a serious problem, often inadequately treated by current analgesics. Eighty five percent of patients with bone metastases experience significant pain, complicated with increased morbidity, decreased performance status, intense anxiety and depression, and poor quality of life.[45,61–63] Tumors that most often result in metastatic CIBP originate from breast, lung, and prostate cancers.[64,65] CIBP is a complex pain syndrome involving background pain (usually opioid responsive), described as a dull ache of increased intensity with disease progression.[42] Certain individuals with cancer may also suffer from multiple painful syndromes of diverse causation and underlying mechanisms.

CLASSIFICATION & TYPES OF NCP—ETIOLOGY—PATHOPHYSIOLOGY—MECHANISMS

Cancer pain patients commonly experience more than one type of pain. Pain may be constant, persistent, intermittent, or acute, superimposed on chronic background. Clinicians describe cancer pain as acute, chronic, nociceptive (somatic), visceral, or neuropathic. One other suggestion identifies three basic categories: nociceptive, neuropathic and psychogenic.[49,66] Multiple pain taxonomies exist, including a research-oriented and a treatment-based classification that groups together patients with similar pain mechanisms.[67] Clearly, no individual classification is optimal in capturing such a multidimensional phenomenon. Clinically, patients experience pain of varying intensity, frequency, anatomic location, duration, and body system involvement. They may describe both nociceptive and neuropathic features, rather than distinct elements of a single process. Thus, it is instructive to adopt common terminology, applied to cancer pain patients.[49]

NCP arises following damage or inflammation of peripheral or central neurons, in a similar manner to pain arising from a noncancer injury. It can be divided in peripheral NCP (directly from tumor nerve infiltration/compression, or indirectly by cancer therapy such as radiotherapy, chemotherapy and PHN) and central NCP (poststroke or tumor involvement of spinal cord). Suggested mechanisms include peripheral sensitization, ectopic foci of hyperexcitability in neuron, maintained sympathetic activity, loss of inhibition of dorsal horn neuron, central sensitization, rewiring of synaptic connection in the dorsal horn and phenotypic switch.[12,21,23,49] NCP could be nondisease related, disease related, or treatment induced.[12] Additionally, chronic pain conditions, such as low back pain, that were present prior to cancer may continue to be problematic. Psychological factors such as depression, anxiety and cognitive status influence pain perception and contribute to pain intensity.[21,23,49] Common NCP syndromes are listed in Table 1.

Numerous and complex elements can lead to NCP. Thus, NCP may result from direct damage (directly tumor-related pain) because of tumor expansion and pressure on surrounding organs, from compression or

Table 1. Common Cancer-related Neuropathic Pain (NP) Syndromes

Common Cancer-related NP Syndromes
Cancer-related NP
Brachial plexus neuropathies–Plexopathies
Cranial neuropathies
Metastatic cancer-induced bone pain
Cancer therapy-induced NP
Chemotherapy-induced peripheral neuropathy
Postradiation NP
Plexopathies
Tissue fibrosis
Mucositis
Surgical neuropathies
Phantom limb pain
Postmastectomy syndrome
Post-thoracotomy syndrome

direct infiltration of nerves, plexuses, bones, ligaments and soft tissues (entrapment, nerve tissue damage) by the growing tumor, from hollow viscera stretching and solid organs capsule distortion, followed by mucosa inflammation/ischemia/necrosis (visceral nociceptors activation) and from rapid weight loss, muscle hypercatabolism, immobilization, or increased muscular tension, causing muscular pain.[21,49]

Secondarily, NCP may derive from neuronal milieu alterations, due to cancer growth and from the consequent local and systemic inflammatory response, such as tissue acidosis, tumor secretion of pro-inflammatory, inflammatory and pro-hyperalgesic mediators, production and release of tumor algogens or circulating chemokines and cytokines.[7,27] These inflammatory events facilitate pain transmission and in NCP are likely to be more common and important than in other neuropathies; in these, an acute tissue response subsides, leaving restricted neuropathic mechanisms within peripheral nerve and CNS.[7]

Under this concept and regarding directly tumor-related NCP, cancer cells can cause invasion of mechanically sensitive tissues (eg, visceral pain) or nerve entrapment and injury (eg, NP). Tumors contain immune system cells releasing factors, including endothelin, prostaglandins, and tumor necrosis factor alpha (TNF-α), which excite or sensitize peripheral nociceptive primary afferents. Tumors release protons, causing local acidosis, with similar effects. The ongoing pain is induced and is partially maintained by central sensitization. Proteolytic enzymes produced by tumor cells can damage sensory and sympathetic nerve fibers, causing NP.[12]

Metastatic spread of cancer to bone is one of the most important causes of NCP and painful muscle spasm,[68] whereas breakthrough pain (defined as transitory flare of pain occurring on a background of relatively well-controlled baseline pain) may be prevalent, due to numerous etiological factors (bone metastases, triggering pain on movement).[69] Infiltration and injury of sensory neurons that innervate the bone marrow cause pain. Alterations in normal bone turn over occur, with loss of mechanisms that normally regulate the balance between osteoclast and osteoblast activity. As disease advances, the bone loses mechanical strength and is subject to osteolysis, pathological fracture, and microfractures. Mechanical distortion of the periosteum may also be a major source of pain.[61,70]

NCP can arise as a consequence of cancer-directed therapy, such as surgery, radiotherapy and chemotherapy (treatment-related therapy).[7,71–75] Treatment adverse effects include joint pain following chemotherapy and hormonal therapy and/or painful mucositis due to radiotherapy and chemotherapy with certain agents. It has been widely reported that drugs such as paclitaxel, vincristine, cisplatin and bortezomib may produce sensory neuropathies. Surgical interventions can give rise to nerve damage and chronic postoperative pain. Mastectomy and debulking tumors' excision often result in deafferentiation pain. Postmastectomy patients report constellation of symptoms. Radiotherapy can induce injury, leading to microvascular insufficiency and fibrotic changes (radiation-induced fibrosis), affecting peripheral nerves and perineural tissues (eg, brachial plexus fibrosis) and causing chronic NP that begins months to years following treatment.[7,27,74] Depending on structures involved, cancer neuropathies can present as mononeuropathies, polyneuropathies, radiculopathies, plexopathies or opioid-induced hyperalgesia, following surgery, chemotherapy or radiation.[21,75] Additionally, debilitated patients are more likely to suffer from secondary infections, such as herpes zoster and bacterial or fungal infections, directly leading to neuropathic damage, or further hypersensitivity.

Chemotherapy associated NP has been widely reported in controlled and uncontrolled studies. On one hand, more patients experience the excellent outcomes of chemotherapy, with prolonged survival. On the other hand, increasing numbers of patients are unable to complete full treatment because of CIPN development. Long-term pain management is therefore a challenging treatment aspect for neurologists, oncologists and pain specialists.[12,27,76]

CIPN incidence is rising due to neurotoxic agents' increased number and because patients live longer, receiving multiple chemotherapy drugs. The severity of peripheral neuropathy varies with the type of agent used, the cumulative dose, and the treatment duration. Serious painful sensory disturbances tend to occur in patients who are more vulnerable, because of pre-existing nerve disorders, associated for example with diabetes mellitus or alcoholism. Patients experience sensory symptoms that are quite similar, regardless of the chemotherapeutic agent. CIPN onset is progressive, although some patients may describe rapid symptoms onset following chemotherapy. CIPN symptoms are often under-recognized, in part because of difficulties in diagnosis, in addition to patients' underreporting. CIPN is documented frequently with vincristine, taxanes and platinum-based agents, as it is depicted in Table 2.[7,71,77]

Vincristine is a frontline plant-derived, anticancer agent, being very effective in a number of lymphoid malignancies. However, its use can be limited by peripheral neuropathy onset, which is sometimes severe enough to require a lower dose, resulting in a less effective treatment, or even termination of chemotherapy altogether. Pain in the hands and feet, muscle cramps, numbness and tingling in the finger tips and toes have been reported in over 50% of patients receiving vincristine therapy.[78] Recovery from neuropathy may take up to 2 years, may worsen after vincristine is stopped, and is not always reversible. Decreasing dose may minimize toxicity. However, there is no other known effective prevention of peripheral NP caused by vincristine.[71]

Since the introduction of cisplatin treatment, mortality from testicular cancer has been drastically reduced with a cure rate above 80%. Unfortunately, significant peripheral neuropathy occurs in patients who receive more than 400 to 500 mg/m^2, generally 3 to 6 months into treatment. Neuropathy affects predominantly the large sensory fibers, with patients complaining of paraesthesias in extremities, due to loss of large fiber sensory function. Symptoms may also continue for months or years after therapy discontinuation.[7,21,23,61]

Oxaliplatin, a newer platinum compound, effective in advanced colon cancer, as well as in gastric, ovarian, breast and lung cancers, causes two types of neurotoxicity: an early acute reaction of dysaesthesia within hours of treatment in up to 90% of patients, and a chronic sensory neuropathy similar to that seen with cisplatin. Signs of oxaliplatin chronic neuropathy consist of proprioception alterations, which do not disappear between treatments. If severe, this problem can make daily activities (writing, buttoning shirts or picking up objects) extremely difficult.[7,23,61]

Taxanes are indicated for the treatment of lung, breast and ovarian cancer, prolonging emissions and improving survival. Taxanes affect many sensory neurons and especially nerve fibers that conduct vibration sensation and proprioception, reducing the quality of life of cancer patients. Paclitaxel induces paresthesias, sensation loss and dysaesthetic pain in feet and hands. This neurotoxicity is dose related.[7,21] Pre-existing neuropathy and co-administration of other chemotherapeutics enhance NCP risk.[71]

Certain malignancies (such as breast, kidney, thyroid cancer & multiple myeloma) are frequently complicated by metastatic disease or lytic lesions, affecting bones. Bone metastasis affects more than half of the women with breast cancer during their disease's

Table 2. Neuropathies Associated with Specific chemotherapeutic Agents and Biological Therapies

Chemotherapy	Neuropathy Type (Incidence)	Onset Time	Duration and Recovery	Type of Cancer Treated
Vinca alkaloids	*Chronic—30% severe* pain in hands/feet muscle cramps numbness/tingling paraesthesias common	2 to 3 weeks (+)	1 to 3 months up to 2 years	Lymphoid malignancies
Platinum Compounds Cisplatin Carboplatin	*Chronic*	1 month up to 3 to 6 months (+)	Some resolution in 80% over months/years	Testicular cancer
Platinum Compounds Oxaliplatin	Cold induced *Acute (90%) chronic*	Acute: hours chronic: 1 month (+)	Chronic: as Cisplatin	Colon cancer Gastric cancer Ovarian cancer Breast cancer Lung cancer
Taxanes	*Chronic* More CIPN with Frequent Dosing	Within days (+)	6 to 24 months 19% complete recovery 25% no recovery	Lung cancer Breast cancer Ovarian cancer
Bortezomide	Chronic (35%)	Any time (+)	71% some recovery at 2 years	
Thalidomide	Chronic	Any time (+)	Recovery less likely	

course, with pain management being challenging. Tumors that compromise bone or nervous structures due to bone destruction process may be very painful and direct tumor invasion of bone or osseous metastases development contribute to persistent bone pain. Pain occurs as a result of bone devastation and, as more destruction continues, increased pain is experienced. Functional limitation and neurological impairment may be additional problems. Bone metastases are not necessarily painful, with pain often being disproportionate to radiological findings.[23,61]

Although it is not strictly a neuropathic injury, CIBP consists a unique state with features of both neuropathy and inflammation. Recent studies demonstrated that osteoclasts damage peripheral nerves, leading to deafferrentiation. Glial cell activation and neuronal hyperexcitability within the dorsal horn are similar to neuropathy.[7,12,79,80] Nociceptive afferents are mostly concentrated in the periosteum, whereas bone marrow and cortex are less sensitive to pain. Some of the mechanisms contributing to CIBP include periosteum stretching by tumor expansion, bony distortion by local microfractures, nerve compression due to collapsed vertebrae or direct tumor encroachment, and algesic substances local release from the bone marrow.[23,72,81,82]

CIBP perhaps best illustrates the complexity of malignancies, clinically demonstrating a hallmark of cancer pain, with presence of painless disease at some sites and severely painful at others.[7] Bone pain has been correlated with osteoclastic activity.[83] In normal bone, the net activity of bone-resorbing cells (osteoclasts) equals the net activity of bone-forming cells (osteoblasts). In metastatic disease, there is evidence of increased osteoclastic activity. Both tumor and humoral factors, including prostaglandins, cytokines, local growth factors, and parathyroid hormone, enhance osteoclastic activity and act locally to stimulate nociceptors. Despite increased osteoclastic activity, bone formation also increases. Consequently, the proportion of immature bone increases and likelihood of fractures is higher. Bone metabolic activity is a predominantly surface-based phenomenon. Since cancellous bone provides a large surface area compared with the cortical one, it is not surprising that neoplastic disorders of bone remodeling are expressed earlier at cancellous sites.[23,61,72]

NCP is characterized by spontaneous burning, with intermittent sharp, stabbing, or lancinating characteristics, hyperalgesia and allodynia. Relationship between mechanisms and symptomatology is complex. The underlying mechanisms can be different for the same symptom, while the same mechanism can result in different symptoms. Whatever the etiology of NCP is, it definitely arises from changes initiating in the damaged nerves, which in turn alter spinal cord and brain function, leading to altered plasticity at a number of sites.[7] Much of our knowledge on NP is based on peripheral and spinal originating events of hyperexcitability, with little known about central NP in patients with persistent pain.[7,83,84] A long-term pathological state of central sensitization can be maintained via central feedforward loops, with or without continued peripheral input. These multiple NCP mechanisms are the basis for the application of combinations of agents, attacking more than one sites, thus, providing the possibility of synergy in controlling difficult pain states.[7,21,29]

NCP may arise from several different mechanisms, some of which have been investigated in animal models. However, in clinical practice all causes may arise simultaneously or sequentially in patients, adding new complexity to neuronal signatures. NCP may be considered the result of a multistep process, with each causative factor contributing to neuronal sensitization in a different way. The final event that triggers NCP initiation or maintenance will differ between individuals. This may, in some way, explain the diversity of clinical presentations.[7]

Similarities and differences between cancer and noncancer NP have been explored up to a point. The neural pathways, ion channels, receptors and neurotransmitters that are potentially altered in both neuropathies, are the same; however, nature of injury, timing, repeated injuries and co-existence of simultaneous non-NP states lead to potential unique constellations of neuroreceptor and neurotransmitter expression in the context of cancer pain. This in turn may lead to different clinical presentation and to specific treatment options. Since cancer and appropriate treatment result in mixed pain mechanisms, the resulting neuronal and higher center stimulation induces a complexity and "chaos," producing a unique signature, on a familiar background.[7,49]

DIAGNOSIS

NP diagnosis is based on detailed medical history, analytical systems' review, meticulous physical and neurological examination, magnetic resonance imaging, electrophysiological and appropriate laboratory studies

(blood/serological tests). In some instances, nerve or skin biopsy is necessary to directly visualize nerve fibers.[21,29,85] Diagnosis of peripheral or central NP is made only when history and signs are indicative of neuropathy, in conjunction with neuroanatomically correlated pain distribution and sensory abnormalities within the area of pain. Cornerstones of the diagnostic work-up in NP, which also aim at disclosing the etiology of this pain type, are depicted in Table 3 and can be easily applied in NCP patients.[28,29,31,86]

NP diagnosis can be difficult. Physicians should keep in mind that psychosocial factors are a major component of chronic pain experience and should be routinely addressed when patients are evaluated. Psychological processes may influence pain report and could potentially produce exaggerated responses. However, sincere communication, with the patient's pain being seriously taken, would minimize the possibility of unreliable or noninterpretable neurological examination due to psychological processes. Proper diagnosis is the key for effective treatment, and complex patterns of signs and symptoms demand multiple medical specialties involvement.[24,28,29,87]

The most reliable methods for NP assessment are laser-evoked potential (LEP) recordings and skin biopsy, which selectively assess nociceptive pathways, obtaining a rapid diagnosis and hence determining treatment.[40] To find out whether LEPs also provide a useful neurophysiological tool for assessing antinociceptive drug efficacy, the group of Truini measured, in a double-blind, placebo-controlled study, changes induced by tramadol on LEPs, in 12 healthy subjects.[88] They found that tramadol decreased LEPs amplitude, whereas placebo left LEPs unaltered. The opioid antagonist naloxone partially reversed the tramadol-induced LEP amplitude decrease. They concluded that LEPs may be reliably used in clinical practice and research, in order to assess antinociceptive drugs efficacy.

Table 3. Cornerstones of the Neuropathic Cancer Pain Diagnostic Work-Up

Basic Components of Diagnostic Work-up	Detailed Workup-Neurophysiological Testing
Careful medical history	Electroneurography
Detailed clinical examination Motor, sensory, autonomic system	Electromyography
	Microneurography
Pain drawing	Somatosensory evoked potentials
Word descriptors	Quantitative sensory testing
Questionnaires/Scales	Magnetic resonance imaging
Comprehensive neurological examination	Positron emission tomography
Survey of somatosensory functions	Functional MRI
	Pharmacological fMRI
	Laser-evoked potentials
	Skin biopsy

NCP diagnosis is based more on word descriptors and less on scales or questionnaires, although some of the latter can be sensitive and specific for NCP diagnosis in specific cancer types.[89] For head and neck cancers, Leeds Assessment of Neuropathic Pain Symptoms and Signs was successful; however there was some criticism that it cannot be used for symmetrical neuropathies and that patients with central NP may score low, leading to several clinical disadvantages, as published studies show methodological weaknesses.[90] Other scales (Northwick Park Neck Pain Questionnaire, NPQ; Neuropathic Pain Questionnaire Short Form, NPQ-SF; Neuropathic Pain Symptom Index, NPSI) have been evaluated as useful tools to facilitate communication between physicians.[91] Limited data supporting the use of DN4 scale for diagnosing NCP exist.[92]

Diagnosing NCP still remains problematic and many factors are responsible for this. Cancer patients often experience more than one types of pain simultaneously, making NP difficult to be distinguished. Another barrier in CIPN assessment is that many oncologists believe that treatment-induced pain will improve over time, in such a way that pain's issue tends to be underestimated. When assessment does take place, the current grading system is too broad to adequately detect changes in neuropathy. Additionally, tools to measure painful peripheral neuropathy have been validated in patients with diabetic or post herpetic neuropathy, but rarely in patients with CIPN.[7,77]

In the past, NCP was under-diagnosed. Nowadays, it may be hyper-diagnosed. As our awareness of the possibility for a neuropathic element in cancer pain is raised, clinicians try to diagnose NCP in the same way they do for noncancer NP. In part, they are successful. This is an easy way to diagnose all the "certain" cases of NCP, as well as to rule out cases where neuropathic elements are absent. However, by using these techniques, they tend to enlarge the "gray zone" of doubtful NCP cases.

In noncancer patients, NP stands alone, just waiting for the clinician to diagnose it. In cancer, NP is often paired with nociceptive and bone pain, making clinical picture difficult to elucidate. Considering the possibility that certain descriptors or signs, such as those

relevant to hyperalgesia, may in fact be the result of opioid administration and not of NP per se, diagnosis becomes more complicated. A practical way to diagnose "gray zone" NCP is to administer drugs alleviating NP, such as anticonvulsants and antidepressants, although a trial of NP-specific drugs is usually mandatory. Cancer is a dynamic entity with pain characters progressing over time and whatever until now was considered just nociceptive pain, in the future may grow, presenting neuropathic features. Therefore, clinical alertness is necessary and re-evaluation of the patient is warranted.[91]

PHARMACOLOGICAL TREATMENT

As few studies specific to cancer patients have been conducted, NCP therapeutic options remain largely the same with those for nonmalignant NP. In cancer pain therapy, opioids have a definite place, when this is not so clear for chronic noncancer pain. NCP does respond to opioids, but usually higher doses are needed.[91] In the following paragraphs, data regarding NP therapy in general (regardless etiology) are presented, as some of the available treatment options may also be applied to cancer patients, suffering from pain characterized by neuropathic elements. During NCP management, an important recommendation in initiating pharmacological therapy is to introduce one drug at a time, with gradual upward titration, according to patient's response. Administering several agents together precludes determination of the most effective one or which caused the side effects that might occur.[21]

Even though historically the earliest NP treatment strategies were invasive in nature, none of them was consistently successful.[24] The heterogeneity of aetiologies, symptoms and underlying mechanisms leads to poor response to conventional therapy and makes NP a challenging condition to treat. The complexity of this phenomenon limits the clinicians' awareness of the evidence-based options, thus making available data difficult in interpretation.[93]

Another obstacle is that agents used in NP treatment are commonly classified according to their original therapeutic category (antidepressants, anticonvulsants, etc.), and this confuses physicians not familiar with NP. Such a classification may be misleading, since with its interpretation administration of other drugs belonging to the same category (antidepressants, anticonvulsants) may be considered comparable to those with proven efficacy.[93] Recent studies have shown that most of NP patients, including those with malignant disease, were receiving medication of unproven efficacy, or suboptimum doses of the appropriate medication.[94,95] It is accepted that with appropriate therapy a significant percentage of patients report substantial pain alleviation. Another reason for NP treatment failure is that it is used in a uniform fashion across a patient population. Consequently, a drug shown to be useful in one group of patients is actually used to treat patients, whose NP is caused by a completely different pathology.[93]

Improvement in NP pharmacotherapy can be accomplished only with treatment tailored to the individual patient based on the corresponding underlying pain mechanisms.[6,61] NP management currently aims to treat underlying mechanisms as opposed to disease modifying therapy. However, at present, this is neither readily feasible, nor totally achievable. The difficulty lies in the underlying mechanisms' identification. The clinicians' main indications are usually based upon the symptoms generated by the mechanisms, which, however, are not equivalent to the mechanisms.[7,61]

Up until the year 2000, no official consensus on the optimal NP therapeutic management existed, with practices varying among therapists. Possible explanations include difficulties in developing common diagnostic protocols and co-existence of neuropathic, nociceptive and, occasionally, idiopathic pain in the same patient. As mentioned before, NP had historically been classified according to its etiology, without regard for the potential mechanism(s), underlying the specific symptoms. Management was empirical and consisted of various therapeutic approaches, including both invasive and noninvasive strategies.[24] However, specific and sensitive diagnostic tools revealing clear-cut evidence of the nature of the particular pathophysiological process have more recently appeared in literature.[1,21,61,93]

In 2000 and early in 2003, the first treatment algorithms were published.[24,96] Recommendations for NP treatment in general, as well as for NP management associated with specific syndromes, such as PDN [97,98] and trigeminal neuralgia,[99] were published based on anecdotal evidence or clinical trials showing efficacy of a therapy in some patients. Additionally, many of these early trials randomized small numbers of patients and were often poorly designed.

It is generally accepted that pharmacotherapy remains the mainstay of NP management. It soon became apparent that, as NP may be partially or

completely unresponsive to primary analgesics, applied therapies had to involve adjuvant analgesics, such as antiepileptic drugs (AEDs), antiarrythmics and antidepressants. Table 4 summarizes the pharmacological treatment recommendations that were suggested in 2003, by the faculty members of the 4th International Conference of the Mechanisms and Treatment of NP. These recommendations were based on positive results from multiple RCTs, a single RCT and inconsistent results of multiple RCTs.[87]

The percentage of patients with NP who do not respond to 1 of the 5 First-Line medications, but who then experience satisfactory pain relief from a different one is unknown. Even within a class of drugs, patients fail to respond to one medication but then respond to another. Drug selection depends on clinician's experience, patient needs and side effects. Current understanding of NP is consistent with the existence of multiple mechanisms, each of which may produce a different response to medications having diverse actions. Therefore, on both empirical and theoretical grounds it can be recommended that nonresponders to 1 of these 5 First-Line medications may be treated with a different drug.[87,100]

When partial response to a single drug is observed, combination with other agents should be considered. Existing data on NP combination drug therapy are still inadequate; pain management by combining drugs is entirely empirical. The guiding principle in drug selection is their additional therapeutic effects, rather than their adverse events. Combination therapy can be tried at the beginning of therapy in order to increase the likelihood of a beneficial response or whenever an agent requiring titration is used.

The interest in NP pharmacotherapy can be estimated by reviewing the number of NP medication patents that are filed. Before 2000 there were fewer than 27. In 2002 there were 54; in 2003 104; and in 2004 about 100 applications were filed. These agents include cannabinoid receptor antagonists, a2-adrenergic agonists, NMDA receptor antagonists, lysine B antagonists, NR2B-selective agents, glycine antagonists, nicotinic receptor agonists, NK1 receptor antagonists, bradykinin B1 receptor antagonists, vanilloid VR1 receptor antagonists, cholocystokinin antagonists, oral TNF antagonists, interleukin antagonists, neuroimmunomodulators and many others.[85,101,102] Completely new drug classes, which derived from exotic animal sources like conotoxins from a marine snail family and epitadine from a species of frog, seem to modulate neuronal transmission in pain pathways.[103] Innovative pathways in therapeutic aspects include development of gamma-aminobutyric acid (GABA) and serotonin secreting neuron grafts for spinal cord injury pain and the use of herpes simplex or HIV-like viruses as drug or gene vectors to transport therapeutic agents into the dorsal root ganglion or dorsal horn. Although efficacy, side effects and cost are crucial, it will be fascinating to see if we can further improve pain relief, compared to the present options.[85]

In 2006 and 2007, new treatment guidelines and recommendations were published, presented in Table 5 [104] and Table 6.[105] Table 7 summarizes the most recent guidelines on the pharmacological treatment of NP.[106]

For these guidelines the authors used top-level studies, from 2005 to 2009, found in the Cochrane Library, Medline and other electronic databases. The

Table 4. First-Line, Second-Line and Beyond Second-Line Treatment Recommendations for Neuropathic Pain

Neuropathic Pain		
First-Line	Second-Line	Beyond Second-Line
Gabapentin	Other Antiepileptic Drugs (AEDs) Lamotrigine Carbamazepine Levetiracetam Oxcarbazepine Tiagabine Topiramate Zonisamide	Capsaicin Clonidine Dextromethorphan Mexiletine
5% Lidocaine patch	Other Antidepressants	
Opioid analgesics	Paroxetine	
Tramadol hydrochloride	Citalopram	
Tricyclic Antidepressants (TCAs)	Bupropion Hydrochloride	
Nortryptiline hydrochloride	Venlafaxine Hydrochloride	
Desipramine hydrochloride		

Table 5. EFNS Guidelines on Pharmacological Treatment of Neuropathic Pain

First Line	Second Line	Third Line
Pregabalin	Topical lidocaine (PHN)	Strong opioids
Gabapentin	Tramadol	
TCAs (tricyclic antidepressants)	Venlafaxine	
	Duloxetine (especially for PDN)	

PDN, painful diabetic neuropathy; PHN, post herpetic neuralgia.

Table 6. Recommendations for the Pharmacolocical Management of Neuropathic Pain

First Line	Second Line	Third Line
Pregabalin Gabapentin TCAs SNRIs Topical lidocaine for PHN	Tramadol Strong opioids	NMDA antagonists, Mexiletine Topical capsaicin

TCAs, tricyclic antidepressants; NMDA, *N*-methyl-D-aspartic acid; SNRIs, serotonin-norepinephrine reuptake inhibitors.

Table 7. Guidelines on Pharmacological Treatment of Neuropathic Pain

Pharmacological Treatment	
First Line for various conditions TCAs (25 to 150 mg/day) Gabapentin (1200 to 3600 mg/day) Pregabalin (150 to 600 mg/day)	Second Line Tramadol (200 to 400 mg/day)
First Line for restricted conditions Lidocaine plaster (up to three plasters/day): PHN Duloxetine (60 to 120 mg/day): PDN Venlafaxine (150 to 225 mg/day): PDN Capsaicin 8% patch: PHN, HIV neuropathies Cannabinoids: MS Pregabalin SCI	Second or Third Line Opioids
First Line for neuropathic cancer pain Gabapentin Tramadol, TCAs level B of evidence	
Combination therapy Gabapentin & TCAs Gabapentin & opioids	

TCAs, tricyclic antidepressants; PHN, post herpetic neuralgia; PDN, painful diabetic neuropathy; MS, multiple sclerosis; SCI, spinal cord injury; HIV, human immunodeficiency virus.

authors also extracted information regarding efficacy on pain, symptoms/signs, quality of life, sleep, mood and side effects. The recommended agents, with level A evidence (tricyclic antidepressants [TCAs], pregabalin and gabapentin) can be used in various conditions (except trigeminal neuralgia). Drugs specific to restricted conditions with level A evidence, include duloxetine and venlafaxine for DPN, and topical lidocaine plaster 5% and capsaicin 8% patches for PHN. For cancer pain relief, basic principles of pharmacological management should follow the World Health Organisation (WHO) guidelines,[107] which, in specialists' units, relieve 80% of cancer pain.[108–110]

ADJUVANT ANALGESICS

NCP and especially CIBP can be controlled with difficulty during cancer pain therapy. Even though most complex cancer pain types have more than one component, there is usually a dominant one.[111] NCP can be poorly responsive to opioids because higher doses are often required, which in turn increase the likelihood of unacceptable side effects, therefore limiting dose escalation.[112–114] The widely used adjuvants represent a major aspect in our NCP armamentarium. These include gabapentinoids (gabapentin, pregabalin), AEDs, antidepressants (TCAs, duloxetine, venlafaxine), corticosteroids, bisphosphonates, NMDA antagonists, canabinoids and other substances.[115,116]

An adjuvant analgesic is an agent, whose primary indication is other than pain, exerting analgesic effects in certain painful conditions.[117] Apart from the adjuvants' importance per se, they also impart opioid-sparing effects. All adjuvants have a number-needed-to-treat (NNT) of about three (NNT = 3). This means that of every three patients treated, one is likely to get pain relief; their selection is not based on potency superiority.[118] Selection depends on individual's likely sensitivity to a specific side-effect profile and choice should be based on appropriate identification of the exact nature of pain, guided by a precise diagnosis.[23]

The use of adjuvants that are effective in NP in general is justified in NCP patients as the difficulties in performing RCTs in them lead to evidence insufficiency. However, antidepressants and anticonvulsants are recommended by evidence-based guidelines in NCP therapy.[119] Adjuvants can be added at any stage of the WHO ladder and are selected following underlying pain pathophysiology, although it is common to be generally prescribed early during NCP treatment.[111] At present, a number of approaches target at reducing levels of cancer-related pain. Therapies that aim to decrease tumor size are often effective and include radiation, chemotherapy and/or surgery—but these are usually complicated, burdensome and accompanied by significant side effects. Moreover, medications that may reduce inflammation-associated pain, such as NSAIDs or opiates, are also characterized by numerous side effects. The relative ineffectiveness of current treatments reflects the fact that therapies have not changed for decades. It is challenging to develop new approaches to relieve NCP, as the neurobiological basis for pharmacological treatment is largely empirical and based on scientific studies of painful conditions other than cancer.[12]

EFNS Task Force has suggested specific guidelines on NCP pharmacological treatment. These are the first ever recommendations for NCP, according to which

gabapentin is an agent with level A evidence, Tramadol and TCAs are drugs with level B evidence and valproate is considered inefficient.[104,106,120–122] Moreover, according to the recent ESMO (European Society of Medical Oncology) clinical recommendations on management of cancer pain, nonopioid and opioid analgesics may be combined with antidepressants or neuroleptics, or even AEDs, in the case of NCP.[123]

ESMO recommends that NCP should be treated not only with TCAs, pregabalin, and gabapentin, but also with the selective serotonin reuptake inhibitor fluoxetine (in doses of up to 80 mg/day), neuroleptics (haloperidol, chlorpromazine) and the antiepileptic carbamazepine. However, we should mention that the recommendation of potentially using high dosages of fluoxetine, which have not been tested in NP patients, holds the increased risk of serotonin syndrome if used in combination with tramadol. Carbamazepine is recommended as a first choice in the classical trigeminal neuralgia and not in NCP. Neuroleptics are ineffective in NCP management on the basis of good quality RCTs.

Long-lasting pain, especially of neuropathic etiology, may cause psychological problems that should be specifically addressed. Steroids should be considered in cases of nerve compression. There is sufficient evidence supporting bisphosphonate use for refractory bone pain, but not for general use as First-Line therapy of CIBP.

Tricyclic Antidepressants

TCAs inhibit norepinephrine and serotonin reuptake, followed by augmentation of biogenic amine activity. Their action includes sodium channel modulation in the periphery and NMDA antagonism. As a result, TCAs enhance dorsal root inhibition and reduce peripheral sensitization.[124,125]

Paoli was one of the first physicians to administer antidepressants for chronic pain treatment in 1960. Many scientists have described TCAs as effective for NP treatment over the last 30 years. According to their trial results, TCAs may exert a direct analgesic action, although some of these trials were uncontrolled or complicated by co-administration of an adjuvant.[24] Basic evidence for TCAs efficacy in NP alleviation (peripheral origin) results from meta-analysis of many old and relatively small-scale trials, which conclude that approximately 30% of patients were responders (> 50% relief), 30% complained of minor side effects and 4% suffered from major ones, leading to therapy interruption.

Trials of patients with HIV sensory neuropathy, pain from spinal cord injury and cicplatin-induced neuropathy report minor improvement of NP by amitryptiline when compared with placebo. Additionally, a Cochrane review provided a valuable summary regarding current evidence on TCA administration in nonmalignant NP, suggesting that these drugs provide at least moderate pain relief (NNT = 3.6).[67,87,111,126–129]

TCAs are started with a low bedtime dose (10 to 25 mg), which is gradually increased or titrated weekly, every 3 to 7 days (10 to 25 mg/day increments), usually up to 150 mg, or until further dose increase is forbidden due to adverse effects.[93] Although TCAs analgesic properties probably occur at lower dosages than those for an antidepressant effect, no systematic evidence supporting this assumption exists. Some data suggest a possible dose–response relationship. An adequate trial of a TCA should have duration of 6 to 8 weeks, with at least 1 to 2 weeks at the maximum tolerated dosage. For NP, dosing escalation to antidepressant blood levels is advised for 4 to 6 weeks.[85,87]

Common side effects of TCAs are sedation, anticholinergic consequences (dry mouth, constipation, postural hypotension and weight gain).[93] In one large-scale study, TCA long-term administration was associated with a 2.2-fold greater relative risk of myocardial infarction and a 1.7-fold increase in overall mortality, compared with placebo.[130] Thus, caution is necessary when TCAs are prescribed in the elderly, especially if cardiovascular risk factors or preexisting conduction abnormalities are present. A screening ECG is recommended prior to therapy initiation. The secondary amines nortryptiline and desipramine are safer than the parent drugs amitryptiline and imipramine respectively. TCAs are also contraindicated in cases of glaucoma, urinary retention or autonomic neuropathy.[24,85,87,93] Recent studies conducted in cancer patients demonstrate only slight analgesic effects from amitryptiline and nortryptiline.[21,131,132]

Other Antidepressants (ADs): SSRIs, SNRIs (Venlafaxine, Duloxetine), NDRIs (Bupropion)

Selective serotonin reuptake inhibitors (SSRIs) produce less side effects and are better tolerated than TCAs. Paroxetine and citalopram resulted in significantly better pain relief than placebo in patients with PDN,

whereas fluoxetine was no more efficacious compared to placebo. Although fluoxetine occasionally induces antinociception in animal models of NP, it exerts minor or no analgesic effect on its own and is effective only in patients with peripheral NP and co-morbid depression. At present, in NCP treatment the evidence to support the use of SSRIs is not sufficient.[21]

Sustained release bupropion, a norepinephrine and dopamine reuptake inhibitor (NDRI) was more effective than placebo in patients with NP of peripheral and central origin. It has a low incidence of sexual dysfunction and is associated with weight loss. Side effects include agitation and insomnia. For NP it is given at a dosage of 150 to 300 mg daily.[85,87,133]

Venlafaxine, with a different chemical structure compared to TCAs and SSRIs, inhibits norepinephrine and serotonin reuptake (SNRI) at a dose > 150 mg daily. Recent data support the use of venlafaxine in NP states (NNT = 3.6).[111] In a randomized, 3-period, crossover trial of venlafaxine and imipramine administered in patients with painful polyneuropathy, both antidepressants resulted in superior pain relief, compared with placebo, with no differences between them.[134] Venlafaxine at doses > 150 mg/day improved pain in PDN while a dose of 75 mg daily was ineffective.[135] Side effects of venlafaxine include hypertension, especially in cases of pre-existing hypertension. Further trials on venlafaxine titration are required as are trials with antiepileptics combined with this antidepressant.[85]

Duloxetine, a newer antidepressant agent, belongs to SNRIs and is FDA approved for PDN treatment.[129] Duloxetine doses range between 60 and 120 mg/day, without any significant differences between the two doses, but with better efficacy vs. placebo. Improvement should be noted within 2 weeks at 60 mg before increasing the dose further.[85,136] Duloxetine's efficacy in PDN was confirmed in three large-scale trials[137,138] and its effects were reported to persist for one year.[139] It has minimal or no effect on blood pressure and body weight, with few sexual adverse effects in studies published up to now. Frequent adverse events observed were nausea, somnolence, dry mouth, constipation, diarrhea, hyperhidrosis and dizziness, and discontinuation rates were 15% to 20%.[140] Duloxetine induces little or no cardiovascular side effects, but rare cases of hepatotoxicity have been reported.

The advantage of venlafaxine and duloxetine application in NCP treatment is that, apart from pain relief, they can serve a useful therapeutic role for clinical depression.[111] Venlfaxine may be more effective in ameliorating neuropathies in cancer patients,[141,142] although it appears to have more side effects, compared with duloxetine. Venlafaxine significantly reduced the incidence of postmastectomy pain syndrome 6 months after breast cancer surgery.[143]

Antiepileptic Drugs—Gabapentinoids

Similar to epilepsy, the pathophysiological basis of NP is neuronal hyper-excitability. Thus, multiple AEDs have been effectively included in NP management due to their ability in suppressing neuronal excitation, ultimately resulting in optimal pain relief.[100] The first published trial of an AED for the NP therapy appeared in 1942 when Bergouignan used phenytoin to treat trigeminal neuralgia, based on the observation that this condition was similar to the neuronal hyper-excitability seen in some epilepsy models.[144,145] Later on, carbamazepine and phenytoin were used for trigeminal neuralgia and PDN alleviation respectively.[145] Currently, gabapentinoids (gabapentin and pregabalin) are commonly used as adjuvants, although so far they do not provide a lower NNT compared to older anticonvulsants.[111,118]

Gabapentin is an AED, holding the broadest evidence for efficacy in NP treatment, due to central sensitization reduction. Loss of inhibitory regulation in the dorsal horn contributes to spontaneous firing of nociceptive pathways through complex mechanisms. Levels of GABA, a dorsal horn inhibitory transmitter, are reduced, and GABA receptors in dorsal horn neurons are down-regulated. Gabapentin, an anticonvulsant structurally related to GABA and not acting on GABA receptors, is efficacious for the treatment of NP of various etiologies.[146,147]

Gabapentin is characterized by its antihyperalgesic properties, acting as an inhibitor of voltage-gated calcium channels, which control neurotransmitter release on peripheral sensory neurons. Thus, it is widely used in the management of pain originating from peripheral nerve injury.[23,146,148–150] Gabapentin exerts its action directly in the brainstem via a glutamate-dependent mechanism, which stimulates descending inhibition, producing antihypersensitivity after peripheral nerve injury.[151] Furthermore, it may produce its antiallodynic effects through microglial cell function alteration.[152,153]

It has an FDA-approved indication for PHN in the United States and it is licensed for the treatment of NP in the U.K.[87,105,154,155] At least eight published double

blind, placebo controlled, RCTs of gabapentin for chronic NP therapy exist in literature. These studies examined patients with PHN, PDN, mixed NP syndromes, phantom limb pain, Guillain-Barre syndrome and acute or chronic pain from spinal cord injury.[146,147,156–161] Gabapentin at dosages up to 3600 mg/day significantly reduced pain vs. placebo; improvement in sleep, mood, and quality of life were also reported in some trials.[87] This agent yielded optimistic results not only in PHN and PDN,[154,162,163] but also in a broad range of NP conditions such as CRPS, radiculitis, poststroke, postoperative and postthoracotomy pain,[163] as well as in cancer-related and multiple sclerosis-related NP, at doses up to 3600 mg/day.[164,165] Gabapentin combined with morphine achieved better analgesia at lower doses of each drug than either as a single agent, with constipation, sedation, and dry mouth reported as the most frequent adverse effects.[166] According to a meta-analysis, including 15 studies and 1,468 participants, gapapentin is effective in treating NP, with a NNT of 2.9 and 3.9 for PDN and PHN respectively and a Number-Needed-to-Harm of 3.7.[154,155]

Basic experimental studies, employing animal cancer pain models, as well as clinical ones, confirmed that gabapentin is effective in treating NCP.[23,164,167–181] In a study investigating the efficacy and safety of gabapentin monotherapy in the management of CIPN, 75 cancer patients, who had previously received chemotherapy and had experienced at least one symptom of NP, were included in the intervention group. They received a fixed low dose of gabapentin (800 mg daily). The control group consisted of 35 cancer patients with similar treatment history and symptomatology, who refused treatment with gabapentin and, therefore, received a fixed-dose combining naproxen and codeine/paracetamol. Patients were grouped in three categories according to the severity of their neuropathic symptoms at baseline: mild, moderate, and severe. Analgesic efficacy of the study drug was assessed by means of a patient-answered questionnaire. Four stages of analgesic response were established: complete, partial, minor, and no response. In the intervention arm, gabapentin led to a complete response in 25.3%, partial response in 44%, minor response in 25.3%, and no response in 5.3% of patients. The response to gabapentin correlated with the severity of the underlying neurotoxicity. In the control group, none experienced complete response, while partial, minor, and no response were observed in 5.7%, 45.7%, and 48.6%, respectively.[182]

Gabapentin has also been studied in a multicenter, randomized, double-blind, placebo-controlled trial, including 121 cancer patients with NCP. Patients had ineffective analgesia with opioids and they were started on gabapentin at a dose of 600 to 1800 mg/day. The authors concluded that gabapentin is effective in improving analgesia in NCP patients already treated with opioids.[164] In addition, results from a systematic review (eight studies: five RCTs and 465 patients), controlling the efficacy of either antiepileptics or antidepressants when added to opioids for cancer pain, suggest that adjuvants improved pain control within 4 to 8 days when added to opioids and the strongest evidence supported gabapentin.[183] Similarly, low dose of gabapentin (400 mg) has been characterized as useful adjuvant to opioids for NCP when combined with low dose of imipramine (40 mg), leading to a significant reduction of pain and severe adverse events.[184]

In a recent study 818 NCP patients were treated according to the WHO analgesic ladder, having a follow-up of 6 months.[185] The researchers used adjuvant drugs such as amitryptiline (29.9%), gabapentin (29.9%), gabapentin and dexamethasone (19.9%) and dexamethasone (20.2%). Opioids such as tramadol, codeine and morphine were used; 52% of patients received morphine as rescue analgesic. Results pointed out that 53.2%, 41.9% and 4.9% of patients had no pain, mild pain and moderate pain respectively. The authors concluded that NCP can be relieved by multimodal treatment following WHO guidelines, as the majority of cancer patients experienced more than one type of pain. This conclusion was in agreement with a previous study on NCP.[186]

Gabapentin can be particularly helpful in patients with NCP (burning pain, shooting pain, allodynia), particularly when pain does not respond to opioids, leading to a reduction of opioids dose. Additionally, combination of gabapentin with morphine results in improvement of sleep, daily activity, mood and quality of life in patients with cancer-related pain syndromes.[164,175,180,181,187] Both pain and dysesthetic symptoms respond well to this drug, which also has an opioid-sparing effect.[175] Gabapentin has been also helpful in relieving abdominal pain from upper abdominal malignancies, such as pancreatic cancer infiltrating the celiac plexus, thus sparing the need for blockade of the latter structure.[178] It is helpful in

reducing pain associated with painful procedures in cancer patients,[173] as well as in reducing myoclonic movements associated with the use of high doses of opioids in cancer pain.[176] Furthermore, evidence-based approaches to pain in advanced cancer support the use of gabapentin and single fraction radiation for neuropathic cancer and bony pain respectively.[188] It has also been reported that intrathecal co-administration of gabapentin and clonidine, in the L5 spinal-nerve ligated rats, exerted a synergistic action on the mechanical antiallodynic effect.[189]

Effective doses range between 100 and 3600 mg daily, according to the results of eigth published double-blind, placebo-controlled, randomized trials published in 2003. Side effects of gabapentin include somnolence, dizziness and less commonly gastrointestinal symptoms and mild peripheral edema. All these effects require close monitoring and dosage adjustment, but usually not drug discontinuation.

To limit adverse effects and increase patient adherence to treatment, gabapentin should be commenced at low dosages (100 to 300 mg as single dose at bedtime or 100 to 300 mg three times daily) and then titrated every 1 to 7 days by 100 to 300 mg, as tolerated. Although three times daily is the target, more rapid titration can be accomplished if most of the daily dose is initially given at bedtime to minimize daytime sedation. A dose achieving complete pain relief or developing unacceptable adverse effects, not resolving promptly, is considered to be the final. Dworkin et al. suggested that gabapentin be used as a First-Line medication for NP with a 3 to 8 week titration period to allow development of tolerance to adverse effects, plus 1 to 2 weeks at the maximal tolerated dosage.[87]

Pregabalin has been FDA approved for PHN and PDN and its action is similar to that of gabapentin, with a significantly greater affinity for the a2-δ subunit of voltage-gated calcium channels vs. gabapentin. Pain improvement is noted from the second day. Although pregabalin is not metabolized by the liver and important pharmacokinetic drug–drug interactions do not occur, the dosage must be adjusted for patients with renal dysfunction. Its side effects are mild to moderate (dizziness, somnolence, headache, dry mouth and peripheral edema). During the first 3 days 150 mg daily are prescribed, followed by 300 mg daily for the next 4 days. From the beginning of the second week 600 mg/day are usually prescribed to patients, whose creatinine clearance is more than 60 mL/minute (max dose 300 mg twice a day).[85,93,190,191] Pregabalin discontinuation rates range from 0 (150 mg/day) to 20% (600 mg/day).[192] Patients with chronic pain of peripheral neuropathic origin receiving pregabalin, both in monotherapy and as add-on therapy, showed substantial improvements in severity of pain and in the spectrum of associated symptoms, such as sleep disturbances, mood disorders, disability, and health-related quality of life.[193]

In a recent prospective, open-label study, the administration of pregabalin in cancer patients with a NP component was studied.[194] One hundred-two cancer patients with definite NCP resistant to a combination of paracetamol, codeine, NSAIDs and methylprednisolone were randomly divided into two groups (pregabalin vs. opioids). In the first group, pregabalin was added and titrated up to 600 mg/day until significant pain relief or poor tolerability where observed (whichever occurred first). In the second group, TTS fentanyl 25 μg/hour was added and the dose was escalated by 25 μg/hour every 72 hours, up to a maximum dose of 125 μg/hour, until significant pain relief or problematic tolerability. The conclusion was that pregabalin prescription in NCP patients provided significant pain alleviation and minimized the need for rescue opioids, thus reducing opioid-induced adverse effects and tolerance.

Apart from gabapentinoids, lamotrigine is effective in treating HIV sensory neuropathy, PDN, central poststroke pain, as well as pain from spinal cord injury due to incomplete spinal cord lesions, when gabapentin presents negative results.[195–199] Lamotrigine is not considered as a First-Line drug for NP treatment because of the slow and careful titration required and the associated risk of severe rash and Stevens-Johnson syndrome (occurring in up to 10% of patients). Dosage of lamotrigine for NP is < 200 mg twice daily.[85,87]

All other AEDs in the context of a clinical trial showed variable and sometimes discrepant results. Evaluation of the efficacy of other second-generation anticonvulsants (levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide) for NP treatment must await publication of the results of RCTs. Although several AEDs block sodium channels, available anticonvulsants have different and often multiple mechanisms. Therefore, lack of response to one anticonvulsant does not necessarily predict lack of response to all AEDs.[87] Despite the wide application of anticonvulsants in NP management, only few trials show analgesic efficacy in cancer cases, with one study

identifying considerable relief in pediatric oncological patients suffering from NCP.[200]

TRAMADOL HYDROCHLORIDE

Tramadol is a norepinephrine and serotonin reuptake inhibitor, centrally acting analgesic, which has direct, but weak opioid action (the M1 metabolite being responsible for its μ-opioid agonist effect) and indirect monoaminergic action (like TCAs). It is also devoid of immunosuppressive activity.[201] RCTs have yielded positive results from tramadol and tramadol/acetaminophen combination[202–204] in PDN,[202] PHN[205] and various NP states.[206] In all trials, tramadol, titrated to a maximum dosage of 400 mg/day significantly relieved pain compared with placebo. Beneficial effects on allodynia and quality of life are also reported.

The NNT with tramadol, compared to placebo, to reach at least 50% NCP relief was 3.8. Tramadol has also been used with good results for mild to moderate cancer pain, with a NNT of 3.4 for musculoskeletal and NCP states.[201,207] Accordingly, tramadol is a therapeutic option for NCP control, improving quality of life in such patients. Changes in anxiety, depression and nervous system function do not affect the analgesic effect of tramadol.[120]

A common starting dose is 100 mg/day titrated up to 200 to 400 mg daily (in divided doses, four times daily). Efficacy in NP treatment is usually evident at 250 mg/day in divided doses. It has a low abuse liability and the development of tolerance and dependence during long-term treatment is usually uncommon.

The most frequent side effects of tramadol include dizziness, nausea, constipation, somnolence and orthostatic hypotension. These occur more frequently when the dosage is escalated rapidly, with concurrent administration of other drugs presenting similar side effects. Seizures could also appear, whereas serotonin syndrome can occur with simultaneous prescription of SSRIs (fluoxetine or sertraline) or monoamine oxidase inhibitors (MAOIs). Tramadol may cause or exacerbate cognitive dysfunction in the elderly.[85,87,93]

In order to decrease the likelihood of adverse effects and increase patients' adherence to treatment, tramadol can be initiated at lower dosages (50 mg once or twice daily) and then titrated every 3 to 7 days by 50 to 100 mg/day in divided doses, as tolerated. The maximum dosage of tramadol is 100 mg 4 times/day (in patients above 75 years of age, 300 mg/day) and adequate 4-week trial period is necessary.[87]

OPIOID ANALGESICS

Opioids act through the descending inhibitory pathways, modulating nociceptive impulses in the dorsal horn. Until recently, the role of opioids in NP management was considered controversial.[72,208–215] In the past, NP was often referred to as "opioids—nonresponsive pain" and for many years opioids were excluded from the treatment of any type of NP syndrome. Today, there is increasing positive evidence regarding efficacy of oral opioids in chronic NP treatment.[87,93] Few trials on oral opioids for NP that have been published present promising results.[208–214] If an adequate dose is used, at least a partial result may be observed.[208,210,212]

In the spinal cord, mu, delta, and kappa opioid receptors are found in presynaptic sites on the afferent nociceptive fiber terminal and postsynaptic sites, located on the secondary neuron of nociceptive circuitry. The highest concentration of opioid receptors is around the C-fiber terminal zone, in laminae I and II, and greater than 70% of mu receptors are on the afferent presynaptic terminals.[216] Peripheral nerve section will lead to loss of presynaptic opioid receptors. This is likely to result in marked reduction of opioid receptors pool at the spinal level, and it contributes to the opioid insensitivity in NP states.[217] Another transmitter, cholecystokinin (CCK), also exerts control in opioid sensitivity at spinal and supraspinal levels. CCK application can selectively decrease the analgesic actions of morphine, whereas antagonists of the CCK-B receptor enhance morphine analgesia. CCK is also up-regulated after nerve damage or in NP models.[218,219]

Although the insensitivity can be relative, the greater dose of opioids can produce intolerable or unmanageable adverse effects that render opioids therapy undesirable. In contrast, intrathecal administration of morphine produces greater dose-dependent inhibition of neuronal responses to noxious and C-fibers evoked stimuli, compared with those by the systemic route in spinal nerve ligated rats.[220] The problem of opioid responsiveness in NP states may not simply be that of a reduced opioid sensitivity, but rather the failure to deliver a sufficiently high concentration of systemic opioids to the spinal cord in the absence of adverse effect.[220]

This is probably why in the early 1990s, opioids were re-examined in relation to NP, with trials showing that up to 50% of patients with certain types of

NP might respond to opioids.[21,25,75] Recent studies suggest that opioids may be effective in relieving NP,[21,214,221] usually in higher doses. Scheduled dosing is suggested, starting with a low dose and gradually titrating upward. Due to the wide variability in response, failure to respond to one opioid should not eliminate them as a possible treatment; rather, rotation/switching to another should be considered.[222,223] In most cancer patients, pain is successfully treated with pharmacological measures such as opioid analgesics or with opioid rotation.[223] An opioid with lower potency might be better tolerated compared to another more potent drug, allowing higher dosing and treatment customization.[21] Increase in opioid dosage, whenever pain is inadequately controlled, still remains a current practice. Unfortunately, in the case of NCP, this practice often shows poor results and increased burden of side effects. As with any use of opioids, attention must be given to prevention and management of potential side effects, particularly constipation.

In patients with PHN, controlled-release oxycodone hydrochloride titrated to a maximum dosage 60 mg/day significantly relieves pain, disability and allodynia compared with placebo.[210] In patients with PDN, controlled-release oxycodone titrated to a maximum dosage of 120 mg/day significantly improves pain, performance of daily activities and sleep, compared with placebo, with an average dose of 37 mg/day,[208,224] whereas a maximum dose of 40 mg/day in PDN proved to be effective, by improving pain and quality of life.[209] Controlled-release morphine titrated to a maximum dose of 300 mg/day was found to be superior to placebo in patients with phantom limb pain.[211] The efficacy of methadone and levorphanol in the treatment of NP was demonstrated in trials, including patients with mixed peripheral and central NP.[213,214] Morphine combined with gabapentin achieved better analgesia, at lower doses of each drug, than either as a single agent, with constipation, sedation and dry mouth as the most frequent adverse effects.[166]

The role of opioids has been re-evaluated during NCP therapy. Controlled-release oxycodone has been applied, because it is safe, well tolerated and effective,[225] although it is unlikely that opioids will replace antidepressants and AEDs for NCP therapy.[226] However, co-administration of oxycodone and paracetamol resulted in a low-dose synergic combination in different pain types. It has been reported that such a combination can be useful in cancer-related pain, including those situations that are complicated by a neuropathic component.[227]

CIBP definitely responds to opioids. In sarcoma-injected mice, acute treatment with fentanyl, sufentanil, and morphine, were effective in reducing CIBP and related behaviors, in a dose-dependent manner.[228] Nevertheless, this analgesic response is rather poor compared to the ones in other types of pain.[229] Clinically, opioids provide effective relief of cancer pain, although occasionally high doses must be administered, to suppress ''breakthrough'' pain or pain from nerve involvement. Their direct effect on tumor growth has been investigated in vitro and in vivo. In vitro morphine has an inhibitory effect on growth of several human cancer lines, suppressing tumor promoters, such as TNF-α.[23,230] On the other hand, morphine may increase tumor growth in animals inoculated with tumor cells through immunosuppression,[231] and can reduce survival of rats with tumors.[232]

The most common adverse effects of opioids are constipation, sedation, drowsiness and nausea. These effects lead to the high withdrawal rates, found in the placebo-controlled trials. In elderly patients cognitive impairment and problems with mobility can occur. Most patients become tolerant to the adverse effects, although constipation often persists. Opioids must be used carefully in patients with a history of substance abuse or attempted suicide, since accidental death or suicide may occur with overdose. Opioid abuse must be distinguished from the appropriate desire to continue receiving medication that effectively relieves pain and from apprehension about not having adequate access to medications that are often difficult to obtain. Concerns about causing a substance abuse disorder, when there is no history of one, do not justify refraining from using opioid analgesics in patients with chronic NP. Even though patients treated with opioids may develop analgesic tolerance, in responsive patients a stable dosage can usually be achieved. All patients receiving opioids develop physical dependence and must be advised not to discontinue their medication abruptly.[85,87,100,233]

Numerous short- and long-acting opioids are available and multiple diverse opinions regarding the administration algorithms exist. One approach recommends to begin with a short-acting opioid (oxycodone, hydrocodone) at dosages equianalgesic to the oral administration of morphine at 5 to 15 mg, every four hours as needed, in combination with acetamoniphen, aspirin, or ibuprofen. After 1 to 2 weeks of therapy,

the patient's total dosage of the short-acting opioid can be converted to an equianalgesic daily dosage of the long-acting one (CR-morphine, CR-oxycodone, TTS fentanyl, levorphanol, methadone).

Limited access to short-acting medication for breakthrough pain may be appropriate. Once the patient is receiving a stable dosage of a long-acting opioid, an adequate trial requires 4 to 6 weeks to access both pain and function. With careful titration and monitoring, there is no clear maximum dosage of opioids. However, evaluation by a pain specialist should be considered when morphine equianalgesic dosages exceeding 120 to 180 mg/day are reached, as the benefits of such doses in patients with NP have not been established in double-blind trials.[85,87,100]

Methadone, a drug that has been thoroughly examined, is a synthetic opioid and a NMDA-antagonist. It was originally developed in Germany as an analgesic and was introduced in the sixties as the treatment of choice for opioid addiction. Since then, there is an increase in methadone prescriptions in both U.S. and U.K.

Recently, according to a systematic review of 35 years, conducted by WHO (2005), due to its favorable analgesic properties and low cost, methadone has been recognized as an important agent in the treatment of both nociceptive and NP and has been characterized as an essential analgesic in cancer pain management. Methadone is believed to bind not only to opioid receptors, but also to be an antagonist at the NMDA receptor as well. As a result, this opioid is often selected when treating NP and NCP. Candidates for a trial of methadone might include, but are not limited to, patients with poor pain control, who have received an adequate trial of other strong opioids, especially if NP components are obvious, patients experiencing severe or multiple toxicities to other strong opioids and patients receiving high opioids doses that are difficult to swallow, due to numerous tablets per dose.[21]

One needs to monitor patients on methadone carefully because it may accumulate systematically, unless titration is done carefully. The recommendation is to adjust the dose no sooner than every 3 to 4 days. In patients with NP and a coexistence of drug addiction, methadone can be prescribed for pain treatment, in addition to the maintenance dose for addiction. This strategy obviously requires coordination with the patient's counselor at the addiction program. The patient would continue in the program, where he receives his addiction dose on a daily or weekly basis, with the pain practitioner prescribing methadone solely for the treatment of pain. This additional amount of methadone can be titrated to pain and side effects, independently of the maintenance dose, which may remain constant.[21]

The use of opioids for NP remains controversial, partly because published studies are small, providing ambiguous results by not establishing opioids risk-benefit ratio. Large variability in trial design in terms of the type of NP treated, the type of opioid administered and the duration of treatment have yielded contradictory conclusions. Concerns about adverse effects and potential for abuse, addiction, hormonal abnormalities, dysfunction of the immune system, and sometimes a paradoxical hyperalgesia, often discourage opioid use in NP states.[234,235]

Short-term studies provide only equivocal evidence regarding opioid efficacy in treating NCP. Intermediate-term studies demonstrate significant efficacy of opioids over placebo, which is likely to be clinically important. Reported adverse effects are common, but not life threatening. The practitioner who prescribes opioids should obtain a signed opioid agreement and is sometimes advised to use random urine screening to check for compliance. Follow-up discussions on side effects and treatment results should be documented. Further RCTs are needed to establish opioid long-term efficacy, safety, addiction potential and interaction on quality of life.[23,85,234]

NON-OPIOID ANALGESIC DRUGS

Non-opioids, such as NSAIDs and acetaminophen, have limited role in the management of NCP.[21,23,236,237] However, some patients who use them, report relief, so a trial is indicated. Many patients have concomitant neuropathic and nociceptive pain, which may respond to non-opioids.[21]

TOPICAL ANTINEURALGICS

Lidocaine 5% Patch

Topical lidocaine is available as a 5% patch or gel. Three studies of the 5% lidocaine patch for NP have published positive results, two in PHN [238,239] for which the patch is FDA approved, and one in focal NP syndromes.[240] In these studies patients reported greater pain relief with lidocaine patch vs. vehicle-controlled patches containing placebo.

The efficacy of the lidocaine patch has been demonstrated only in patients with PHN and focal NP syndromes, expressed with allodynia, without controlled studies being conducted for other pain conditions. Anecdotal evidence of a beneficial effect in patients who have other NP types has been published.[241] In our department, we have used the 5% lidocaine patch in 36 patients (17 PHN, 6 post-thoracotomy pain, four postmastectomy pain, two PDN, five CRPS, two peripheral ischemia) in an open, observational study, for the treatment of NP of diverse origin. The therapy had a 2-month to 4-year duration, resulting in good and very good analgesia in 50% of patients.[242]

Topical lidocaine is effective in approximately 25% of patients with localized peripheral NP. It can be used alone or in combination with other medications.[113] Although systemic absorption from the patch is minimal, local skin absorption is believed to modulate sodium channels, by blocking them at the periphery. Blood levels of the drug are minimal and accumulation does not occur, even with application of three patches for 12 hours daily. The only side effects reported include mild skin reactions (erythema, rush) in some patients. Systemic absorption from the patch must be considered in patients receiving oral class I antiarrythmic drugs (eg, mexiletine). Titration of the patch is not necessary, and an adequate trial should last 2 weeks.[85,87,93] Lidocaine patches are generally safe, because of their low systemic absorption, and well-tolerated adverse events (mild skin reactions such as erythema or rash).[243,244]

Lidocaine patches have been used in NCP where allodynia exists.[113] It has also been used for central NCP in a patient with metastatic epidural spinal cord compression, with promising results, offering new treatment options.[245] However, lidocaine patch application did not reduce pain intensity ratings significantly or related secondary endpoints in cancer patients with persistent incisional pain.[246]

Capsaisin 8% Patch

A high concentration capsaicin patch (8%), applied to the skin for 60 minute in 402 patients, was found to be more effective in treating NP vs. a low concentration patch (0.04%).[247,248] Adverse effects were primarily attributable to local capsaicin-related reactions at the application site. The patch has also been used for the treatment of painful HIV neuropathy.[249] Although one study (post surgical NP) supports the use of topical capsaicin, other studies in noncancer patients suggest that the pain associated with the application of this drug precludes its use.[21,250–252]

CORTICOSTEROIDS

Despite the absence of RCTs, corticosteroids have long been used to treat a variety of NP states, particularly those related to cancer, regarding the sense of general well-being.[23,128,253,254] Dexamethasone has the least mineralocorticoid effect, and, due to its long duration of effect, dosing can be scheduled once per day. Choosing afternoon or evening administration fosters adherence and prevents sleep disturbances, resulting from its stimulant effects. Unfortunately, immunosuppressant and endocrine effects limit long-term use. Proximal muscle wasting can also occur after 4 to 6 weeks of therapy.[21]

LOCAL ANESTHETICS

Local anesthetics inhibit pain primarily by blocking sodium channels and are particularly useful in NP syndromes. Sodium channel blockers are the mainstay in treating NP. There are two types of sodium channels —sensitive and insensitive to tetrodotoxin, a potent puffer-fish toxin. Sodium channels, sensitive to tetrodotoxin, exist in all sensory neurons, while channels insensitive to tetrodotoxin are found only on nociceptive sensory neurons and are implicated in pathological pain states.[255] After nerve injury, sensory afferents may display ectopic discharge properties due to accumulation of sodium channels in the injured and uninjured neurons, with the tetrodotoxin-insensitive ones particularly implicated in the latter. Sodium channel blockers that are currently available are not selective enough, with their clinical use resulting in undesirable CNS and cardiovascular system side effects.

Oral lidocaine analogs, such as mexiletine, are effective in some patients. Intravenous lidocaine infusions are gaining acceptance in a variety of pain-management settings.[256] A bolus intravenous dose of lidocaine (1 to 2 mg/kg) is given over 15 to 30 minutes. If effective, it may be followed by a continuous infusion of 1 to 2 mg/kg/hour. In some patients, the effects can be quite prolonged, gaining weeks of relief. An early warning sign of potential toxicity is perioral numbness. Hepatic dysfunction and significant cardiac conduction abnormalities are contraindications to treatment,

depending upon patient's prognosis and goals of care. Epidural or intrathecal administration of local anesthetics, alone or in conjunction with an opioid, may provide relief in patients who cannot receive systemic delivery.[7,21,23]

NMDA ANTAGONISTS: KETAMINE, DEXTROMETHORPHAN, AMANTADINE, MAGNESIUM

The *N*-methyl-D-aspartate (NMDA) receptors within the spinal cord play a significant role in the pathophysiology of chronic NP. NMDA receptor antagonists have been used in an attempt to abolish wind-up at the spinal cord level. The role of excitatory amino acids in hyperalgesia and the development of tolerance to opioids were recognized 20 years ago.[257] Additionally, the benefits of simultaneous administration of opioids and dextromethorphan in animal models have been explored.[258] Based on these observations, several clinical trials were designed utilizing a variety of NMDA antagonists alone or in combination with opioids, but the results were disappointing.[21]

The NMDA receptor antagonists ketamine and dextromethorphan are being explored for relieving NP. Evidence exists for ketamine use, either orally or parenterally.[259,260] Ketamine is a potent analgesic at subanesthetic doses, by reducing hypersensitivity in the dorsal horn.[261] Recently, it has been suggested that ketamine and amantadine reduce opioids resistant NCP.[261,262] Therapeutic synergism is seen when ketamine is added to morphine, probably explained by their differing actions on wind-up.[72] However, despite promising case reports and evidence-based original protocols on intravenous ketamine as adjuvant for NCP management, it often produces adverse effects (dissociative reactions, hallucinations), which have limited its use.[128,263]

Magnesium has been administered intravenously to patients with NCP, with reported pain relief.[264] Moreover, magnesium and calcium infusion, 1 g of each, before and after oxaliplatin infusion, is the only approach that appears effective for the prevention of neurotoxicity of oxaliplatin. Minerals are an economical treatment and do not interfere with chemotherapy. A recent trial of calcium and magnesium infusion described a significantly decreased oxaliplatin-induced neuropathy, associated also with improved patient-reported quality of life, with regards to muscle cramps, numbness in fingers and toes, and swallowing discomfort.[265] Since more than half of patients with metastatic colon cancer discontinue oxaliplatin because of neurotoxicity, we need strategies to allow patients to remain on therapy longer. One option that has been studied is to give oxaliplatin to patients intermittently, as opposed to continuously. This procedure does appear to decrease neuropathy and allows similar survival probabilities. Of course, additional studies are needed.

OPIOID ANTAGONISTS: NALTREXONE

Crain and Shen observed that ultra-low doses of naltrexone (opioid antagonist for reverting opioids overdose) can potentiate the effect of many opioids tested.[266,267] This bimodal effect is the result of the simultaneous activation of opioid-mediated excitation (caused by ultra-low doses of opioids) and inhibition (elicited by the "pharmacological" dose of the same opioids). Thus, excitation (hyperalgesia) can be blocked with ultra-low doses of an antagonist, resulting in inhibition's potentiation. The mechanism could be mediated by a $G_S\alpha$ protein, via intrathecal administration of antisense oligonucleotides, directed against the $G_S\alpha$ mRNA.[268] These results agree with in vitro experiments performed by Crain and Shen.[266] The notion of two systems mediating hyperalgesia in NP suggests that successful intervention will occur only if both systems are shut down simultaneously. Clinical trials focusing on concomitant blockade of NMDA receptors and ultra-low doses of opioid antagonists will test this model.

SYMPATHETIC BLOCKADE

Sympathetic activity has been implicated in NP generation. Specific treatments such as sympathetic block, intravenous regional guanethidine block, nonselective α-antagonists and selective α2-agonists have been used widely. However, evidence to support their use is limited, and only a small proportion of patients benefit from these treatments.[269]

BISPHOSPHONATES

Apart from treating cancer itself, pain relief from bone metastases is also based on radiotherapy, conventional analgesics (opioids and/or NSAIDs), adjuvants and specific drugs, such as bisphosphonates (pamidronate, clodronate, zoledronate or zoledronic acid), and calcitonin or radioactive agents.[23,270]

In the mouse bone cancer pain model it has been demonstrated that bisphosphonate compounds inhibit osteoclast-mediated bone resorption and suppress associated pain behaviors,[23] making them important therapeutic tools in treating CIBP and tumor-related hypercalcaemia. A review regarding their clinical efficacy in treating CIBP, quality of life and survival included 21 randomized studies.[271] In women with advanced breast cancer and clinically evident bone metastases, bisphosphonates use decreased the risk of developing an adverse skeletal event or fracture. The most effective bisphosphonate in reducing such risks by 41% was intravenous zolendronate (4 mg). Bisphosphonates may also significantly reduce bone pain in women with advanced breast cancer and bone metastases, thus improving global quality of life. Nevertheless, such treatment does not necessarily affect patients' survival with advanced disease. Bisphosphonates toxicity is generally mild and infrequent.[23]

Zoledronic acid exerts analgesic effects in experimental models of peripheral neuropathy and inflammation, whereas pamidronate and clodronate are not effective, independently of their bone-preserving action.[272] In a review that included 1,955 patients from 10 RCTs, the bisphosphonates efficacy in relieving CIBP from prostate cancer was studied.[273] Response rates to therapy were higher for the treatment group, showing a trend toward improved pain relief in the bisphosphonate group, while the rates for skeletal events and pathological fractures were also lower in this group. The only adverse effect that the bisphosphonates group experienced more, compared to placebo, was nausea. There was no statistically significant difference between the bisphosphonate and the control group in terms of prostate cancer death, disease progression, radiological response and prostate specific antigen levels.[23] The data about the bisphosphonate agent, exact dose and route of administration, are still not sufficient. Therefore, bisphosphonates are a potential option for patients with metastatic prostate cancer, for refractory CIBP treatment and for fracture prevention, but further studies are needed for selection guidance, optimal treatment schedule and cost-benefit comparisons.[23]

Results of a recent meta-analysis of 11 RCTs (1,113 patients with multiple myeloma vs. 1,070 patients under placebo or no treatment) suggest that bisphosphonate addition to standard therapy decreases skeletal-related morbidity, skeletal-related mortality and overall mortality.[274] The authors determined the effects of bisphosphonates on pain, quality of life and incidence of hypercalcaemia. According to the analysis, bisphosphonates are beneficial in preventing pathological vertebral fractures and in providing adequate pain relief. The benefit was most evident with clodronate and pamidronate. However, there was no significant effect of bisphosphonates on mortality, on decrease of nonvertebral fractures, or hypercalcaemia incidence. No significant side effects were reported.

CALCITONIN

The hormone calcitonin, by limiting osteoclastic activity, potentially relieves nonmalignant chronic pain (complex regional pain syndrome, Paget's disease, osteoporosis)[275–277] or cancer-induced pain[278] and retains bone density, leading to fractures risk reduction.

Martinez et al. evaluated the efficacy of calcitonin in controlling metastatic CIBP and in decreasing bone complications rates in patients with bone metastases (hypercalcaemia, pathological fractures and nerve compression).[279] From the two studies examined, the first showed a nonsignificant effect of calcitonin in the number of patients with total pain reduction, and the second provided no evidence of minimized analgesics consumption due to hormone administration.

Overall, calcitonin was not efficacious in controlling complications due to bone metastases, nor in improving quality of life or patients' survival. Furthermore, more adverse effects were observed in subject who received calcitonin. In conclusion, the limited evidence currently available does not support calcitonin administration for metastatic CIBP pain control. Nevertheless, individually selected patients might be benefit if other treatment options are unsuccessful.[23]

OTHER DRUGS: BACLOFEN, CANNABINOIDS, ZICONOTIDE, ANTIOXIDANTS, VITAMINS, TAPENTADOL

Other medications occasionally prescribed for NP management include baclofen, cannabinoids, ziconotide, antioxidants, vitamins and the recently released tapentadol. According to the existing clinical experience and due to inconsistent results of clinical trials, these medications could potentially be effective under specific circumastances.[21]

Baclofen, a GABA-B agonist, is an antispasmodic that might contribute in NP relief, although no studies

in cancer patients are available.[280] *Cannabinoids* are valuable adjuvants in pain and palliative care settings.[281] A recent randomized, placebo-controlled, double-blind study concluded that *vitamin E* (400 mg/day) exerts neuroprotective effects in patients treated with cisplatin.[21,282] This finding should be replicated and the safety of vitamin E needs better evaluation in patients receiving cytotoxic chemotherapy before such treatment is routinely applied in clinical practice. Neuropathy and NCP prevention create a potentially promising area. For example, both laboratory and clinical studies are under way to evaluate glutamine and glutathione use for CIPN prevention.[283,284]

Tapentadol is the first FDA-approved centrally acting analgesic, having both μ-opioid receptor agonist and norepinephrine reuptake inhibition activity, with minimal serotonin reuptake inhibition. Because of the combined mechanisms of action it offers a broad therapeutic spectrum for pain pharmacotherapy and it makes it particularly useful in acute nociceptive, acute and chronic inflammatory, as well as in chronic NP treatment, such as PDN. Using several preclinical approaches it was shown that the noradrenergic component of tapentadol interacts with the opioid component and that both synergistically contribute to the analgesic effect of the substance. In comparison to known drugs with only one of the two modes of action, tapentadol, despite its high potency, has an improved tolerability profile in relevant animal models and in clinical settings, particularly with regard to gastrointestinal and central side effects. Tapentadol acts directly without metabolic activation and without formation of analgesically relevant metabolites, providing a safe pharmacodynamic-pharmacokinetic profile. Tapentadol has not yet been studied in cancer patients.[285–287]

BEYOND PHARMACOLOGICAL THERAPY

Despite the numerous analgesic modalities in clinicians' armamentarium and a 66% increase in the number of relevant published trials, NCP often persists with a limited NP improvement with 10% to 15% of patients being refractory to pharmacotherapy.[118] Consequently, a large proportion of NP patients are not sufficiently relieved.[288] Treatment decisions may be tough and available treatment recommendations should be based on positive results from multiple RCTs.[86] After exhausting all available monotherapy options, combination therapy of drug classes should be attempted carefully. More large-scale drug comparative trials should be conducted to determine the value of combination therapy.[106,121] Meticulous monitoring of patients initiated with combination of medications is strongly recommended to avoid severe side effects or occurrence of drug interactions. Such patients should consult pain clinicians, where additional interventional techniques can be applied.[100] When a specialized physician conducts pharmacologic approach toward a mechanism-based NP therapy, pain relief can be achieved.[285]

Clinicians should always keep in mind that in NCP management, the WHO analgesic ladder should be used alongside other strategies such as chemotherapy, radiotherapy and nonpharmacological pain treatment modalities. Clearly, a small number of patients will need anesthetic interventions and even though these are classified in Step 4 of the analgesic ladder, we may consider them at any appropriate point. Despite the proper use of all treatment options by multidisciplinary teams, a considerable number of patients will still have uncontrolled pain, unacceptable side effects, or both. Such patients, carefully selected, should be scheduled for invasive analgesic techniques, such as simple nerve blocks or more invasive methods (regional or neurodestructive blocks and spinal delivery drug systems). The choice of technique is influenced by patients' expectations, prognosis, required analgesia duration, pathology, expertise and availability of trained staff. A basic rule is that the technique with the least likelihood of severe side effects should be selected and that interventional techniques should be reserved for when other measures have failed or when life span is obviously limited.[111]

Cancer pain treatment is integral to the successful management of such patients. The WHO analgesic ladder principles should be followed and integrated with other aspects of care. NCP can be a clinical challenge. Early involvement of a pain specialist with an interest in NCP is critical in cases, where pain remains uncontrolled. Refractory NCP is associated with marked changes in CNS (central wind-up), which may result in opioid resistance. Such patients need complicated pharmacological or interventional analgesia more often. At all points, management of general distress will have a positive effect on pain control, through a direct influence on pain pathways (Figure 1).

Taking into account the potential for variability in efficacy of various therapeutic tools, logical and succinct treatment algorithms are required to successfully

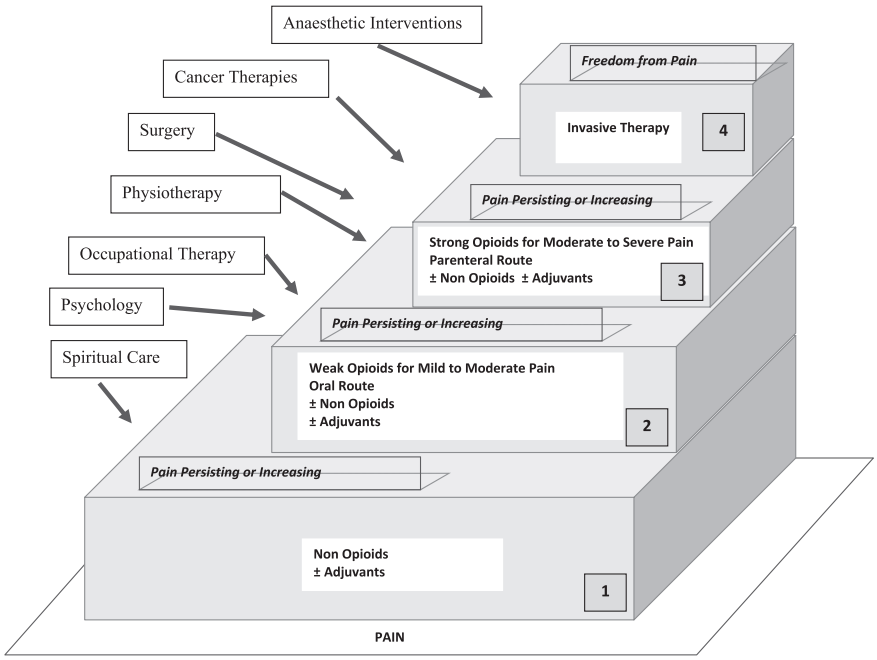

Figure 1. Integration of interventions according to the World Health Organization (WHO) analgesic ladder during neuropathic cancer pain treatment.

manage symptoms of chronic NP. Such algorithms have been developed and published, providing physicians with sequential guide for planning therapeutic strategies, bearing in mind that the multifactorial nature of NP, together with patients' dynamic needs, may alter the available therapeutic options.[100] These evidence-based algorithms are usually supported by available RCTs and mostly refer to peripheral NP pharmacotherapy.[118] Since few studies exist regarding central NP, a treatment algorithm for these conditions needs to be based partly on the experience in peripheral NP conditions, until further studies are published. Despite the limited number of trials in NCP, a variety of pharmacologic therapies have been suggested as effective in relieving nonmalignant NP and algorithms have been published accordingly. Such algorithms, however, can be easily applied for NCP management.[21] Additionally, algorithms specific to CIBP have turned up, providing an overview of the recommended current therapeutic modalities.[61]

CONCLUSIONS—FUTURE DIRECTIONS

In conclusion, NCP is a complex pain problem that is often refractory to treatment. Its pathophysiology may involve diverse aetiologies, which can vary with the evolution and progression of the disease, although, fundamentally they include peripheral sensitization, hyperexcitability in neurons, maintained sympathetic activity, loss of inhibition of dorsal horn neuron, central sensitization, rewiring of synaptic connections in the dorsal horn and phenotypic switch. NCP can be cancer related, noncancer related or treatment induced. Skilled assessment and awareness of various NCP syndromes will lead to exact diagnosis and rapid treatment initiation. Present therapeutic strategies rely heavily upon pharmacotherapy. Combination of drugs, with completely different mechanisms of action is the ideal approach. Such observations support the notion of polypharmacy for NCP treatment. Polypharmacy within the same group of agents might be beneficial as simultaneous administration of certain opioids can result in synergistic analgesia. Research is needed to identify new techniques and therapies that will not only relieve pain and suffering, but also prevent neuropathy.

For the first time, cancer pain animal models begin to mirror the clinical picture of humans with NCP. Such models over the last years have significantly enriched our current knowledge on the pathophysiologicy and pharmacology of NCP, especially from metastatic to bones disease. Generated data provide significant information about mechanisms that induce and maintain different types of cancer pain. These models offer insight into one of the main conundrums of NCP, such as the variability in severity from patient to patient, tumor to tumor and even site to site. These models are useful tools in guiding current pharmacological management by providing a testing ground for

mechanism-based novel therapeutic approaches. Ultimately, gaining insight into the exact mechanisms will lead to the design of specific and effective analgesics for NCP, such as osteoprotogerin, endothelin-receptor antagonists, VR1 or purinergic-receptor antagonists, and others.[12]

Despite the increasing availability of efficient therapeutic possibilities, NCP treatment often remains frustrating for the patient and the physician. The interest in mechanisms and therapy has fortunately increased, resulting in significant treatment advances for the future. These advances will achieve to go beyond the determination of treatment efficacy and far beyond the identification of drugs that are effective on an individual basis. Progress in basic science will lead to a greater understanding of NCP pathophysiology. Important goals for clinical research are the discovery of methods to reliably identify specific NCP mechanisms, the capacity to reverse these mechanisms and the targeted therapy.

REFERENCES

1. Woolf CJ, Max MB. Mechanism-based pain diagnosis: issues for analgesic drug development. *Anesthesiology*. 2001;95:241–249.
2. McCleskey EW, Gold MS. Ion channels of nociception. *Annu Rev Physiol*. 1999;61:835–856.
3. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science*. 2000;288:1765–1768.
4. Mogil JS, Yu L, Basbaum AI. Pain genes? Natural variation and transgenic mutants. *Annu Rev Neurosci*. 2000;23:777–811.
5. Woolf CJ, Bennet GJ, Doherty M, et al. Towards a mechanism based classification of pain? *Pain*. 1998;77:227–229.
6. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms and management. *Lancet*. 1999;353:1959–1964.
7. Urch CE, Dickenson AH. Neuropathic pain in cancer. *Eur J Cancer*. 2008;44:1091–1096.
8. Bostrom B, Sandh M, Lundberg D, Fridlund B. A comparison of pain and health – related quality of life between two groups of cancer patients with differing average levels of pain. *J Clin Nurs*. 2003;12:726–735.
9. Williams LS, Jones WJ, Shen J, Robinson RL, Weinberger M, Kroenke K. Prevalence and impact of depression and pain in neurology outpatients. *J Neurol Neurosurg Psychiatry*. 2003;74:1589–1599.
10. Caraceni APR, Portenoy RK. IASP task force: an international survey of cancer pain characteristics and syndromes. *Pain*. 1999;82:263–274.
11. Grond S, Radbruch L, Meuser T, Sabatowski R, Loick G, Lehmann KA. Assessment and treatment of neuropathic cancer pain following WHO guidelines. *Pain*. 1999;79:15–20.
12. Mantyh PW, Clohisy DR, Koltzenburg M, Hunt SP. Molecular mechanisms of cancer pain. *Nat Rev*. 2002;2:201–209.
13. Honore P, Rogers SD, Schwei MJ, et al. Murine models of inflammatory, neuropathic and cancer pain each generates a unique set of neurochemical changes in the spinal cord and sensory neurons. *Neuroscience*. 2000;98:585–598.
14. Cain DM, Wacnik PW, Turner M, et al. Functional interactions between tumor and peripheral nerve: changes in excitability and morphology of primary afferent fibers in a murine model of cancer pain. *J Neurosci*. 2001;21:9367–9376.
15. Wacnik PW, Eikmeier LJ, Ruggles TR, et al. Functional interactions between tumor and peripheral nerve: morphology, algogen identification and behavioral characterization of a new murine model of cancer pain. *J Neurosci*. 2001;21:9355–9366.
16. Bennett MI, Smith BH, Torrance N, Lee AJ. Can pain be more or less neuropathic? Comparison of symptom assessment tools with ratings of certainty by clinicians. *Pain*. 2006;122:289–294.
17. Besson JM. The neurobiology of pain. *Lancet*. 1999;353:1610–1615.
18. Shimoyama M, Tatsuoka H, Ohtori S, Tanaka K, Shimoyama N. Change of dorsal horn neurochemistry in a mouse model of neuropathic cancer pain. *Pain*. 2005;114:221–230.
19. Flatters SJ, Bennett GJ. Studies of peripheral sensory nerves in paclitaxel-induced painful peripheral neuropathy: evidence for mitochondrial dysfunction. *Pain*. 2006;122:245–257.
20. Donovan-Rodriguez T, Dickenson AH, Urch CE. Gabapentin normalizes spinal neuronal responses that correlate with behaviour in a rat model of cancer – induced bone pain. *Anesthesiology*. 2005;102:132–140.
21. Paice JA. Mechanisms and management of neuropathic pain in cancer. *J Support Oncol*. 2003;1:107–120.
22. Foley KM. Opioids and chronic neuropathic pain. *N Engl J Med*. 2003;348:1279–1280.
23. Sarantopoulos CD. Advances in the therapy of cancer pain: from novel experimental models to evidence-based treatments. *Signa Vitae*. 2007;2(suppl 1):S23–S41.
24. Chong MS, Bajwa ZH. Diagnosis and treatment of neuropathic pain. *J Pain Symptom Manage*. 2003;25:S4–S11.
25. Merskey H, Bogduk N. *Classification of chronic pain*, 2nd ed. Seattle: IASP Press; 1994.
26. IASP (International Association for the Study of Pain). IASP Pain Terminology. http://www.halcyon.com/iasp/terms-p.html.
27. Polomano RC, Farrar T. Pain and neuropathy in cancer survivors. *Am J Nurs*. 2006;106(suppl 3):39–47.

28. Cruccu G, Anand P, Attal N, et al. EFNS guidelines on neuropathic pain assessment. *Eur J Neurol*. 2004;11:153–162.

29. Hansson P. Neuropathic pain: clinical characteristics and diagnostic workup. *Eur J Pain*. 2002;6(A):47–50.

30. Treede DR, Jensen ST, Cambell NJ, et al. Neuropathic pain: redifinition and a grading system for clinical and research purposes. *Neurology*. 2008;70:1630–1635.

31. Meyer-Roseberg K, Burckhardt CS, Kvarnstrom A, Nordfors LO, Kristofferson A. A comparison of the SF – 36 and Nottingham Health Profile in patients with chronic neuropathic pain. *Eur J Pain*. 2001;5:391–403.

32. Meyer– Roseberg K, Kvarnstrom A, Kinnman E, Gordh T, Nordfors LO, Kristofferson A. Peripheral neuropathic pain – a multidimensional burden for patients. *Eur J Pain*. 2001;5:379–389.

33. Smith TE, Chong MS. Neuropathic pain. *Hosp Med*. 2000;61:760–766.

34. Bowsher D. Neurogenic pain syndromes and their management. *Br Med Bull*. 1991;47:644–666.

35. Carter GT, Galer BS. Advances in the management of neuropathic pain. *Phys Med Rehabil Clin North Am*. 2001;12:447–459.

36. Sunderland S. Brachial plexus injuries. *Clin Neurol Neurosurg*. 1993;95(S):S1–S2.

37. Boivi J. Central pain. In: Wall PD, Melzak R, eds. *Textbook of Pain*. Edinburgh: Churchill Livingstone;1999: 879–914.

38. Bonica JJ. Introduction: semantic, epidemiologic and educational issues. In: Casey KL, ed. *Pain and central nervous system disease: The central pain syndromes*. New York, NY: Raven Press; 1991:13–29.

39. Andersen G, Vestergaard K, Ingeman-Nielsen M, Jensen TS. Incidence of central post – stroke pain. *Pain*. 1995;61:187–193.

40. Cruccu G, Truini A. Neuropathic pain and its assessment. *Surg Oncol*. 2010;19:149–154.

41. Niv D, Devor M. Refractory neuropathic pain: the nature and extend of the problem. *Pain Pract*. 2006;6:3–9.

42. Mercadante S. Malignant bone pain: pathophysiology and treatment. *Pain*. 1997;69:1–18.

43. Mercadante S, Arcuri E. Breakthrough pain in cancer patients: pathophysiology and treatment. *Cancer Treat Rev*. 1998;24:425–432.

44. Portenoy RK, Lesage P. Management of cancer pain. *Lancet*. 1999;353:1695–1700.

45. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain*. 1999;81:129–134.

46. NIH. NIH State of the Science Statement on symptom management in cancer: pain, depression and fatigue. *NIH Consens State Sci Statements*. 2002;19:1–29.

47. Kreefe FA, Abernethy AP, Campbell CL. Psychological approaches to understanding and treating disease related pain. *Ann Rev Psychol*. 2005;56:1–22.

48. Forman AD. Peripheral neuropathy and cancer. *Curr Oncol Rep*. 2004;6:20–25.

49. Christo PJ, Mazloomdoost D. Cancer pain and analgesia. *Ann NY Acad Sci*. 2008;1138:278–298.

50. Bonica J. *The management of pain*, Vol I. Philadelphia: Lea & Febiger;1990.

51. ESMO. Management of cancer pain: clinical Recommendations. *Ann Oncol*. 2007;18(suppl 2):ii92–ii94.

52. Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO Guidelines: a longitudinal follow up study of symptom prevalence, severity and etiology. *Pain*. 2001;93:247–257.

53. de Wit R, van Dam F, Loonstra S, et al. The Amsterdam Pain Management Index compared to eight frequently used outcome measures to evaluate the adequacy of pain treatment in cancer patients with chronic pain. *Pain*. 2001;91:339–349.

54. Grond SZD, Diefenbach C, Radburch L, Lehman KA. Assessment of cancer pain: a prospective evaluation in 2266 cancer patients referred to a pain service. *Pain*. 1996;64:107–114.

55. Hansson PT, Lacerenza M, Marchettini P. Aspects of clinical and experimental neuropathic pain: the clinical perspective. In: Hansson PT, Fields HL, Hill RG, Marchettini P, eds. *Neuropathic Pain: Pathophysiology and Treatment, Progress in Pain Research and Management*. Seattle: IIASP Press, 2001;21:1–18.

56. Garcia de Paredes, del Moral Gonzalez, Martinez de Prado, et al. First evidence of oncologic neuropathic pain prevalence after screening 8615 cancer patients. Results of the on study. *Ann Oncol*. 2011;22:924–930.

57. Mantyh PW. Cancer pain and its impact on diagnosis, survival and quality of life. *Nat Rev Neurosci*. 2006;7:797–809.

58. Olsen NK, Pfeiffer P, Mondrup K, Rose C. Radiation-induced brachial plexus neuropathy in breast cancer patients. *Acta Oncol*. 1990;29:885–890.

59. Manas A, Monroy JL, Ramos AA, et al. Prevalence of neuropathic pain in radiotherapy oncology units. *Int J Radiat Oncol Biol Phys*. 2010. September 9 [epub ahead of print]. DOI: 10.1016/j.ijrobp.2010.05.047.

60. Ververs JM. Risks, severity and predictors of physical and psychological morbidity after axillary lymph node dissection for breast cancer. *Eur J Cancer*. 2001;37: 991–999.

61. Delaney A, Fleetwood-Wlker SM, Colvin La, Fallon M. Translational medicine: cancer pain mechanisms and management. *Br J Anaesth*. 2008;101:87–94.

62. Bruera E, Kim HN. Cancer pain. *JAMA*. 2003;290:2476–2479.

63. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev*. 2001;27:165–176.

64. Coleman RE, Rubens RD. The clinical course of bone metastasis from bone cancer. *Br J Cancer*. 1987;55:61–66.

65. Coleman RE, Rubens RD. Bone metastasis and bone cancer. *Cancer Treat Rev*. 1985;12:251–270.

66. Portenoy RK. Mechanisms of clinical pain. Observations and speculations. *Neurol Clin North Am*. 1989;7:205–230.

67. Loeser J. *In Bonica's Management of Pain*, 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2001:19–21.

68. Banning A, Sjogren P, Henriksen H. Treatment outcome in a multidisciplinary cancer pain clinic. *Pain*. 1991;47:129–134.

69. Caraceni A, Mertini C, Zecca E, et al. Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. *Palliat Med*. 2004;18:177–183.

70. Colvin L, Fallon M. Challenges in cancer pain management. *Eur J Cancer*. 2008;44:1083–1090.

71. Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. *J Periph Nerv Syst*. 2008;13:27–46.

72. Regan JM, Peng P. Neurophysiology of cancer pain. *Cancer Control*. 2000;7:11–119.

73. Cleeland CS, Bennett GJ, Dantzer R, et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. *Cancer*. 2003;97:2919–2925.

74. Henry DH, Viswanathan HN, Elkin EP, Traina S, Wade S, Cella D. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the US. *Support Care Cancer*. 2008;16:791–801.

75. Portenoy R. Pain syndromes in patients with cancer and HIV/AIDS. In Portenoy R, ed. Contemporary Diagnosis and Management of Pain in Oncologic and AIDS Patients. 3rd ed. Newton, PA: Handbooks in Healthcare;2000; 49–78.

76. Colleau SM. Neuropathic pain from chemotherapy in cancer: diagnosis and treatment dilemmas. *Cancer Pain Release (WHO Pain and Palliative Care Communication Programs)* 2008;21. Nos 1& 2.

77. Kaley TJ, Deangelis LM. Therapy of chemotherapy-induced peripheral neuropathy. *Br J Haematol*. 2009;145:3–14.

78. Loprinzi LC, Paice J. Neuropathic pain from chemotherapy in cancer: diagnosis and treatment dilemmas. *Cancer Pain Release (WHO Pain and Palliative Care Communication Programs)* 2008; 21. Nos 1 & 2.

79. Honore P, Schwei J, Rodgers SD, et al. Cellular and neurochemical remodeling of the spinal cord in bone cancer pain. *Prog Brain Res*. 2000;129:389–297.

80. Urch CE, Donovan-Rodriguez T, Dickenson AH. Alterations in dorsal horn neurons in a rat model of cancer-induced bone pain. *Pain*. 2003;106:347–356.

81. Bjurholm A, Kreicbergs A, Brodin E, et al. Substance P and CGRP: immunoreactive nerves in bone. *Peptides*. 1988;9:165–171.

82. Campa JA III, Payne R. The management of intractable bone pain: a clinician's perspective. *Semin Nucl Med*. 1992;22:3–10.

83. Hudson AJ. Pain perception and response: central nervous system mechanisms. *Can J Neurol Sci*. 2000;27:2–16.

84. Gebhart GF. Descending modulation of pain. *Neurosci Biobehav Rev*. 2004;27:729–737.

85. Irving G. Contemporary assessment and management of neuropathic pain. *Neurology*. 2005;64(suppl 3):S21–S27.

86. Vadalouca A, Siafaka I, Ergyra E, Vrachnou E, Moka E. Therapeutic management of chronic neuropathic pain. An examination of pharmacological treatment. *Ann NY Acad Sci*. 2006;1088:164–186.

87. Dworking RH, Backonja M, Rowbotham MC, Allen RR, Hewitt DJ, Loeser JD. Advances in neuropathic pain: diagnosis, mechanisms and treatment recommendations. *Arch Neurol*. 2003;60:1524–1535.

88. Truini A, Panuccio G, Galeotti F, et al. Laser evoked potentials as a tool for assessing the efficacy of antinociceptive drugs. *Eur J Pain*. 2010;14:222–225.

89. Wilkie DJ, Huang HY, Reilly N, Cain KC. Nociceptive and neuropathic pain in patients with lung cancer: a comparison of pain quality descriptors. *J Pain Symptom Manage*. 2001;22:899–910.

90. Potter J, Higginson IJ, Scadding JW, Quigley C. Identifying neuropathic pain in patients with head and neck cancer: use of the Leeds assessment of neuropathic symptoms and signs scale. *J R Soc Med*. 2003;96:379–383.

91. Mercadante S, Gebbia V, David F, et al. Tools for identifying cancer pain of predominantly neuropathic origin and opioids responsiveness in cancer patients. *J Pain*. 2009;10:594–600.

92. Vadalouca A, Demosthenous E, Raptis E, Siafaka I, Argyra E. *The use of DN4 questionnaire for the diagnosis of neuropathic cancer pain*. Mykonos, Greece: International Symposium of WIP, ''ALGOS 2009'', 2009. Abstract Book, pp 59.

93. Beniczky S, Tajti J, Timea Varga E, Vescei L. Evidence-based pharmacological treatment of neuropathic pain syndromes. *J Neural Transm*. 2005;112:735–749.

94. Finnerup NB, Johannesen IL, Sindrup SH, Bach FW, Jensen TS. Pain and dysaesthesia in patients with spinal cord injury: a postal survey. *Spinal Cord*. 2001;39:256–262.

95. Richeimer SH, Bajwa ZH, Kahraman SS, Ransil BJ, Warfield LA. Utilization patterns of tricyclic antidepressants in a multidisciplinary pain clinic: a survey. *Clin J Pain*. 1997;13:324–329.

96. Orza F, Boswell MV, Rosenberg SK. Neuropathic pain: review of mechanisms and pharmacologic management. *NeuroRehabilitation*. 2000;14:15–23.

97. Boulton AJM, Gries FA, Jervell JA. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. *Diabet Med*. 1998;15:508–514.

98. Page JC, Chen EY. Management of painful diabetic neuropathy. A treatment algorithm. *J Am Podiatr Med Assoc*. 1997;87:370–379.

99. Perkin GD. Trigeminal neuralgia. *Curr Treat Options Neurol*. 1999;1:458–465.

100. Namaka M, Gramlich CR, Ruhlen D, Melanson M, Sutton I, Major J. A treatment algorithm for neuropathic pain. *Clin Ther*. 2004;26:951–979.

101. Semenchunk MR, Sherman S. Effectiveness of tizanidine in neuropathic pain: an open-label study. *J Pain*. 2000;1:285–292.
102. Takahashi H, Miyazaki M, Nanbu T, Yanagida H, Morita S. The NMDA-receptor antagonist ketamine abolishes neuropathic pain after epidural administration in a clinical case. *Pain*. 1998;75:391–394.
103. Mac Pherson RD. New directions in pain management. *Drugs Today (Barc)*. 2002;38:135–145.
104. Attal N, Cruccu G, Haanpaa M, et al. EFNS Guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol*. 2006;13:1153–1169.
105. Dworkin RH, O' Connor AB, Backonja M, et al. Pharmacological management of neuropathic pain: evidence-based recommendation. *Pain*. 2007;132:237–251.
106. Attal N, Cruccu G, Baron R, et al. EFNS Guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2011;17:1113–1123.
107. Walker VA, Hoskin PJ, Hanks GW, White ID. Evaluation of WHO analgesic guidelines for cancer pain in a hospital-based palliative care unit. *J Pain Symptom Manage*. 1988;3:145–149.
108. Ventafridda V, Tamburini M, Caraceni A, De COnno F, Naldi F. A validation study of the WHO method for cancer pain relief. *Cancer*. 1987;59:850–856.
109. Quasthoff S, Hartung HP. Chemotherapy-induced peripheral neuropathy. *J Neurol*. 2002;249:9–17.
110. Ashburn MA, Lipman AG. Management of pain in the cancer patient. *Anesth Analg*. 1993;76: 402–416.
111. Laird B, Colvin L, Fallon M. Management of cancer pain: basic principles and neuropathic cancer pain. *Eur J Cancer*. 2008;44:1078–1082.
112. Mercadante S, Fulfaro F, Casuccio A, Barresi L. Investigation of an opioid response categorization in advanced cancer patients. *J Pain Symptom Manage*. 1999;18:347–352.
113. Colvin L, Forbes K, Fallon M. Difficult pain. *BMJ*. 2006;332:1081–1083.
114. Fallon MT, Hanks GW. Opioid-resistant pain: sense or nonsense? *The Pain Clin*. 1993;6:205–206.
115. Knotkova H, Pappagallo M. Adjuvant analgesics. *Med Clin North Am*. 2007;91:113–124.
116. Guindon J, Walczak JS, Beaulieu P. Recent advances in the pharmacological management of pain. *Drugs*. 2007;67:2121–2133.
117. Fallon M, Hanks G, Cherny N. Principles of control of cancer pain. *BMJ*. 2006;332:1022–1024.
118. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence-based proposal. *Pain*. 2005;118:289–305.
119. McGeeney BE. Adjuvant agents in cancer pain. *Clin J Pain*. 2008;24(suppl 10):S14–S20.
120. Arbaiza D, Vidal O. Tramadol in the treatment of neuropathic cancer pain: a double-blind, placebo-controlled study. *Clin Drug Investig*. 2007;27:75–83.
121. Attal N. Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (IASP). *Ann Oncol*. 2010;21:1134–1135.
122. Hardy JR, Rees EA, Gwilliam B, Ling J, Broadley H, A' Hern R. A phase II study to establish the efficacy and toxicity of sodium valproate in patients with cancer-related neuropathic pain. *J Pain Symptom Manage*. 2001;21:204–209.
123. Jost L, Rollia F. ESMO Guidelines Working Group. Management of cancer pain: ESMO clinical recommendations. *Ann Oncol*. 2009;20(suppl 4):170–173.
124. Beydoun A, Backogna MM. Mechanistic stratification of antineuralgic agents. *J Pain Symptom Manage*. 2003;25:S18–S30.
125. Sanchez C, Hyttel J. Comparison of the effects of antidepressants and their metabolites on the reuptake of biogenic amines and on receptor binding. *Cell Mol Neurobiol*. 1999;19:467–489.
126. Max MB. Thirteen consecutive well designed randomized trial show that antidepressants reduce pain in diabetic neuropathy and post herpetic neuralgia. *Pain Forum*. 1995;4:248–253.
127. McQuay HJ, Tramer M, Nye BA, et al. A systematic review of antidepressants in neuropathic pain. *Pain*. 1996;68:217–227.
128. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain*. 1999;83:389–400.
129. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*. 2007;4:CD005454.
130. Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medication: association with use of tricyclic agents. *Am J Med*. 2000;108:2–8.
131. Hammack JE, Michalak JC, Loprinzi CL, et al. Phase III evaluation of nortryptiline for alleviation of symptoms of cisplatin-induced peripheral neuropathy. *Pain*. 2002;98:195–203.
132. Mercadante S, Arcuri E, Tirelli W, et al. Amitryptiline in neuropathic cancer patients in morphine therapy: a randomized, placebo-controlled, double-blind, crossover study. *Tumori*. 2002;88:239–242.
133. Semenchuk MR, Sherman S, Davis B. Double-blind, randomized, controlled trial of bupropion SR for the treatment of neuropathic pain. *Neurology*. 2001;57:1583–1588.
134. Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy: a randomized–controlled trial. *Neurology*. 2003; 60:1284–1289.
135. Rowbotham MC, Goli V, Kunz NR, et al. Venlafaxine-extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain*. 2004;110:697–706.
136. Wernicke JF, Pritchett YL, D' Souza DN, et al. Duloxetin at doses of 60 mgr QD and 60 mgr BID is effective in treatment of diabetic neuropathic pain (DNP). [abstract] *Neurology*. 2004;62(supple 5): A192.

137. Kajdasz DK, Iyengar S, Desaiah D, et al. Duloxetine for the management of diabetic peripheral neuropathic pain: evidence-based findings from post hoc analysis of three multicentre, randomized, double-blind, placebo-controlled, parallel-group studies. *Clin Ther*. 2007;29(suppl):2536–2546. (Class I SR).

138. Veves A, Backonja M, Malik RA. Painful diabetic neuropathy: epidemiology, natural history, early diagnosis and treatment options. *Pain Med*. 2008;9:660–674.

139. Skljarevski V, Desaiah D, Zhang Q, et al. Evaluating the maintenance of effect of duloxetine in patients with peripheral neuropathic pain. *Diabetes Metab Res Rev*. 2009;25:623–631.

140. Sultan A, Gaskel H, Derry S, Moore RA. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomized controleed trials. *BMC Neurol*. 2008;8:29. (1–9).

141. Tasmuth T, Hartel B, Kalso E. Venlafaxine in neuropathic pain following treatment of breast cancer. *Eur J Pain*. 2002;6:17–24.

142. Durand JP, Goldwasser F. Dramatic recovery of paclitaxel-disabling neurosensory toxicity following treatment with venlafaxine. *Drugs*. 2002;13:777–780.

143. Arm YM, Yousef AA. Evaluation of the efficacy of the administration of venlafaxine or gabapentin on acute and chronic post-mastectomy pain. *Clin J Pain*. 2010;26:381–385.

144. Bergouignan M. Cures heureuses de nevralgies facials essentielles par le diphenylhydantoinate de soude. *Rev Laryngol Otol Rhinol*. 1942;63:34–41.

145. Beydoun A. Symptomatic treatment of neuropathic pain: a focus on the role of anticonvulsants. *Medscape CME Circle Lecture*. 2001. Medscape CME Circle Lecture, www.medscape.com/cmecircle/neurology/2001cme01/pnt-cme01.html (accessed October 9, 2005).

146. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropahy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*. 1998; 280: 1831–1836.

147. Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized, controlled trial. *JAMA*. 1998; 280: 1837–1842.

148. Sarantopoulos C, McCallum B, Kwok WM, Hogan Q. Gabapentin decreases membrane calcium currents in injured as well as in control mammalian primary afferent neurons. *Reg Anesth Pain Med*. 2002;27:47–57.

149. Patel MK, Gonzalez MI, Bramwell S, Pinnock RD, Lee K. Gabapentin inhibits excitatory synaptic transmission in the hyperalgesic spinal cord. *Br J Pharmacol*. 2000;130: 1731–1734.

150. Backonja MM. Gabapentin monotherapy for the symptomatic treatment of painful neuropathy: a multicenter, double-blind, placebo-controlled trial in patients with diabetes mellitus. *Epilepsia*. 1999;40(suppl 6):S57–S59. discussion S73–S74.

151. Hayashida K, Obata H, Nakajima K, Eisenach JC. Gabapentin acts with the locus coeruleus to alleviate neuropathic pain. *Anesthesiology*. 2008;109:1077–1084.

152. Wodarski R, Clark AK, Marchand F, Malcangio M. Gabapentin reverses microglial activation in the spinal cord of streptozocin-induced diabetic rats. *Eur J Pain*. 2009;13: 807–811.

153. Kim D, You B, Jo EK, Han SK, Simon MI, Lee SJ. NADPH oxidase 2-derived reactive oxygen species in spinal cord microglia contribute to peripheral nerve injury-induced neuropathic pain. *Proc Natl Acas Sci USA*. 2010;107:14851–14856.

154. Wiffen PJ. Gabapentin for acute and chronic pain. *Cochrane Database Syst Rev*. 2005;3:CD005452.

155. Wiffen PJ, Collins S, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain. *Cochrane Database Syst Rev*. 2005;3:CD001133.

156. Gorson KC, Schott C, Herman R, Ropper AH, Rand WM. Gabapentin in the treatment of painful diabetic neuropathy: a placebo-controlled, double-blind, crossover trial. *J Neurol Neurosurg Psychiatry*. 1999;66:251–252.

157. Rice AS, Maton S. Gabapentin in postherpetic neuralgia: a randomized, double-blind, placebo controlled study. *Pain*. 2001;94:215–224.

158. Bone M, Critchley P, Buggy D Jr. Gabapentin in postamputation phantom limb pain: a randomized, double-blind, placebo-controlled, cross-over study. *Reg Anesth Pain Med*. 2002;27:481–486.

159. Pandey CK, Bose N, Carg G, et al. Gabapentin for the treatment of pain in Guillan–Barre syndrome: a double-blind, placebo-controlled, cross-over study. *Anesth Analg*. 2002;95:1719–1723.

160. Tai Q, Kirshblum S, Chen B, Milliss J, Johnston M, De Lisa JA. Gabapentin in the treatment of neuropathic pain after spinal cord injury: a prospective, randomized, double-blind, crossover trial. *J Spinal Cord Med*. 2002;25:100–105.

161. Van de Vusse AC, Stomp Van De Berg SGM, Kessels AHF, Weber WEJ. Randomized, controlled trial of gabapentin in complex regional pain syndrome type I. *BMC Neurol*. 2004;4:13–19.

162. Moka E, Katafygioti A, Argyra E, Siafaka I, Vadalouca A. *The Role of Gabapentin as an Add-on Therapy in Chronic Neuropathic Pain [Abstract]*. Tokyo: 11th International Pain Clinic WSPC, 2004, Abtracts Book, p. 188.

163. Serpell M. Gabapentin in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. *Pain*. 2002;99:557–566.

164. Caraceni A, Zecca E, Bonezzi C, et al. Gabapentin for neuropathic cancer pain: a randomized, controlled trial from the gabapentin cancer pain study group. *J Clin Oncol*. 2004;22:2909–2917.

165. Moka E, Stamatakis E, Vretakos G, Argyra E, Siafaka I, Vadalouca A. *The Role of Gabapentin in Chronic Neuropathic Pain in MS Patients: A 4-Year Experience [Abstract]*. Chile: 2nd International Symposium of Regional Anaesthesia and Pain Therapy; 2004.

166. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF. Morphine, gabapentin or their combination for neuropathic pain. *N Engl J Med*. 2005;352:1324–1334.
167. Shimoyama M, Shimoyama N, Hori Y. Gabapentin affects glutamatergic excitatory neurotransmission in the rat dorsal horn. *Pain*. 2000;85:405–414.
168. Alam M, Rabinowitz AD, Engler DE. Gabapentin treatment of multiple piloleiomyoma-related pain. *J Am Acad Dermatol*. 2002;46:S27–S29.
169. Bennett MI. Gabapentin significantly improves analgesia in people receiving opioids for neuropathic cancer pain. *Cancer Treat Rev*. 2005;31:58–62.
170. Bosnjak S, Jelic S, Susnjar S, Luki V. Gabapentin for relief of neuropathic pain related to anticancer treatment: a preliminary study. *J Chemother*. 2002;14:214–219.
171. Caraceni A, Zecca E, Martini C, De Conno F. Differences in gabapentin efficacy for cancer pain more apparent than real? *J Pain Symptom Manage*. 2001;21: 93–94.
172. Chandler A, Williams JE. Gabapentin, an adjuvant treatment for neuropathic pain in a cancer hospital. *J Pain Symptom Manage*. 2000;20:82–86.
173. Devulder J, Lambert J, Naeyaert JM. Gabapentin for pain control in cancer patients' wound dressing care. *J Pain Symptom Manage*. 2001;22:622–626.
174. Keskinbora K, Pekel AF, Aydinli I. The use of gabapentin in a 12-year-old boy with cancer pain. *Acta Anaesthesiol Scand*. 2004;48:663–664.
175. Lossignol DA, Plehiers B, Body JJ. Gabapentin (Neurontin) and cancer pain: a pilot study. *Rev Med Brux*. 2004;25:429–435.
176. Mercadante S, Villari P, Fulfaro F. Gabapentin for opiod-related myoclonus in cancer patients. *Support Care Cancer*. 2001;9:205–206.
177. Oneschuk Dal-Shahri MZ. The pattern of gabapentin use in a tertiary palliative care unit. *J Palliat Care*. 2003;19:185–187.
178. Pelham A, Lee MA, Regnard CB. Gabapentin for coeliac plexus pain. *Palliat Med*. 2002;16:355–356.
179. Ripamonti C, Dickerson ED. Strategies for the treatment of cancer pain in the new millennium. *Drugs*. 2001;61:955–977.
180. Ross JR, Goller K, Hardy J, et al. Gabapentin is effective in the treatment of cancer-related neuropathic pain: a prospective, open-label study. *J Palliat Med*. 2005;8:1118–1126.
181. Ross JR, Waight C, Riley J, Broadley K. Gabapentin: resistant neuropathic pain and malignancy. *Palliat Med*. 2001;15:348–349.
182. Tsavaris N, Kopteridis P, Kosmas C, et al. Gabapentin monotherapy for the treatment of chemotherapy-induced neuropathic pain: a pilot study. *Pain Med*. 2008;9:1209–1216.
183. Bennett MI. Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review. *Palliat Med*. 2011;25:553–559.
184. Arai YC, Matsubara T, Shimo K, et al. Low-dose gabapentin as useful adjuvant to opioids for neuropathic cancer pain when combined with low-dose imipramine. *J Anesth*. 2010;24:407–410.
185. Mishra SH, Bhatnagar S, Gupta D, et al. Management of neuropathic cancer pain following the WHO analgesic ladder: a prospective study. *Am J Hosp Palliative Care*. 2009;25:447–451.
186. Stute P, Soukup J, Menzel M, Sabatowski R, Grond S. Analysis and treatment of different types of neuropathic cancer pain. *J Pain Symptom Manage*. 2003;26:1123–1131.
187. Bar Ad V. Gabapentin for the treatment of cancer-related pain syndromes. *Rev Recent Clin Trials*. 2010;5:174–178.
188. Dy SM. Evidence-based approaches to pain in advanced cancer. *Cancer*. 2010;16:500–506.
189. Yamama Y, Nishikawa K, Funao T, Mori T, Asada A. Intrathecal gabapentin and clonidine synergistically inhibit allodynia in spinal nerve-ligated rats. *Life Sci*. 2010;87:565–571.
190. Dworkin RH, Corbin AE, Young JD, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized placebo-controlled trial. *Neurology*. 2003;60:1274–1283.
191. Rosenstock J, Tuchman M, La Moreaux L, Sharma U. Pregabalin for the treatment of painful, diabetic, peripheral neuropathy: a double-blind, placebo controlled trial. *Pain*. 2004;110:628–638.
192. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev*. 2009;3:CD007076.
193. Navarro A, Saldana MT, Perez C, Torrades S, Rejas J. Patient-reported outcomes in subjects with neuropathic pain receiving pregabalin: evidence from medical practice in primary care settings. *Pain Med*. 2010;11:719–731.
194. Vadalouca A, Raptis E, Moutzouri A, Stavropoulou E, Siafaka I, Argyra E. *Pregabalin for the Management of Neuropathic Cancer Pain. Preliminary Results*. Athens, Greece: Third International Congres on Neuropathic Pain of Neu PSIG; 2010, Abstract Book, p.73.
195. Eisenberg E, Lurie Y, Bracker C, Daond D, Ishay A. Lamotrigine reduces painful diabetic neuropathy: a randomized controlled study. *Neurology*. 2001;57:505–509.
196. Vestergaard K, Andersen G, Gottrup P, Kristensen BT, Jensen TS. Lamotrigine for central poststroke pain: a randomized controlled trial. *Neurology*. 2001;56: 184–190.
197. Finnerup NB, Sindrup SH, Bach FW, Johannesen IL, Jensen TS. Lamotrigine in spinal cord injury pain: a randomized controlled trial. *Pain*. 2002;96:375–383.
198. Simpson DM, McArthur JC, Olney R, et al. A placebo controlled trial of lamotrigine for painful HIV-associated neuropathy. *Neurology*. 2000;54:2115–2119.
199. Macdonald J, Young LT. Newer antiepileptic drugs in bipolar disorder: rationale for use and role in therapy. *CNS Drugs*. 2002;16:549–562.

200. Vondracek P, Oslejkova H, Kepak T, et al. Efficacy of pregabalin in neuropathic pain in paediatric oncological patients. *Eur J Paediatr Neurol*. 2009;13:332–336.
201. Mattia C, Coluzzi F. *Tramadol. Focus on musculoskeletal and neuropathic pain. Minerva Anaesthesiol*. 2005;71:565–584.
202. Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology*. 1998; 50: 1842–1846.
203. Hollingshead J, Duhmke RM, Cornblath DR. Tramadol for neuropathic pain. *Cochrane Database Syst Rev*. 2006;3:CD003726.
204. Freeman R, Raskin P, Hewitt DJ, et al. Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy. *Curr Med Res Opin*. 2007;23:147–161.
205. Boureau F, Legallicier P, Kabir Ahmadi M. Tramadol in post-herpetic neuralgia: a randomized double-blind placebo-controlled trial. *Pain*. 2003;104:323–331.
206. Sindrup SH, Andersen G, Madsen C, Smith T, Brosen K, Jensen TS. Tramadol relieves pain and allodynia in polyneuropathy: a randomized double-blind controlled trial. *Pain*. 1999;83:85–90.
207. Leppert W. Tramadol as an analgesic for mild to moderate cancer pain. *Pharmacol Rep*. 2009;61:978–992.
208. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy. A randomized controlled trial. *Neurology*. 2003;60:927–934.
209. Watson CP, Watt– Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain*. 2003;105:71–78.
210. Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology*. 1998;50:1837–1841.
211. Huse E, Labrig W, Flor H, Birbaumer N. The effect of opioids on phantom limb pain and cortical reorganization. *Pain*. 2001;90:47–55.
212. Raja SN, Haythornthwaite JA, Pappagalo M, et al. Opioids versus antidepressants in postherpetic neuralgia. *Neurology*. 2002;59:1015–1021.
213. Morley JS, Bridson J, Nash JP, et al. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. *Palliat Med*. 2003;17:576–587.
214. Rowbotham MC, Twilling L, Davies PS, Taylor K, Mohr D, Reisner L. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med*. 2003; 348:1223–1232.
215. McQuay H. Opioids in pain management. *Lancet*. 1999;353:2229–2232.
216. Besse D, Lombard MC, Zakac JM, et al. Pre-and post-synaptic distribution of mu, delta and kappa opioid receptors in the superficial layers of the cervical dorsal horn of the rat spinal cord. *Brain Res*. 1990;521:15–22.
217. Dickenson AH. Spinal cord pharmacology of pain. *Br J Anaesth*. 1995;75:193–200.
218. Xu XJ, Puke MJC, Verge VMK, et al. Up-regulation of cholecystokinin in primary sensory neurons is associated with morphine insensitivity in experimental neuropathic pain in the rat. *Neurosci Lett*. 1993;152:129–132.
219. Stanfa LC, Sullivan AF, Dickenson AH. Alterations in neuronal excitability and the potency of spinal mu, delta and kappa opioids after carrageenan induced inflammation. *Pain*. 1992;50:345–354.
220. Suzuki R, Chapman V, Dickenson AH. The effectiveness of spinal and systemic morphine on rat dorsal horn neuronal responses in the spinal nerve ligation model of neuropathic pain. *Pain*. 1999;80:215–228.
221. Cherny NI, Thaler HT, Friedlander-Klar H, et al. Opioid responsiveness of cancer pain syndromes caused by neuropathic or nociceptive mechanisms. *Neurology*. 1994;44:857–861.
222. Indelicato RA, Portenoy RK. Opioid rotation in the management of refractory cancer pain. *J Clin Oncol*. 2002;20:348–352.
223. Vadalouca A, Moka E, Argyra E, Sykioti P, Siafaka I. Opioid rotation in patients with cancer: a review of the current literature. *J Opioid Manage*. 2008;4:213–250.
224. Eisenber E, McNicol ED, Carr DB. Efficacy of mu-opioids agonists in the treatment of evoked neuropathic pain: systematic review of randomized controlled trials. *Eur J Pain*. 2006;10:667–676.
225. Ong EC. Controlled-release oxycodone in the treatment of neuropathic pain of nonmalignant and malignant causes. *Oncology*. 2008;74(suppl 1):72–75.
226. Allen SC. Neuropathic pain – the case for opioids therapy. *Oncology*. 2008;74(suppl 1):76–82.
227. Gatti A, Sabato E, Di Paolo AR, Mammucari M, Sabato AF. Oxycodone/Paracetamol: a low dose synergic combination useful in different types of pain. *Clin Drug Invest*. 2010;30(suppl 2):3–14.
228. El Mouedden M, Meert TF. Evaluation of pain-related behaviour, bone destruction and effectiveness of fentanyl, sufentanyl, and morphine in a murine model of cancer pain. *Pharmacol Biochem Behav*. 2005;82:109–119.
229. Menendez L, Lastra A, Fresno MF, et al. Initial thermal heat hyperalgesia and delayed hyperalgesia in a murine model of bone cancer pain. *Brain Res*. 2003;969:102–109.
230. Sueoka N, Sueoka E, Okabe S, Fujiki H. Anti-cancer effects of morphine through inhibition of tumour necrosis factor-alpha release and mRNA expression. *Carcinogenesis*. 1996;17:2337–2341.
231. Ishikawa M, Tanno K, Kamo A, Takayanagi Y, Sasaki K. Enhancement of tumor growth by morphine and its possible mechanism in mice. *Biol Pharm Bull*. 1993;16:762–766.
232. Lewis JW, Shavit Y, Terman GW, Gale RP, Liebeskind JC. Stress and morphine affect survival of rats challenged with a mammary ascites tumor (MAT 13762B). *Nat Immun Cell Growth Regul*. 1983;3:43–50.

233. Wiffen PJ, Edward JE, Barden J, McQuay HJ. Oral morphine for cancer pain. *Cochrane Database Syst Rev*. 2003;4:CD003868.
234. Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of non-malignant origin. *JAMA*, 2005;293:3043–3052.
235. Ballantyne J, Mao J. Opioid therapy for chronic pain. *N Engl J Med*. 2003;349:1943–1953.
236. Max MB, Schafer SC, Culnane M, et al. Association of pain relief with drug side effects in postherpetic neuralgia: a single dose study of clonidine, codeine, ibuprofen and placebo. *Clin Pharmacol Ther*. 1998;43:1427–1432.
237. McNicol E, Strassels SA, Goudas L, Lau J, Carr DB. NSAIDs or paracetamol, alone or combined with opioids, for cancer pain. *Cochrane Database Syst Rev*. 2005;1:CD005180.
238. Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine patch: double-blind, controlled study of a new treatment for post-herpetic neuralgia. *Pain*. 1996;65:39–44.
239. Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain*. 1999;80:533–538.
240. Meier T, Wasner G, Faust M, et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. *Pain*. 2003;106:151–158.
241. Barbano RL, Herrmann DN, Hart-Gouleau S, Pennella-Vaughan J, Lodewick PA, Dworkin RH. Effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in diabetic polyneuropathy. *Arch Neurol*. 2004;61:914–918.
242. Argyra E, Siafaka I, Moka E, Vadalouca A. 5% Lidocaine patch in the treatment of neuropathic pain of diverse origin [abstract]. Aachen: 9th Congress of the European Association for Palliative Care (EAPC), Eur J Pall Care, 2005, Abstracts Book, p.80.
243. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. 5% Lidocaine patch medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority, two-stage, RCT study. *Curr Med Res Opin*. 2009;27:1663–1676.
244. Hans G, Sabatowski R, Binder A, Boesl I, Rogers P, Baron R. Efficacy and tolerability of a 5% lidocaine medicated plaster for the topical treatment of post-herpetic neuralgia: results of a long-term study. *Curr Med Res Opin*. 2009;25:1295–1305.
245. Hans GH, Robert DN, Van Maldeghem KN. Treatment of an acute severe central neuropathic pain syndrome by topical application of lidocaine 5% patch: a case report. *Spinal Cord*. 2008;46:311–313.
246. Cheville AL, Sloan JA, Northfelt DW, et al. Use of a lidocaine patch in the management of postsurgical neuropathic pain in patients with cancer: a phase III double-blind crossover study (N01CB). *Support Care Cancer*. 2009;17:451–460.
247. Backonja M, Wallace MS, Blonsky ER, et al. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomized, double-blind study. *Lancet Neurol*. 2008;12:1106–1112.
248. Backonja MM, Malan TP, Vanhove GF, Tobias JK. NG X-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomized, double-blind, controlled study with an open-label extension. *Pain Med*. 2010;4:600–608.
249. Simpson DM, Brown S, Tobias J. NGX – 4010 C107 Study Group. Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy. *Neurology*. 2008;70:2305–2313.
250. Ellison N, Loprinzi CL, Kugler J, et al. Phase III placebo-controlled trial of capsaicin cream in the management of surgical neuropathic pain in cancer patients. *J Clin Oncol*. 1997;15:2974–2980.
251. Paice JA, Ferrans CE, Lashley F, et al. Topical capsaicin in the management of HIV-associated peripheral neuropathy. *J Pain Symptom Manage*. 2000;19:45–52.
252. Noto C, Pappagalo M, Szallasi A. NGX – 4010, a high concentration capsaicin patch for lasting relief of peripheral neuropathic pain. *Curr Opin Investig Drugs*. 2009;10:702–710.
253. Kanner R. Diagnosis and management of neuropathic pain in patients with cancer. *Cancer Invest*. 2001;19:324–333.
254. Mercadante SL, Berchovich M, Casuccio A, Fulfaro F, Mangione S. A prospective randomized study of corticosteroids as adjuvant drugs to opioids in advanced cancer patients. *Am J Hosp Palliat Care*. 2007;24:13–19.
255. Novakovic SD, Tzoumaka E, McGivern JG, et al. Distribution of the tetrodoxin-resistant sodium channel PN3 in rat sensory neurons in normal and neuropathic conditions. *J Neurosci*. 1998;18:2174–2187.
256. Ferrini RL. Parenteral lidocaine for severe intractable pain in 6 hospice patients continued at home. *J Palliat Med*. 2001;3:193–201.
257. Trujillo KA, Akil H. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. *Science*. 1991;251:85–87.
258. Mao J, Price DD, Caruso FS, Mayer DJ. Oral administration of dextromethorphan prevents the development of morphine tolerance and dependence in rats. *Pain*. 1996;67:361–368.
259. Mercadante S, Arcuri E, Tirelli W, Casuccio A. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, cross-over, double-dose study. *J Pain Symptom Manage*. 2000;20:246–252.
260. Mitchell AC, Fallon MT. A single infusion of intravenous ketamine improves pain relief in patients with critical limb ischaemia: results of a double-blind, randomized, controlled trial. *Pain*. 2002;97:275–281.

261. Javery KB, Ussery TW, Steger HG, et al. Comparison of morphine and morphine with ketamine for postoperative analgesia. *Can J Anaesth*. 1996;43:212–215.
262. Pud D, Eisenberg E, Spitzer A, et al. The NMDA receptor antagonist amantadine reduces surgical neuropathic pain in cancer patients: a double-blind, randomized, placebo-controlled trial. *Pain*. 1998;75:349–354.
263. Okon T. Ketamine: an introduction for the pain and palliative medicine physician. *Pain Physician*. 2007;10:493–500.
264. Crosby V, Wilcock A, Corcoran R. The safety and efficacy of a single dose (500 mg or 1 g) of intravenous magnesium sulfate in neuropathic pain poorly responsive to strong opioid analgesics in patients with cancer. *J Pain Symptom Manage*. 2000;19:35–39.
265. Nikcevich DA, Grothey A, Sloan JA, et al. Effect of intravenous calcium and magnesium (IV Ca, Mg) on oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: results of the phase III, placebo-controlled, double-blind NCCTG trial N04C7. *J Clin Oncol*, 2008;26(suppl 15): p4009. [abstract].
266. Crain SM, Shen KF. Opioids can evoke direct receptor-mediated excitatory effects on sensory neurons. *Trends Pharmacol Sci*. 1990;11:77–81.
267. Crain SM, Shen KF. Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate opioid tolerance/dependence liability. *Pain*. 2000;84:121–131.
268. Cruciani RA, Pasternak GW. Blockade of hyperalgesia by antisense oligodeoxynucleotide to Gsa. Seatle, WA: Program of the 31st International Narcotic Research Conference, July 15–20; 2000, Abstract Book, p. 59.
269. Kingery WS. A critical review of controlled trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain*. 1997;73:123–139.
270. Gralow J, Tripathy D. Managing metastatic bone pain: the role of bisphosphonates. *J Pain Symptom Manage*. 2007;33:462–472.
271. Pavlakis N, Schmidt R, Stockler M. Bisphosphonates for breast cancer. *Cochrane Database Syst Rev*. 2005;3: CD003474.
272. Walker K, Medhurst SJ, Kidd BL, et al. Disease modifying and anti-nociceptive effects of the bisphosphonate zoledronic acid in a model of bone cancer pain. *Pain*. 2002;100:219–229.
273. Yuen KK, Shelley M, Sze WM, Wilt T, Mason MD. Bisphosphonates for advanced prostate cancer. *Cochrane Database Syst Rev*. 2006;4:CD006250.
274. Djulbegovic B, Wheatley K, Ross J, et al. Bisphosphonates in multiple myeloma. *Cochrane Database Syst Rev*. 2010;3:CD003188.
275. Gobelet C, Meier JL, Schaffner W, Bischof-Delaloye A, Gerster JC, Burckhardt P. Calcitonin and reflex sympathetic dystrophy syndrome. *Clin Rheumatol*. 1986;5:382–388.
276. Martin TJ. The therapeutic uses of calcitonin. *Scott Med J*. 1978;23:161–165.
277. Rifat SF, Kiningham RB, Peggs JF. Calcitonin in the treatment of osteoporotic bone pain. *J Fam Pract*. 1992; 35:93–96.
278. Szanto J, Ady N, Jozsef S. Pain killing with calcitonin nasal spray in patients with malignant tumors. *Oncology*. 1992;49:180–182.
279. Martinez- Zapata MJ, Roque M, Alonso-Coello P, Catala E. Calcitonin for metastatic bone pain. *Cochrane Database Syst Rev*. 2006;3:CD003223.
280. Farrar JT, Portenoy RK. Neuropathic cancer pain: the role of adjuvant analgesics. *Oncology*. 2001;15:1435–1442.
281. Pace A, Carpano S, Galie E, et al. Vitamine E in the neuroprotection of cisplatininduced peripheral neurotoxicity and otoxicity. *J Clin Oncol*, 2007;25(suppl 18):p9114. [abstract].
282. Peat S. Using cannabinoids in pain and palliative care. *Int J Palliat Nurs*. 2010;16:481–485.
283. Cascinu S, Catalano V, Cordella L, et al. Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol*. 2002;20:3478–3483.
284. Boyle FM, Wheeler HR, Shenfield GM. Glutamate ameliorates experimental vincristine neuropathy. *J Pharmacol Exp Ther*. 1996;279:410–415.
285. Hartrick CT, Rozek RJ. Tapentadol in pain management. *CNS Drugs*. 2011;25(5):359–370.
286. Hartrick CT. Tapentadol immediate-release for acute pain: a drug profile. *Expert Rev Neurother*. 2010;10:861–869.
287. Scwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin*. 2011;27:151–162.
288. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain*. 2010;150:573–581.